MINIREVIEW

Tumor Necrosis Factor (TNF)–α and TNF Receptors in Viral Pathogenesis (44487)

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Abstract. **Tumor necrosis factor–α (TNF-α) and TNF receptors (TNFR) are members of the growing TNF ligand and receptor families that are involved in immune regulation. The present report will focus on the role of the prototypic ligand TNF and its two receptors, TNFR1 and TNFR2, in viral pathogenesis. Although TNF was reported years ago to modulate viral infections, recent findings on the molecular pathways involved in TNFR signaling have allowed a better understanding of the molecular interactions between cellular and viral factors within the infected cell. The interactions of viral proteins with intracellular components downstream of the TNFR have highlighted at the molecular level how viruses can manipulate the cellular machinery to escape the immune response and to favor the spread of the infection. We will review here the role of TNF and TNFR in immune response and the role of TNF and TNFR signaling in viral pathogenesis.** [P.S.E.B.M. 2000, Vol 223]

Members of the TNF ligand and receptor family act *via* a common set of signaling molecules to regulate cell differentiation, activation, and viability. Among TNF family members, the first discovered TNF-α, formerly cachectin, is a proinflammatory cytokine that plays a key role in both inflammatory and infectious diseases, especially in viral infections (1–3). TNF binds to two TNF receptors, TNF-R1 and TNF-R2, that transduce intracellular signals when expressed on the cell surface, while blocking TNF signaling when released as soluble decoys in body fluids. TNF interferes with viral replication in several ways. TNF enhances or inhibits viral replication depending on the virus involved and the cell type infected. The binding of TNF to the TNF receptors can activate, differentiate, or kill target cells thereby interfering with the viral life cycle. In contrast, viruses have evolved to appropriate the TNF/TNFR pathway to evade immune responses and favor viral dissemination. TNF is also involved in a network of cytokines and chemokines that stimulate the recruitment of immune cells in the infectious foci, thereby enhancing the spread of the viral infection. TNF also can block the viral replication by interfering with the viral life cycle especially the viral entry. Thus an intricate balance between the viral life cycle and the cytokine network, especially the TNF/TNFR pathway, is a key component that will influence the pathogenesis of many viral diseases. We will define the role of both TNF and TNFR in immune modulation, describe their signaling pathway, and delineate their role in viral pathogenesis.

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TNF and TNF Receptors in the Immune Response

TNF-α binds to two distinct TNFR called TNFR1 and TNFR2 that belong to a broader group of related proteins, the TNFR family. The members of the TNFR family have a

characteristic repeating extracellular cysteine-rich motif (Fig. 1) (4). Among the members of the TNFR family are the TNFR1 and TNFR2, TNFRrp (TNFR related protein), the low-affinity nerve growth factor (NGF) receptor, the Fas antigen, CD40, CD27, CD30, 4–1BB, OX40, DR3, DR4, DR5, and HVEM (herpesvirus entry mediator). Although the extracellular domains of TNFR members are very similar, the intracellular domains that are involved in signal transduction show more diversity. The family of ligands for these receptors is composed of TNF-α, lymphotoxin (LT), nerve growth factor (NGF), Fas ligand, CD40 ligand, CD27 ligand, CD30 ligand, 4–1BB ligand, OX40 ligand, APO3 ligand, TRAIL, and LIGHT. Three of these ligands, TNF, LT-α homotrimers, and TRAIL, are each capable of binding to two of the receptors, the TNFR1 and the TNFR2 for TNF and LT, and DR4 and DR5 for TRAIL. All of the other ligands and their receptors interact, as far as is known, with one-to-one correspondence; each ligand has one and only one receptor target. All of the TNF ligand family members are believed to be trimeric proteins, and all exert their effects by causing receptor trimerization at the cell surface.

In this review we will focus our attention on the role of the TNF/TNFR (1 and 2) pathway in viral pathogenesis. TNF is expressed on two forms, a 26-kDa transmembrane and a 17-kDa secreted form. The 26-kDa pro-TNF, the precursor of mature TNF, is a type-II transmembrane protein that is first displayed on the plasma membrane and then proteolytically cleaved by a metalloproteinase to release the mature 17-kDa TNF. Both secreted and membrane-bound TNFs are present as trimers, and the trimeric structure of TNF is important for its biological activity (5).

TNF is produced by a wide variety of cells including T cells and macrophages (1). In macrophages, TNF synthesis can be induced by various pathogens including viruses, bacteria, and parasites as well as by cytokines (IL-1, IL-2, IFN-γ, GM-CSF, M-CSF, and TNF itself). Lipopolysaccharide (LPS), a component of the wall of Gram negative bacteria, induces TNF, among other proinflammatory cytokines. Inhibitors of TNF production in macrophages, such as cytokines (TGF-β, IL-4, IL-10) and viral products (adenovirus), have also been described. TNF inhibits interferon-γ priming for production of high levels of IL-12 by macrophages (6). By blocking TH1 cytokine production, TNF might limit the extent and duration of inflammatory response *in vivo*. Chronic TNF exposure suppresses the response of both TH1 and TH2 T-helper subsets and attenuates T-cell receptor signaling (7). Thus chronic TNF stimulation suppresses T-cell function *in vivo* and might have important implications for our understanding of pathogenesis in chronic inflammatory diseases (7).

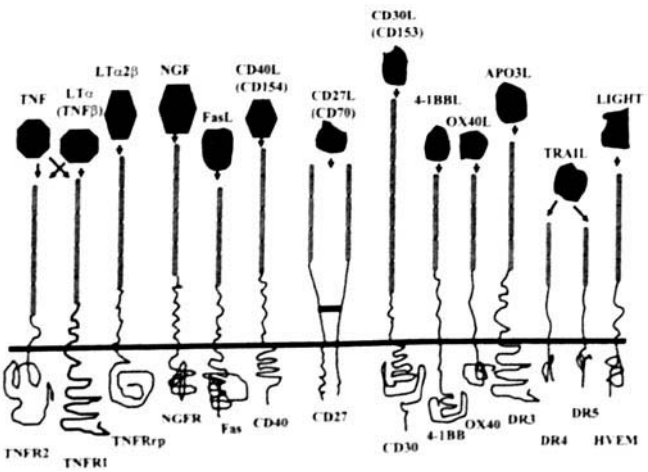

Figure 1. The TNF ligand and receptor families.

The biosynthesis of TNF is highly regulated at multiple levels, transcriptional, translational, but also post-translational. TNF is produced in small quantities in quiescent cells, but becomes one of the major factors secreted in activated cells (1). The multiple activities of TNF are mediated through two distinct but structurally homologous TNFR, type 1 (p55 or p60) and type 2 (p75 or p80) with molecular masses of 60 and 80 kDa, respectively. Both TNFR are type I transmembrane glycoproteins and members of the TNFR superfamily characterized by the presence of multiple cysteine-rich repeats of about 40 amino acids in the extracellular amino-terminal domain (Fig. 1). These two receptors are present virtually on all cell types except for the red blood cells (8), but TNFR1 is more ubiquitous, and TNFR2 is often more abundant on endothelial cells and cells of hematopoietic lineage (8–10). TNFR2 signaling appears to be mainly confined to cells of the immune system that makes it of high relevance in understanding immune processes involved in viral infections. Both receptors can bind to TNF with high affinity, but the exact role of the two receptors in mediating the effects of TNF is still debated. Although recent data suggest that 17-kDa soluble TNF binds with high affinity to TNFR1, the 26-kDa membrane-bound TNF interacts with high affinity to TNFR2 (11, 12). It has been generally believed that TNFR1 is responsible for the majority of biological activities of TNF. A "passive model" has been suggested to explain the role of TNFR2 in mediating the TNF response (13). The rapid rate of dissociation of the TNF/TNFR2 complex may facilitate the interaction of TNF with TNFR1, suggesting a role for the TNFR2 in passing TNF to TNFR1, which has been postulated to be the main TNF signal transducer. However, recent data have demonstrated that TNFR2 is able to mediate TNF biological activity independently (14, 15). TNFR1 is the major mediator of TNF biological functions including the effects on apoptosis or programmed cell death, cytotoxicity, fibroblast proliferation, synthesis of prostaglandin E2, and resistance to chlamydiae (13, 16, 17). These various activities and their coordinated induction are likely to be mediated by the heterogeneity of the adapter proteins with which TNFR1 functional domains interacts (18). TNFR2 is involved in the proliferation of thymocytes and the murine cytotoxic T-cell line, in the TNF-dependent proliferative response of human mononuclear cells, in the induction of GM-CSF secretion, in the inhibition of early hematopoiesis,

and in downregulating activated T cells by inducing apoptosis (14, 19–22). Due to the lack of intracellular death domain, TNFR2 may use a distinct signaling pathway to induce apoptosis. Recent studies suggest that TNFR2-induced apoptosis is associated with the downregulation of the antiapoptotic proteins, Bcl-xL and/or Bcl-2 (23, 24).

Besides membrane receptors, soluble TNF receptors (sTNFR) can also be produced from both membrane-bound TNFR1 and TNFR2 proteolytic cleavage. Soluble TNFR retain the ability to bind TNF and act as inhibitors of TNF in experimental systems (25–27). *In vivo*, sTNFR may act to neutralize or modulate TNF activity (28). However, in some cases, low levels of sTNFR may stabilize the activity of TNF by stabilizing the trimeric structure of TNF and providing a reservoir of TNF (29). Both sTNFR1 and sTNFR2 are normally present in blood and urine (26, 27) and may be produced by monocytes and macrophages that can release sTNFR spontaneously *in vitro* (30, 31). Increased levels of sTNFR are found in inflammatory diseases or infectious diseases characterized by a chronic immune activation such as AIDS (32–36). Stimuli such as LPS, IL-1, and TNF itself can trigger the cleavage of TNFR. The biological response to TNF is believed to be a result of the balance of multiple signals delivered *via* both TNFR1 and TNFR2. For example, in latently HIV-infected lymphocytic cells (ACH-2), the TNFR1 plays a major role in stimulation of HIV production (37). In contrast, when both TNFR are activated simultaneously by agonistic antibodies or co-culture with cells expressing a noncleavable membrane form of TNF, HIV production is downregulated, and cell death is enhanced (37).

By engaging TNFR1, TNF activates the transcription factors nuclear factor–κB (NF-κB) and activator protein 1 (AP-1), leading to induction of proinflammatory and immunomodulatory genes (38). Unlike CD95 ligand, TNF rarely triggers apoptosis unless protein synthesis is blocked, which suggests the preexistence of cellular factors that can suppress the apoptotic stimulus generated by TNF. Expression of these suppressive proteins probably is controlled through NF-κB and c-*Jun* N-terminal kinase (JNK) JNK/AP-1, as inhibition of either pathway sensitizes cells to apoptosis induction by TNF (39–42).

Recent studies have unveiled the intracellular pathways triggered by TNF binding to TNFR (Fig. 2). TNF trimerizes TNFR1 upon binding (43), inducing association of the receptor's death domains. Subsequently, an adapter termed TRADD (TNFR-associated death domain) (44) binds through its own death domain to the clustered receptor death domains. TRADD functions as a platform adapter that recruits several signaling molecules to the activated receptor: TNFR-associated factor (TRAF)– 2 (45, 46) and receptor-interacting protein (RIP) (46, 47) stimulate pathways leading to activation of NF-κB and JNK/AP-1, whereas Fas-associated death domain (FADD) mediates activation of apoptosis *via* the caspase cascade (46, 48, 49). Of these, only

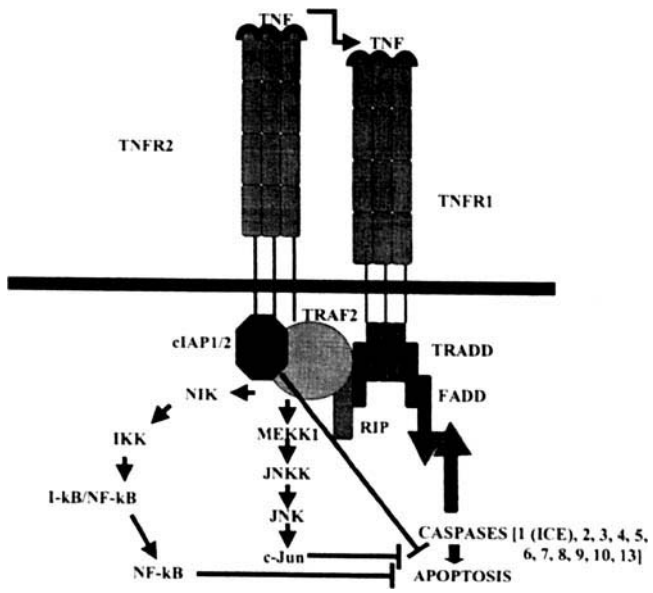

Figure 2. Signaling by TNF receptors.

RIP has enzymatic activity, namely that of a serine-threonine kinase; however, a role for RIP's kinase activity in the activation of NF-κB or JNK/AP-1 has yet to be established.

TRAF2 and RIP activate the NF-κB–inducing kinase (NIK), which in turn activates the inhibitor of κB (I-κB) kinase complex, IKK (50–55). IKK phosphorylates I-κB, leading to I-κB degradation and allowing NF-κB to move to the nucleus to activate transcription. The pathway from TRAF2 and RIP to JNK involves a cascade that includes the mitogen-activated protein (MAP) kinases MEKK1 (MAP/Erk kinase kinase-1), JNKK (JNK kinase), and JNK (56, 57). MEKK1 is related to NIK, and it is implicated in the pathway because kinase-active MEKK1 mutants block JNK activation by TNF; however, MEKK1 does not bind to TRAF2 (58), suggesting that another TRAF2-binding kinase acts upstream or instead of MEKK1.

Cells from TRAF2 gene knockout mice or from transgenic mice expressing a dominant negative TRAF2 mutant have only a slight defect in their NF-κB response to TNF (59, 60). Thus, TRAF2 may not be essential for NF-κB activation by TNF; alternatively, there may be other TRAF family members that bind to TRADD and NIK and substitute for TRAF2. TRAF2-deficient cells are totally lacking in JNK activation in response to TNF, demonstrating a critical role for TRAF2 in this response. The picture emerging from RIP-deficient cells is inverse: NF-κB activation in response to TNF is absent, whereas JNK activation is preserved (61). Hence, RIP is required for coupling TNFR1 to NF-κB, but it may not be crucial for coupling TNFR1 to JNK. Both TRAF2 and RIP knockout mice display atrophy of the thymus, spleen, and adipose tissue, depletion of B-cell precursors that cannot be ascribed to defects in TNF signaling, which suggests that each of these proteins has additional functions. TRAF2 also binds to cIAP1 and cIAP2 (cellular inhibitor of apoptosis-1 and -2) (62), which belong to a

family of mammalian and viral proteins with antiapoptotic activity. In addition to interacting with TNFR1, TRAF2 also binds directly to TNFR2 and, like TNFR1, can stimulate NF-κB *via* the NIK, IKK, and I-κB pathway (45). TNFR2-TRAF2 interaction results in the stimulation of NF-κB, but is not involved in the apoptotic process mediated *via* the caspase pathway.

FADD couples the TNFR1-TRADD complex to activation of caspase-8, thereby initiating apoptosis (46, 48, 49). Cells from FADD knockout mice are resistant to TNF-induced apoptosis, demonstrating an obligatory role of FADD in this response (63). Besides FADD, TNFR1 can engage an adapter called RAIDD (64). RAIDD binds through a death domain to the death domain of RIP and through a CARD (caspase recruitment domain) motif to a similar sequence in the death effector caspase-2, thereby inducing apoptosis. Recently, a widely expressed 60-kDa protein, named SODD for silencer of death domain, has been described to be associated with the death domain of TNFR1 (65). SODD is a negative regulatory protein that is normally associated with the death domain of TNFR1. SODD could inhibit the intrinsic self-aggregation properties of the death domain and maintain TNFR1 in an inactive, monomeric state. This inhibition is relieved by TNFR1 cross-linking, which triggers the rapid release of SODD from the death domain of TNFR1. The uncomplexed death domains of TNFR1 are then able to self-associate and bind the adapter protein TRADD, which in turn recruits TRAF2, RIP, and FADD to form an active TNFR1 signaling complex. These signaling proteins begin to dissociate from the receptor within minutes of complex formation in a process that is accompanied by the phosphorylation of TRADD (65). The subsequent reassociation of SODD with the uncomplexed TNFR1 then reestablishes the normal silent state for TNFR1.

Caspases (cytosolic aspartate-specific proteases) are the components that destroy the cell machinery, either by themselves or by activating other destructive factors. Caspases are a family of proteases that contain cysteine at the active site and cleave the target protein following an aspartic acid residue. The prototype of this family of proteases is interleukin-1β-converting enzyme, ICE, now termed caspase-1. So far more than 10 different human caspases have been discovered and are known by a variety of different names (66–68). All caspases are synthesized as proenzymes and are processed to remove an NH_2-terminal prodomain and are divided into two subunits that associate to form an active heterodimeric enzyme. Among several caspases, caspase-8, caspase-9, and caspase-3 are situated at pivotal junctions in apoptotic patways. Caspase-8 initiates apoptosis in response to extracellular apoptosis-inducing ligands such as TNF and is activated in a complex associated with the receptor's cytoplasmic death domains. The interaction of caspase-8 with the adapter protein FADD on TNFR1/TRADD complex initiates the caspase cascade. Caspase-9 activates apoptosis in response to agents or insults that trigger release of cytochrome-*c* from the mitochondria (69). Both caspase-8 and caspase-9 can activate caspase-3 by proteolytic cleavage (70). Caspase-3 cleaves the 116- kDa death substrate, poly (ADP-ribose) polymerase (PARP), to generate a 102- kDa fragment that will lead to DNA fragmentation and apoptosis.

c-*Myc*, a transcription factor, is widely known as a crucial regulator of cell proliferation in normal and neoplastic cells, but until relatively recently its apoptotic properties, which appear to be intrinsic, were not fully appreciated. Recently connections between the TNF pathway and the c-*Myc* pathway have been found that suggest a role for the c-*Myc*-interacting adaptor protein BinI in mediating cell death (71).

TNF and TNF Receptors in Viral Infections

TNF and TNFR usually have been considered as a main component of antiviral activity, often acting synergistically with IFN-γ. However, in recent years, growing evidence has shown that both DNA and RNA viruses can interfere with the TNF/TNFR pathway to escape the immune surveillance.

DNA Viruses. See Table I for details on TNF, TNFR, and DNA viruses.

Poxviridae. Poxviridae is a family of viruses that includes Myxoma virus, Vaccinia virus, and Tanapoxvirus.

Myxoma virus. Many poxviruses encode a plethora of immunomodulatory proteins, including homologs of host cytokines and cytokine receptors, also referred to as viroreceptors. These receptors mimic function by binding and sequestering host cytokines, thus allowing the virus to escape the immune defense. The T2 protein of myxoma virus (M-T2 protein) is a TNF receptor homolog that displays two distinct activities. The secreted dimeric M-T2 glycoprotein binds TNF with high affinity, and thereby inhibits TNF-mediated cytotoxicity. The intracellular M-T2 is an endoglycosidase H-sensitive species that prevents myxoma-infected $CD4^+$ T lymphocytes from undergoing apoptosis and thereby supporting greater replication of the virus in T lymphocytes (72, 73). To compare the domains of M-T2–mediating extracellular TNF inhibition and intracellular apoptosis inhibition, recombinant myxoma viruses expressing nested C-terminal truncations of M-T2 protein were constructed. One mutant, containing intact copies of only two cysteine-rich domains, was not secreted and was incapable of binding TNF, yet the mutant retained full ability to inhibit virus-induced apoptosis. Thus, the minimal domain of intracellular M-T2 protein required to inhibit apoptosis is distinct from that required by the extracellular M-T2 for functional TNF binding and inhibition. M-T2 is an example of a virus-encoded immunomodular protein with two distinct anti-immune properties.

Vaccinia virus. The vaccinia virus strain Western Reserve *B13R* gene encodes a 38.5-kDa intracellular polypeptide. This polypeptide is nonessential for virus replication and has 92% amino acid identity with the cowpox virus cytokine response modifier A (CrmA) protein that inhibits

Table I. TNF, TNFR, and DNA Viruses

Virus	Family	Effects	Mediated by	Reference
Myxoma virus	Poxviridae	1) Inhibits TNF-mediated cytotoxicity 2) Inhibits apoptosis of infected cells	1) Secreted M-T2 viral protein is a TNFR homolog 2) Intracellular M-T2 viral protein is an endo-glycosidase H-sensitive protein	72, 73
Vaccinia virus (WRB13R)	Poxviridae	Inhibits apoptosis mediated by TNF and anti-Fas antibodies	38.5-kDa intracellular polypeptide similar to CrmA from cowpox virus	75
Tanapox virus	Poxviridae	Inhibits the TNF-mediated induction of cell adhesion molecules	38-kDa glycopeptide inhibits TNF-induced activation of NF-κB	76
Epstein-Barr virus	Herpesviridae	1) Immortalizes EBV-infected B lymphocytes *via* NF-κB activation	1) LMP1 is a pseudo-TNFR with two distinct sites within the cytoplasmic tail: one similar to TNFR1, the other similar to TNFR2	77–85
		2) Protects intestinal cells from apoptosis induced by TNF	2) BHRF1 is involved in blockade of intestinal cell apoptosis	
Herpes simplex virus	Herpesviridae	1) Reduced susceptibility of HSV-infected cells to apoptosis	1) Inhibits caspase-3-independent and caspase-dependent pathways	89–93
		2) Binds and enters into target cells *via* HVEM, a member of the TNFR family	2) Envelope glycoprotein gD binds to HVEM	
Cytomegalovirus	Herpesviridae	Upregulates TNF gene activity	Immediate early (IE) viral products	96
Herpesvirus saimiri	Herpesviridae	Immortalizes infected T lymphocytes	STP oncoproteins associate with TRAFs	103
Hepatitis B virus	Hepdnaviridae	1) Sensitizes infected cells to apoptotic killing by TNF	1) HBx protein effect is not mediated by TNFR upregulation	104, 105
		2) Upregulates TNF gene expression	2) HBx protein activates NF-AT by a cyclosporin A-sensitive mechanism	
Parvovirus	Parvoviridae	Induces apoptosis *via* downregulation of c-*myc*	Activates the caspase-3	111, 112

the interleukin (IL)-1β converting enzyme (ICE) that is involved in the apoptotic process (74). The B13R protein does block apoptosis mediated by TNF and anti-Fas antibodies. Using DNA fragmentation, chromium release and microscopic analyses, it was shown that cells infected with wild-type vaccinia virus strain WR, or a revertant virus in which the *B13R* gene had been re-inserted into the B13R deletion mutant, are more resistant than uninfected cells or deletion mutant–infected cells to apoptosis mediated by TNF and anti-Fas (75).

Tanapoxvirus. Tanapoxvirus (TPV)-infected cells secrete an early 38-kDa glycopeptide that selectively inhibits the induction by TNF of cell-adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) on the surface of endothelial cells (76). Mobility shift assays and Northern blot analyses show that the supernatants from TPV-infected cells inhibit TNF-induced activation of NF-κB and transcriptional activation of the *E-selectin*, *VCAM-1*, and *ICAM-1* genes.

Herpesviridae. Herpesviridae is a family of viruses that includes Epstein-Barr virus, Herpes simplex virus, Cytomegalovirus, and Herpesvirus saimiri.

Epstein-Barr virus. The latent membrane protein 1 (LMP1) of Epstein-Barr virus (EBV) contributes to the immortalizing activity of EBV in primary human B lymphocytes (77). LMP1 is targeted to the plasma membrane and is a constitutively aggregated pseudo-TNFR that activates transcription factor NF-κB through two sites in its C-terminal cytoplasmic domain. One site is similar to activated TNFR2 through interactions with TRAF1 and TRAF2, and the second site is similar to TNFR1 by association with the TNFR1 death domain interacting protein TRADD. TNFR1 recently has been shown to activate NF-κB through association with TRADD, RIP, and TRAF2; activation of the NF-κB–inducing kinase (NIK); activation

of the inhibitor κBα kinases (IKKα and IKKβ); and phosphorylation of I-κBα (Fig. 2). I-κBα phosphorylation on Ser-32 and Ser-36 is followed by its degradation and NF-κB activation and translocation to the nucleus of the cell. NF-κB activation by LMP1 or by each of its effector sites is mediated by a pathway that includes NIK, IKKα, and IKKβ. Dominant negative mutants of NIK, IKKα, or IKKβ substantially inhibits NF-κB activation by LMP1 or by each of its effector sites (78). LMP1 mediates NF-κB activation *via* two independent domains located in its C-terminal cytoplasmic tail, a TRAF-interacting site that associates with TRAF1, -2, -3, and -5 through a PXQXT/S core motif and a TRADD-interacting site. LMP1 has been shown to increase TRAF1 in EBV-negative Burkitt lymphoma cells *via* TRAF binding to the PXQXT/S motif (79). An LMP1 mutant that does not aggregate fails to induce TRAF1 expression confirming the essential role for aggregation in LMP1 signaling. Over-expression of a dominant form of I-κBα blocks LMP1-mediated TRAF1 upregulation, indicating that NF-κB is an important component of LMP1-mediated gene induction from both the TRAF- and TRADD-interacting sites.

LMP1 interacts with TRAFs that bind to the cytoplasmic tail of TNFR1 and TNFR2 (80). Among the several members of TRAF family, TRAF1, TRAF2, and TRAF3 appear to associate independently with LMP1 but bind an overlapping target site. TRAF3 associates with LMP1 the most avidly and can compete with TRAF1 and TRAF2 for binding to LMP1 (81). TRAF2 associates with truncated derivatives of the carboxy terminus of LMP1 more efficiently than with the intact terminus, indicating that LMP1's conformation may regulate its association with TRAF2.

TRAF2 binds *in vitro* to the LMP1 carboxyl-terminal cytoplasmic domain (CT), co-precipitates with LMP1 in B lymphoblasts, and localizes to LMP1 plasma membrane patches. A dominant negative TRAF2 deletion mutant that lacks amino acids 6–86 (TRAF/δ 6–86) inhibits NF-κB activation from the LMP1 CT and competes with TRAF2 for LMP1 binding. TRAF2δ 6–86 inhibits NF-κB activation mediated by the first 45 amino acids of the LMP1 CT by more than 75% but inhibits NF-κB activation through the last 55 amino acids of the CT by less than 40%. A TRAF interacting protein, TANK, inhibits NF-κB activation by more than 70% from both LMP1 CT domains. Thus, TRAF2 aggregation is implicated in NF-κB activation by the first 45 amino acids of the LMP1 CT and shows that a different TRAF-related pathway is involved in NF-κB activation by the last 55 amino acids of the LMP1 CT (82). Re-induction of LMP1 expression or activation of the cellular CD40 receptor, both induce NF-κB activation and JNK cascade and stimulate the proliferation of the B cells. This suggests that LMP1 mimics B-cell activation processes that are physiologically triggered by CD40-CD40 ligand signals (83). Since LMP1 acts in a ligand-independent manner, it replaces the T-cell–derived activation signal to sustain indefinite B-cell proliferation. LMP1-mediated signaling through the TRAF system has been shown to play a role in the pathogenesis of EBV-positive lymphomas that arise in immunosuppressed patients (84). Another EBV protein, BHRF1, has been shown to protect intestinal epithelial cells from apoptosis induced by TNF (85). EBV infection of T-cell lymphoma lines causes upregulation of TNF gene expression and increased secretion of TNF. In combination with interferon-γ, these changes can activate macrophages and might contribute to the pathogenesis of hemophagocytic syndrome (86).

Herpes simplex virus. TNF has been shown to protect mice from infection with herpes simplex virus type 1 (HSV-1) (87). Human monocytes activated with LPS and then infected with HSV-1 secrete higher amounts of TNF and show less susceptibility to HSV-1 infection (88). HSV-1 recently has been reported to block caspase-3-independent and caspase-dependent pathways involved in cell death (89). The block in the caspase-dependent pathway may occur downstream of caspase-3 activation (89). Both mechanisms might account for reduced susceptibility of HSV1-infected cells to apoptosis.

HSV entry into cells is mediated by a recently described novel member of the TNF receptor family (90). Hamster and swine cells resistant to viral entry become susceptible upon expression of a human cDNA encoding this protein, designated HVEM (herpesvirus entry mediator). HVEM mediates the entry of several wild-type HSV strains of both serotypes. Mutations in the HSV envelope glycoprotein gD significantly reduce HVEM-mediated entry (90, 91). Glycoprotein gD is a structural component of the HSV envelope that is essential for entry into the host cells and has been shown to bind directly to HVEM (91, 92). Gel filtration chromatography assays show the formation of a complex of 113 kDa at a molar ratio of 1:2 suggesting that HVEM is a receptor for virion gD and that the interaction between these proteins is a step in HSV entry into HVEM-expressing cells (91). HVEM is a member of the TNFR family by virtue of its four cysteine-rich pseudorepeats (4). HVEM mRNA expression is detected in several human fetal and adult tissues, although the predominant sites of expression are lymphocyte-rich tissues such as adult spleen and peripheral blood leukocytes. Interestingly, the cytoplasmic region of HVEM binds to several members of the TRAF family, namely TRAF1, TRAF2, TRAF3, and TRAF5 (93). Transient transfection of HVEM into human 293 cells causes marked activation of NF-κB, and also marked activation of *Jun* N-terminal kinase, and of the *Jun*-containing transcription factor AP-1 (93). This suggests that the attachment of the HSV envelope glycoprotein gD to HVEM is linked *via* TRAFs to signal transduction pathways that activate the immune response, especially in T lymphocytes. Recently a new member of the TNF family, named LIGHT, has been shown to be the cognate ligand for HVEM (94). LIGHT is a 29-kDa type II transmembrane protein

produced by activated T cells. HSV1 gD inhibits the interaction of HVEM with LIGHT, and LIGHT and gD interfere with HVEM-dependent cell entry by HSV-1 (94).

Cytomegalovirus. The effect of TNF on the major immediate early (IE) enhancer/promoter activity is determined by the degree of differentiation of the infected cells. TNF stimulates human cytomegalovirus (HCMV) major immediate early (IE) enhancer/promoter activity in the HL-60 granulocyte/monocyte progenitor cell line when added to transfected cells. In contrast, in the differentiated HL-60 cells and in the mature THP-1 monocytic cell line, addition of TNF causes inhibition of the IE enhancer/promoter activity (95). Since premonocytic cells are suggested to be sites of HCMV latency, the stimulation by TNF could be of potential physiological significance. Products of the HCMV *IE* gene region are potent trans-activators. *IE* gene products of HCMV have been shown to upregulate *TNF* gene activity as judged by increased promoter activity, steady state mRNA, and protein production (96). These studies suggest that activation of the TNF gene expression by HCMV *IE* gene products may result in the inflammatory response associated with HCMV infections. Furthermore, in *in situ* hybridization experiments, TNF mRNA has been shown to be present abundantly in colonic mucosa from AIDS patients with HCMV colitis but not in colonic mucosa from control (AIDS and normal) subjects. The TNF transcripts are identified in mucosal macrophages containing cytomegalic inclusions that were positively associated with HCMV, but not HIV-1, within the mucosa (97). TNF in synergy with interferon-γ have been shown to be produced by $CD4^+$ T cells specific for the HCMV major regulatory protein IE1 and to have a synergistic effect on the inhibition of HCMV replication and viral protein expression (98). Thus IE1-specific $CD4^+$ T cells display *in vitro* anti-CMV activity through TH1 cytokine secretion and may play a role in the control of *in vivo* latent HCMV infections. In murine models, late gene transcription, assayed by the genes encoding glycoprotein B and the murine CMV (MCMV) homolog of ICP 18.5, is blocked by synergistic TNF/interferon-γ treatment and results in an alteration of nucleocapsid formation (99). MCMV infection also induces release of TNF that inhibits MCMV infection as shown by enhanced viral replication following neutralization of TNF with soluble TNFR (100, 101). Besides the TNF-mediated inhibition of MCMV replication, virus-induced TNF can cause significant liver pathology such as hepatic necrotic foci and increased levels of liver enzymes in the serum (102). Together these data show that, although usually a delicate balance between TNF production and viral replication allows the virus to grow in the absence of tissue damages, in some cases high production of TNF following CMV infection might result in significant tissue injury.

Herpesvirus saimiri. The STP oncoproteins of the herpesvirus saimiri (HVS) are stably associated with TRAF1, 2, or 3. Mutational analyses identified residues of PXQXT/S in STP-A11 as critical for TRAF association. In addition, a somewhat divergent region of STP-C488 is also critical for TRAF association. Mutational analysis reveals that STP-C488 induces NF-κB activation that is correlated with its ability to associate with TRAFs. Thus TRAF/STP association might be involved in immortalization of T lymphocytes following HVS infection (103).

Hepatitis B virus. Hepatitis B virus (HBV) HBx protein sensitizes cells to apoptotic killing by TNF. This effect is not mediated by upregulation of TNFR. Enhanced apoptotic killing by HBx and TNF might select for neoplastic hepatocytes that survive by synthesizing mitogenic growth factors (104). Recently HBx protein has been reported to upregulate transcriptionally the production of TNF in HBV-infected hepatocytes. Upregulation of TNF gene expression by HBx involves nuclear factor of activated T cells (NF-AT)–dependent activation (105). HBx activates NF-AT by a cyclosporine A-sensitive mechanism involving dephosphorylation and nuclear translocation of the transcription factor. Luciferase gene expression assays demonstrate that HBx transactivates transcription through NF-AT–binding sites and activates a Gal4-NF-AT chimeric protein. Thus, HBx may play a role in the intrahepatic inflammatory processes by inducing locally the expression of cytokines that are regulated by NF-AT.

High levels of both TNF and TNFR are detected in infiltrating mononuclear cells and hepatocytes in chronic HBV infection (106, 107). HBV infection is controlled by virus-specific cytotoxic T lymphocytes (CTL) that secrete both TNF and interferon-γ after antigen recognition. Until recently viral clearance during HBV infection has been thought to reflect the destruction of infected hepatocytes by $CD8^+$ CTL. In contrast, recent reports show that the viral clearance during HBV infection results from a noncytopathic antiviral mechanism mediated *via* both TNF and IFN-γ production (108, 109). Both TNF and interferon-γ purge HBV replicative intermediates from the cytoplasm and covalently closed circular DNA from the nucleus of infected hepatocytes (108, 109). A TNF promoter polymorphism at position 238 is associated with the development of chronic HBV infection and linked to defective viral clearance (110).

Parvovirus. Parvovirus H-1 infection leads to the activation of caspase-3, which cleaves the enzyme poly(ADP-ribose) polymerase and induces morphologic changes that are characteristic of apoptosis in a way that is similar to TNF treatment. This effect is also observed when the U937 cells are infected with a recombinant H-1 virus that expresses the nonstructural proteins but in which the capsid genes are replaced by a reporter gene, indicating that the induction of apoptosis can be assigned to the cytotoxic nonstructural proteins in this system. The c-*Myc* protein, which is over-expressed in the monocytoid cell line U937, is rapidly downregulated during parvovirus infection, in keeping with a possible role of this product in mediating the apop-

totic cell death induced by H-1 virus infection. Interestingly several clones derived from U937 cell line and selected for their resistance to H-1 virus (111) fail to decrease c-*Myc* expression upon treatment with differentiation agents and also resist the induction of cell death after TNF treatment (112).

African swine fever virus (ASFV). ASFV induces TNF production both in culture *in vitro* and *in vivo*. TNF mRNA expression is observed in ASFV-infected alveolar macrophages, and high levels of TNF protein are detected by enzyme-linked immunosorbent assay (ELISA) in culture supernatants. When animals are experimentally infected with a virulent isolate (E-75), enhanced TNF expression in mainly affected organs correlates with viral protein expression. TNF-containing supernatants from ASFV-infected cultures induce apoptosis in uninfected lymphocytes. This effect is partially abrogated by preincubation with a neutralizing anti-TNF antibody (113).

RNA Viruses. See Table II for details on TNF, TNFR, and RNA viruses.

Human immunodeficiency virus (HIV). HIV infection is characterized by a progressive depletion of $CD4^+$ T cells resulting in cellular immunodeficiency (114). There are also increases in both cellular and soluble markers of immune activation corresponding to the magnitude and duration of viremia. Among cellular markers, CD38, HLA-DR, CD44, and TNF have been used to determine the state of activation of both T cells and macrophages (115). Markers of activation are also detected in body fluids and include neopterin, β2 microglobulin, soluble CD30, and soluble TNFR2. Thus, both TNF and TNFR are useful markers of immune activation during HIV infection, and their role in HIV pathogenesis has been investigated intensively.

TNF and TNFR modulate the viral life cycle in HIV-infected cells. TNF modulates the viral cycle of HIV-1 in both T cells and macrophages. TNF targets two main stages of the viral life cycle: viral entry and transcription. TNF has been shown to inhibit HIV-1 entry into macrophages, but not into peripheral blood lymphocytes (116). The inhibition of HIV-1 entry has been reported for the HIV-1 ADA strain, which is macrophage-tropic and uses CCR5 as a co-receptor (designated as R5 strain). TNF pre-treatment results in a delayed and reduced detection of HIV DNA long-terminal repeat (LTR) reverse transcripts in primary macrophages, a marker for early events of the viral life cycle that include viral entry. The step(s) of HIV-1 cycle inhibited by TNF is prior to reverse transcription, as shown by reduced detection of genomic viral RNA in the macrophages within 2 hr following infection (116). Thus, the step of the viral life cycle inhibited by TNF might be membrane fusion or viral uncoating. Both CD4 and the C-C chemokine CCR5 are, directly or indirectly, downregulated on the cell surface by TNF (117–119). The CCR5 downregulation on the macrophage surface and the subsequent inhibition of viral entry might also result from increased C-C chemokine production following TNF treatment (120). Another explanation is that TNF triggers the release of granulocyte-macrophage colony-stimulating factor (GM-CSF) that has been shown to downregulate CCR5 and subsequently block entry of R5 viruses into macrophages (121). Macrophages activated by TNF treatment might also display increased ability to degrade viral RNA especially within phagolysosomes. The inhibition of R5 HIV entry into primary macrophages by TNF involves the TNFR2 (116) as shown by the increased inhibition of HIV-1 entry following treatment with an agonistic TNF-mutated protein that recognizes specifically the TNFR2 but not the TNFR1 (116, 122). Interestingly, TNFR2 triggers GM-CSF secretion that has been shown to block R5 HIV-1 entry *via* CCR5 downregulation (121). TNF stimulates HIV-1 replication in chronically infected promonocytic U1 cell line through activation of NF-κB and subsequent transactivation of the proviral LTR (123–125). Stimulation with TNF of HIV-1 replication in U1 cell lines that contain two HIV proviral copies per cell is mediated *via* the TNFR1, but not the TNFR2 (126, 127). During opportunistic infections, a hallmark of progressive HIV-1 disease, tissue macrophages can increase their production of virus dramatically (128). Production of proinflammatory cytokines such as TNF might be involved in increased HIV production by macrophages. TNF binding to TNFR1 stimulates the viral transcription *via* NF-κB activation (123–125); meanwhile, TNFR2 activation by inhibiting viral entry might block HIV superinfection. During opportunistic infections, LPS might also be produced that, either directly or indirectly *via* TNF production, might block HIV entry into macrophages (129, 130). Therefore opportunistic infections during HIV disease might result in a controlled viral production within infected macrophages that could be critical to avoid macrophage death and to optimize viral production.

TNF and TNFR modulate T-cell death in uninfected T cells. HIV-1 infection is characterized by the progressive depletion of $CD4^+$ T cells, but also at a later stage of the disease of $CD8^+$ T cells (114, 131–134). Several hypotheses have been advanced to account for the loss of T cells. They include: (i) direct cell lysis by the virus infection (135, 136); (ii) syncytium formation (137–139); (iii) autoimmunity (140); (iv) cellular and humoral virus-specific immune responses (141); (v) superantigen-mediated depletion of specific T-cell subpopulation (142); and (vi) apoptosis or programmed cell death (143). The potential role of apoptosis in both $CD4^+$ and $CD8^+$ T cell depletion during HIV infection has been examined in several studies (144–146), and increased apoptosis of freshly isolated $CD4^+$ and $CD8^+$ T lymphocytes in cultures grown with blood isolated from HIV-positive individuals has been reported (147–150). Apoptosis occurs in both uninfected and infected T cells (133, 151). Due to the low number of infected T cells and the extent of T cell depletion in HIV-infected patients, most of the apoptosis is observed in uninfected bystander $CD4^+$ and $CD8^+$ T cells. $CD4^+$ T cell apoptosis is mediated usually by Fas/Fas ligand interaction although TNF/TNFR interaction has also been described (152, 153). The viral envelope gly-

Table II. TNF, TNFR, and RNA Viruses

Virus	Family	Effects	Mediated by	Reference
Human immunodeficiency virus	Retroviridae	1) TNF inhibits entry of R5 strains into macrophages	1) TNFR2	116, 123–127, 132, 133, 150, 152–154, 158
		2) TNF stimulates the HIV LTR	2) TNFR1	
		3) Depletes CD4 T cells *via* CD4 cross-linking	3) TNF/TNFR and Fas/FasL interaction	
		4) Depletes CD8 T cells *via* gp120/CXCR4 interaction	4) TNF/TNFR2 interaction	
Hepatitis C virus	Flaviviridae	1) Inhibits TNF-induced cell death in human breast carcinoma cells (MCF7)	1) HCV core protein blocks the TNF-induced proteolytic cleavage of the poly-(ADP-ribose) polymerase	159–162
		2) Chronically activates HCV-infected cells	2) HCV core protein stimulates NF-κB *via* elevated and prolonged retention of p50 and p65 and enhanced degradation of IκB	
		3) Enhances TNF-induced apoptosis (HepG2, HeLa)	3) HCV core protein interacts with the death domain of TNFR1 blocking the TNF-induced activation of RelA/NF-κB	
Influenza virus	Orthomyxoviridae	1) Stimulates TNF gene transcription and stabilizes TNF mRNA		170, 171, 177
		2) Activation of NF-κB binding and transactivation	2) Virion hemagglutinin	
Respiratory syncytial virus	Paramyxoviridae	Persistent NF-κB activation in airway epithelial cells	IκB proteolysis independent of the 26S proteosome pathway	184, 185
Measles virus	Paramyxoviridae	Control of experimental measles virus–induced encephalitis by virus-specific TH cells	TNF in synergy with IFNγ	187
Vesicular stomatitis virus	Rhabdoviridae	Blockade of VSV replication in fibroblasts	TNF in synergy with IFNγ	192
Dengue virus	Togaviridae	Immunopathological response mediated *via* $CD4^+$ CTL clones	Dengue virus capsid protein-specific CD4 CTL clones produce TNF and IFNγ	194
Ebola virus	Arenaviridae	High immune activation	High serum levels of TNF	195

coprotein gp120 cross-links CD4 on the surface of macrophages and $CD4^+$ T cells that results in upregulation of Fas ligand and Fas, respectively. Upregulated Fas ligand on the surface of macrophages interacts with upregulated Fas expressed on the surface of uninfected $CD4^+$ T cells resulting in enhanced $CD4^+$ T-cell apoptosis and depletion (150, 152–154). Depletion of $CD4^+$ T cells by activated macrophages in HIV infection has been reported to involve not only Fas/Fas ligand interaction, but also TNF/TNFR interaction (153). Antigen-induced apoptosis of $CD4^+$ T cells from HIV-infected individuals may be mediated by TNF although other members of the TNFR family known to induce apoptosis, such as the TNF-related apoptosis-inducing ligand (TRAIL), might also play a role (155, 156).

$CD8^+$ T-cell depletion in HIV-infected patients is mediated *via* apoptosis. In AIDS patients, the absolute number of $CD8^+$ T cells is decreased in peripheral blood, and their turnover rate is increased suggesting that there is more cell

death and cell renewal. $CD8^+$ T cell killing in HIV-infection is enhanced by macrophages both *in vitro* and *ex vivo* (132, 133, 157, 158). $CD8^+$ T-cell apoptosis increases proportionally to the number of macrophages present in the co-culture (132). Intercellular contacts between macrophages and $CD8^+$ T cells are required to induce $CD8^+$ T cell apoptosis after HIV infection. $CD8^+$ T-cell apoptosis is mediated by TNF/TNFR2, but not Fas/Fas ligand interaction, and can be blocked by neutralizing antibodies directed against TNF and TNFR2 (132). The TNF/TNFR2 interaction that triggers $CD8^+$ T cell killing by macrophages is a consequence of the immune activation observed in HIV-infected patients especially at the late stage of the disease. Immune activation results in upregulation of TNF on the surface of macrophages following gp120 treatment independently on the tropism of the viral strain (132). In contrast, immune activation of $CD8^+$ T cells by the envelope glycoprotein gp120 of X4 T-cell tropic viruses, usually observed late in the disease, and to a lesser extent of R5 macrophage-tropic viruses, results in TNF/TNFR2 interaction and subsequently $CD8^+$ T-cell killing by macrophages (132). *Ex vivo*, apoptosis of $CD8^+$ T cells isolated from HIV-infected patients is also mediated by macrophages through interaction between TNF and TNFR2 (132). Thus, immune activation, especially TNF/TNFR interaction, plays a critical role in the killing of $CD8^+$ T cells during HIV infection. Because $CD8^+$ T cells are thought to limit the spread of the infection either by their cytotoxic activity and/or the release of soluble factors, the depletion of $CD8^+$ T cells could contribute to the development of AIDS.

Hepatitis C virus. The role of hepatitis C virus (HCV) core protein with regard to apoptosis is controversial. HCV core protein has been shown to inhibit TNF-induced apoptotic cell death of human breast carcinoma cells (MCF7) as determined by cell viability and DNA fragmentation analysis (159). Additionally, HCV core protein blocks the TNF-induced proteolytic cleavage of the death substrate poly(ADP-ribose) polymerase from its native 116- kDa protein to the mature 85- kDa polypeptide. The ability of HCV core protein to inhibit TNF-mediated apoptotic signaling pathway may provide a selective advantage for HCV replication, allowing for evasion of host antiviral defense mechanisms. Recently, HCV core protein has been shown to inhibit TNF-mediated apoptosis *via* NF-κB activation (160, 161). The expression of HCV core protein prolongs or enhances the TNF-induced NF-κB DNA binding activity in HUH-7 and β cells. Stimulation of NF-κB activity by HCV core protein is due to elevated or prolonged nuclear retention of p50 or p65 species of NF-κB in core protein-producing cells. Furthermore, the HCV core protein enhanced or prolonged I-κBβ degradation triggered by TNF. Thus the HCV core protein potentiates NF-κB activation that in turn may contribute to the chronically activated, persistent state of HCV-infected cells.

In contrast, HCV core protein has also been reported to bind to the cytoplasmic domain of TNFR1 and enhances TNF-induced apoptosis (162). HCV core protein binds to amino acid residues 345–407 within the death domain of TNFR1. Stable transfection of the core protein in human cell lines HepG2 and HeLa cells sensitize them to TNF-induced apoptosis as determined by the TNF cytotoxicity or annexin V apoptosis assay. The TNF-mediated enhancement of apoptosis is not due to upregulation of TNFR1, but rather to interaction of the HCV core protein with the death domain of TNFR1 blocking the TNF-induced activation of RelA/NF-κB that delivers an antiapoptotic signal (162). The HCV core protein, by enhancing TNF-mediated apoptosis, may provide a selective advantage for HCV replication, allowing for evasion of host antiviral defense mechanisms. Differences reported in TNF-mediated cell death following HCV core protein expression might result from different cell types used and/or different protocol for TNF stimulation.

In patients with chronic HCV infection, both serum TNF and TNFR are upregulated (163, 164), which corresponds to enhanced hepatocellular expression of both TNF and TNFR as demonstrated by immunohistochemical staining (164). Increased levels of TNF and TNFR are enhanced in chronic HCV infection and reflect histologic activity of the disease. A TNF promoter polymorphism at position 238 is a host factor contributing to the development of chronic active hepatitis C (165).

Influenza virus. Among leukocytes, lymphocytes and especially monocytes/macrophages are highly susceptible to infection with influenza A virus (166–169). After infection of macrophages, *de novo* viral protein synthesis is initiated resulting in production of proinflammatory cytokines, especially TNF and C-C chemokines. TNF production by influenza-infected macrophages is regulated at both transcriptional and post-transcriptional stages (169–171). Influenza A virus stimulates TNF gene transcription and stabilizes TNF mRNA by delaying its degradation (170). Both LPS, which is associated with bacterial infections, and GM-CSF potentiate the production of TNF by influenza-infected macrophages (170, 172, 173). Following the synthesis of proinflammatory cytokines and C-C chemokines, the infected macrophages die by apoptosis within 24–36 hr (168). The release of TNF and C-C chemokines may result in the recruitment of mononuclear leukocytes in the context of proinflammatory reaction that may condition the infected host for subsequent virus-antigen-specific defense. The release of TNF by influenza-infected macrophages and by influenza-primed cytotoxic T lymphocytes (CTL) (174, 175) results in an antiviral effect mediated usually by both TNF and interferon-γ (175, 176). *In vitro*, influenza virus nucleoprotein peptide, SDYEGRLI, associated with the plate-bound class I molecule, and the resulting MHC-peptide complex have been shown to trigger TNF release by influenza-primed CTL (174). The release of TNF also induces systemic effects such as fever. At the molecular level, the expression of the virion surface hemagglutinin activates NF-κB DNA binding and transactivation (177).

Respiratory syncytial virus (RSV). Human alveolar macrophages are susceptible to infection with RSV, although the infection is abortive after the initial cycles of virus replication (178, 179). RSV infection of alveolar macrophages, but also of human respiratory epithelial cells, results in the production of proinflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-8 (178, 180–182), but also of the TH2 cytokine IL-10 (183). IL-10 produced by RSV-infected cells suppresses the production of early proinflammatory cytokines (183) and might account for the ineffective immune response to the virus.

RSV infection of airway epithelial cells results in persistent NF-κB activation. In airway epithelial cells, TNF-induced NF-κB activation is transient. Neither increased I-κBα production that occurs as a result of RSV-induced NF-κB activation nor inhibition of proteosome-mediated I-κBα degradation results in a reversal of RSV-induced NF-κB activation. Thus, whereas manipulation of I-κBα results in reversal of TNF-induced NF-κB activation, manipulation of I-κBα does not result in a reversal of RSV-induced NF-κB activation (184). Although TNF-induced NF-κB activation results in an I-κBα production due to the RelA/I-κBα positive feedback loop, following RSV infection there is no reaccumulation of I-κBα protein (185). This indicates that, following RSV infection, the RelA/I-κBα positive feedback loop is insufficient to restore control I-κBα levels. Although I-κB proteolysis induced by TNF-α occurs through the 26S proteosome, RSV infection produces I-κBα proteolysis through a mechanism independent of the proteosome pathway (185).

Recently a structural homology of the central conserved region of the attachment protein G of RSV with the fourth subdomain of TNFR1 has been described (186). Although the functions for both protein domains are not known, the structural similarity of both protein domains suggests a similar function. This homology suggests that the cysteine noose of RSV-G may interfere with the antiviral and apoptotic effect mediated by TNF-α.

Measles virus. Measles virus infection of the central nervous system in the murine model of experimental measles virus–induced encephalitis is successfully controlled by virus-specific T-helper lymphocytes. T cells from BALB/c mice that are resistant to measles virus encephalitis proliferate well against measles virus *in vitro*, and bulk cultures recognize viral nucleocapsid and hemagglutinin as well as fusion proteins. The measles virus-specific T cells secrete large amounts of IL-2, interferon-γ, and TNF. In contrast, cells obtained from measles virus–infected susceptible C3H mice recognize measles virus proteins only weakly and secrete little TNF and IFN-γ. These results suggest that interferon-γ and TNF play a significant role in the control of measles virus infection of the central nervous system (187).

Measles virus upregulates HLA-class I expression on the surface of glial cells but not on neurons (188, 189). The enhancement of HLA-class I on glial cells depends on the infectious virus, since antibody-neutralized measles virus has no effect on class-I expression (189). Among cytokines known to enhance HLA-class I expression, such as TNFα, IFN-γ, IFN-α, and IFNβ, IFNβ is the primary mediator of enhanced MHC class I expression in measles virus-infected glial cells, whereas TNFα, IFNα, and IFNγ are barely detected in culture supernatants (189). In contrast to glial cells, adult neurons normally lack the expression of MHC class I molecules, which has implications on virus clearance from the central nervous system. Measles virus infection of neuronal cell lines (IMR-32 and CHP-126) fails to upregulate HLA-class I expression, which is associated with an inability of measles virus to induce IFNβ in these cells (190). Induction of IFNβ gene expression by the measles virus requires binding of NF-κB to the positive regulatory domain-II element of the IFNβ promoter. Both measles virus and TNFα induce NF-κB binding to positive regulatory domain II in the glioma cell lines. In contrast, such activity was induced by TNFα but not by measles virus in neuronal cell lines (190). This indicates that HLA-class I expression is differentially regulated in glial and neuronal cell lines in response to the measles virus, which correlates with differential binding of NF-κB for the IFNβ promoter and induction of IFNβ gene expression. The absence of induction of HLA-class I or IFNβ in measles virus-infected neuronal cells is associated with the failure to activate NF-κB in these cells. This results from the inability of the measles virus to induce the phosphorylation and degradation of I-kB, the inhibitor of NF-κB (191). Thus the ability of the measles virus to persist in neurons and to escape immunosurveillance might result from the absence of MHC class I upregulation due to both the absence of TNF-α secretion following infection and the failure of the virus to activate NF-κB.

Vesicular stomatitis virus (VSV). The synergistic antiviral action of both TNF and interferon-γ was described several years ago to block the replication of VSV in fibroblasts (192). TNF inhibits the multiplication of VSV in Hela cells. Comparison of the kinetics of virus multiplication and that of virus-induced apoptosis in the TNF-treated cells revealed that the antiviral effect of TNF is accompanied by a rapid induction of apoptosis in the cells upon infection. This suggests that TNF can inhibit virus multiplication by accelerating an apoptotic response in the infected cells (193).

Dengue virus. Dengue hemorrhagic fever, the severe form of dengue virus infection, is believed to be an immunopathological response to a secondary infection with a heterologous serotype of dengue virus. Dengue virus capsid protein-specific $CD4^+$ cytotoxic T lymphocyte (CTL) clones produce TNF, interferon-γ, and TNFβ in response to stimulation with D2 antigen. Thus, $CD4^+$ CTL clones may contribute to the immunopathology observed upon secondary dengue virus infections through direct cytolysis and/or cytokine production (194).

Ebola virus infection. Markedly elevated serum levels of TNF, interferon-α, and IL-2 are observed in fatal cases of Ebola hemorrhagic fever (EHF). Similarly, mRNA

quantitation from blood clots of the same patients shows relatively elevated levels of TNFα and IFN-α. This suggests that a high degree of immune activation accompanies and potentially contributes to a fatal outcome in EHF patients (195). In EHF, TNF might be produced by macrophages, endothelial cells, and fibroblasts that all have been involved in the replication of Ebola virus (196).

Conclusion

TNF and TNFR are major components of the immune system involved in the control of viral infection *via* direct antiviral activity usually in association with interferon-γ and induction of apoptosis in infected cells. Nevertheless, several viruses commandeer the immune defense by interacting directly with the TNF/TNFR pathway to favor the proliferation of infected cells (EBV), by producing viral decoy proteins that will bind to TNF to diminish its antiviral effect (poxviruses), or by triggering the killing of either infected cells to select for malignant cells (HBV, HCV) or uninfected bystander T cells to exhaust the immune system (HIV). Thus, the TNF/TNFR pathway, which is a critical component of the immune system, by dealing with cell death and survival is also a main target for viruses that subvert this system to escape the immune surveillance and propagate in the organism.

1. Beutler B, Greenwald D, Hulmes JD, Chang M, Pan YCE, Mathison J, Ulevitch R, Cerami A. Identity of tumor necrosis factor and the macrophage-secreted factor cachectin. Nature **316**:552–554, 1985.
2. Beutler B, Cerami A. Cachectin and tumour necrosis factor as two sides of the same biological coin. Nature **320**:584–588, 1986.
3. Cerami A, Beutler B. The role of cachectin/TNF in endotoxic shock and cachexia. Immunol Today **9**:28–31, 1988.
4. Beutler B, Van Huffel C. Unraveling function in the TNF ligand and receptor families. Science **264**:667–668, 1994.
5. Bazzoni F, Beutler B. How do tumor necrosis factor receptors work? J Inflamm **45**:221–238, 1995.
6. Hodge-Dufour J, Marino MW, Horton MR, Jungbluth A, Burdick MD, Strieter RM, Noble PW, Hunter CA, Pure A. Inhibition of interferon-γ–induced interleukin 12 production: A potential mechanism for the anti-inflammatory activities of tumor necrosis factor. Proc Natl Acad Sci U S A **95**:13806–13811, 1998.
7. Cope AP, Liblau RS, Yang XD, Congia M, Laudanna C, Schreiber RD, Probert L, Kollias G, McDevitt HO. Chronic tumor necrosis factor alters T-cell responses by attenuating T-cell receptor signaling. J Exp Med **185**:1573–1584, 1997.
8. Hohmann HP, Remy R, Brockhaus M, van Loon AP. Two different cell types have different major receptors for human tumor necrosis factor (TNF-α). J Biol Chem **264**:14927–14934, 1989.
9. Brockhaus M, Schoenfeld HJ, Schlaeger EJ, Hunziker W, Lesslauer W, Loetscher H. Identification of two types of tumor necrosis factor receptors on human cell lines by monoclonal antibodies. Proc Natl Acad Sci U S A **87**:3127–3131, 1990.
10. Porteu F, Brockhaus M, Wallach D, Engelmann H, Nathan CF. Human neutrophil elastase releases a ligand-binding fragment from the 75-kDa tumor necrosis factor (TNF) receptor: Comparison with the proteolytic activity responsible for shedding of TNF receptors from stimulated neutrophils. J Biol Chem **266**:18846–18853, 1991.
11. Grell M, Wajant H, Zimmermann G, Scheurich P. The type 1 receptor (CD120a) is the high-affinity receptor for soluble tumor necrosis factor. Proc Natl Acad Sci U S A **95**:570–575, 1998.
12. Grell M, Douni E, Wajant H, Lohden M, Clauss M, Maxeiner B, Georgopoulos S, Lesslauer W, Kollias G, Pfizenmaier K, Scheurich P. The transmembrane form of tumor necrosis factor is the prime activating ligand of the 80-kDa tumor necrosis factor receptor. Cell **83**:793–802, 1995.
13. Tartaglia LA, Pennica D, Goeddel DV. Ligand passing: The 75-kDa tumor necrosis factor (TNF) receptor recruits TNF for signaling by the 55-kDa TNF receptor. J Biol Chem **268**:18542–18548, 1993.
14. Grell M, Becke FM, Wajant H, Mannel DN, Scheurich P. TNF receptor type 2 mediates thymocyte proliferation independently of TNF receptor type 1. Eur J Immunol **28**:257–263, 1998.
15. Haridas V, Darnay BG, Natarajan K, Heller R, Aggarwal BB. Overexpression of the p80 TNF receptor leads to TNF-dependent apoptosis, nuclear factor-κB activation, and c-*Jun* kinase activation. J Immunol **160**:3152–3162, 1998.
16. Espevik T, Brockhaus M, Loetscher H, Nonstad U, Shalaby R. Characterization of binding and biological effects of monoclonal antibodies against human tumor necrosis factor receptor. J Exp Med **171**:415–426, 1990.
17. Wiegmann K, Schutze S, Kampen E, Himmler A, Machleidt T, Kronke M. Human 55-kDa receptor for tumor necrosis factor coupled to signal transduction cascades. J Biol Chem **267**:17997–18001, 1992.
18. Weiss T, Grell M, Siemienski K, Muhlenbeck F, Durkop H, Pfizenmaier K, Scheurich P, Wajant H. TNFR80-dependent enhancement of TNFR60-induced cell death is mediated by TNFR-associated factor 2 and is specific for TNFR60. J Immunol **161**:3136–3142, 1998.
19. Gehr G, Gentz R, Brockhaus M, Loetscher H, Lesslauer W. Both tumor necrosis factor receptors mediate proliferative signals in human mononuclear cell activation. J Immunol **149**:911–917, 1992.
20. Vandenabeele P, Declercq W, Van Vercammen D, de Craen M, Grooten J, Loetscher H, Brockhaus M, Lesslauer W, Fiers W. Functional characterization of the human tumor necrosis factor receptor p75 in a transfected rat/mouse T-cell hybridoma. J Exp Med **176**:1015–1024, 1992.
21. Jacobsen FW, Rothe M, Rusten L, Goeddel DV, Smeland EB, Veiby OP, Slordali L, Jacobsen SEW. Role of the 75-kDa tumor necrosis factor (TNF) receptor: Inhibition of early hematopoiesis. Proc Natl Acad Sci U S A **91**:10695–10699, 1994.
22. Zheng L, Fisher G, Miller RE, Peschon J, Lynch DH, Lenardo MJ. Induction of apoptosis in mature T cells by tumour necrosis factor. Nature **377**:348–351, 1995.
23. Boise LH, Gonzalez-Garcia M, Postema CE, Ding L, Lindsten T, Turka LA, Mao X, Nunez G, Thompson CB. *Bcl*-x, a *bcl*-2-related gene that functions as a dominant regulator of apoptotic cell death. Cell **74**:597–608, 1993.
24. Lin RH, Hwang YW, Yang BC, Lin CS. TNF receptor 2-triggered apoptosis is associated with the downregulation of *Bcl*-xL on activated T cells and can be prevented by CD28 costimulation. J Immunol **158**:598–603, 1997.
25. Nophar Y, Kemper O, Brakebusch C, Englemann H, Zwang R, Aderka D, Holtmann H, Wallach D. Soluble forms of tumor necrosis factor receptors (TNF-Rs). The cDNA for the type I TNF-R, cloned using amino acid sequence data of its soluble form, encodes both the cell surface and a soluble form of the receptor. EMBO J **9**:3269–3278, 1990.
26. Seckinger P, Isaaz S, Dayer JM. Purification and biologic characterization of a specific tumor necrosis factor–α inhibitor. J Biol Chem **264**:11966–11973, 1989.
27. Engelmann H, Holtmann H, Brakebusch C, Avni YS, Sarov I, Nophar Y, Hadas E, Leitner O, Wallach D. Antibodies to a soluble form of a tumor necrosis factor (TNF) receptor have TNF-like activity. J Biol Chem **265**:14497–14504, 1990.
28. Mohler KM, Sleath PR, Fitzner JN, Cerretti DP, Alderson M, Kerwar SS, Torrance DS, Otten-Evans C, Greenstreet T, Weerawarna K. Protection against a lethal dose of endotoxin by an inhibitor of tumour necrosis factor processing. Nature **370**:218–220, 1994.
29. Aderka D, Engelmann H, Maor Y, Brakebusch C, Wallach D. Stabilization of the bioactivity of tumor necrosis factor by its soluble receptors. J Exp Med **175**:323–329, 1992.
30. Gatanaga T, Hwang CD, Gatanaga M, Cappuccini F, Yamamoto RS, Granger GA. The regulation of TNF receptor mRNA synthesis, membrane expression, and release by PMA- and LPS-stimulated human monocytic THP-1 cells *in vitro*. Cell Immunol **138**:1–10, 1991.
31. Leeuwenberg JF, Dentener MA, Buurman WA. Lipopolysaccharide (LPS)-mediated soluble TNF receptor release and TNF receptor expression by monocytes: Role of CD14, LPS binding protein, and

bactericidal/permeability-increasing protein. J Immunol **152**:5070–5076, 1994.
32. Kalinkovich A, Engelmann H, Harpaz N, Burstein R, Barak V, Kalickman I, Wallach D, Bentwich Z. Elevated serum levels of soluble tumour necrosis factor receptors (sTNFR) in patients with HIV infection. Clin Exp Immunol **89**:351–355, 1992.
33. Hober D, Benyoucef S, Delannoy AS, de Groote D, Ajana F, Mouton Y, Wattre P. High plasma level of soluble factor receptor type II (sTNFRII) in asymptomatic HIV-1-infected patients. Infection **24**:213–217, 1996.
34. Nokta M, Rossero R, Loesch K, Pollard RB. Kinetics of tumor necrosis factor–α and soluble TNFRII in HIV-infected patients treated with a triple combination of stavudine, didnosine, and hydroxyurea. AIDS Res Hum Retroviruses **13**:1633–1638, 1997.
35. Aderka D, Wysenbeek A, Engelmann H, Cope AP, Brennan F, Molad Y, Hornik V, Levo Y, Maini RN, Feldmann M. Correlation between serum levels of soluble tumor necrosis factor receptor and disease activity in systemic lupus erythematosus. Arthritis Rheum **36**:1111–1120, 1993.
36. Chikanza IC, Roux-Lombard P, Dayer JM, Panayi GS. Tumour necrosis factor soluble receptors behave as acute phase reactants following surgery in patients with rheumatoid arthritis, chronic osteomyelitis, and osteoarthritis. Clin Exp Immunol **92**:19–22, 1993.
37. Lazdins JK, Grell M, Walker MR, Woods-Cook K, Scheurich P, Pfizenmaier K. Membrane tumor necrosis factor (TNF)– induced cooperative signaling of TNFR60 and TNFR80 favors induction of cell death rather than virus production in HIV-infected T cells. J Exp Med **185**:81–90, 1997.
38. Tartaglia LA, Weber RF, Figari IS, Reynolds C, Palladino MAJ, Goeddel DV. The two different receptors for tumor necrosis factor mediate distinct cellular responses. Proc Natl Acad Sci U S A **88**:9292–9296, 1991.
39. Beg AA, Baltimore D. An essential role for NF-κB in preventing TNF-α–induced cell death. Science **274**:782–784, 1996.
40. Wang CY, Mayo MW, Baldwin AS Jr. TNF- and cancer therapy–induced apoptosis: Potentiation by inhibition of NF-κB. Science **274**:784–787, 1996.
41. Van Antwerp DJ, Martin SJ, Kafri T, Green DR, Verma IM. Suppression of TNF-α–induced apoptosis by NF-κB. Science **274**:787–789, 1996.
42. Roulston A, Reinhard C, Amiri P, Williams LT. Early activation of c-*Jun* N-terminal kinase and p38 kinase regulate cell survival in response to tumor necrosis factor–α. J Biol Chem **273**:10232–10239, 1998.
43. Gruss HJ, Dower SK. The TNF ligand superfamily and its relevance for human diseases. Cytokines Mol Ther **1**:75–105, 1995.
44. Hsu H, Xiong J, Goeddel DV. The TNF receptor 1-associated protein TRADD signals cell death and NF-κB activation. Cell **81**:495–504, 1995.
45. Rothe M, Pan MG, Henzel WJ, Ayres TM, Goeddel DV. The TNFR2-TRAF signaling complex contains two novel proteins related to baculoviral inhibitor of apoptosis proteins. Cell **83**:1243–1252, 1995.
46. Hsu H, Shu HB, Pan MG, Goeddel DV. TRADD-TRAF2 and TRADD–FADD interactions define two distinct TNF receptor 1 signal transduction pathways. Cell **84**:299–308, 1996.
47. Ting AT, Pimentel-Muinos FX, Seed B. RIP mediates tumor necrosis factor receptor 1 activation of NF-κB but not Fas/APO-1-initiated apoptosis. EMBO J **15**:6189–6196, 1996.
48. Chinnaiyan AM, Tepper CG, Seldin MF, O'Rourke K, Kischkel FC, Hellbardt S, Krammer PH, Peter ME, Dixit VM. FADD/MORT1 is a common mediator of CD95 (Fas/APO-1) and tumor necrosis factor receptor–induced apoptosis. J Biol Chem **271**:4961–4965, 1996.
49. Varfolomeev E, Boldin M, Goncharov T, Wallach D. A potential mechanism of "cross-talk" between the p55 tumor necrosis factor receptor and Fas/APO1: Proteins binding to the death domains of the two receptors also bind to each other. J Exp Med **183**:1271–1275, 1996.
50. Malinin NL, Boldin MP, Kovalenko AV, Wallach D. MAP3K-related kinase involved in NF-κB induction by TNF, CD95, and IL-1. Nature **385**:540–544, 1997.
51. Regnier CH, Songt HY, Gao X, Goeddel DV, Cao Z, Rothe M. Identification and characterization of an I-κB kinase. Cell **90**:373–383, 1997.
52. DiDonato JA, Hayakawa M, Rothwharf DM, Zandi E, Karin M. A cytokine-responsive I-κB kinase that activates the transcription factor NF-κB. Nature **388**:548–554, 1997.
53. Mercurio F, Zhu H, Murray BW, Shevchenko A, Bennett BL, Li J, Young DB, Barbosa M, Mann M, Manning A, Rao A. IKK-1 and IKK-2: Cytokine-activated I-κB kinases essential for NF-κB activation. Science **278**:860–866, 1997.
54. Zandi E, Rothwarf DM, Delhare M, Hayakawa M, Karin M. The I-κB kinase (IKK) contains two kinase subunits, IKKα and IKKβ, necessary for I-κB phosphorylation and NF-κB activation. Cell **91**:243–252, 1997.
55. Woronicz JD, Gao X, Cao Z, Rothe M, Goeddel DV. I-κB kinase-β: NF-κB activation and complex formation with I-κB kinase-α and NIK. Science **278**:866–869, 1997.
56. Liu ZG, Hsu H, Goeddel D, Karin M. Dissection of TNF-receptor 1 effector functions: JNK activation is not linked to apoptosis while NF-κB activation prevents cell death. Cell **87**:565–576, 1996.
57. Natoli G, Costanzo A, Ianni A, Templeton DJ, Woodgett JR, Balsano C, Levrero M. Activation of SAPK/JNK by TNF receptor 1 through a noncytotoxic TRAF-2-dependent pathway. Science **275**:200–203, 1997.
58. Song H, Regnier C, Kirschning C, Goeddel D, Rothe M. Tumor necrosis factor (TNF)–mediated kinase cascades: Bifucation of nuclear factor-κB and c-*jun* N-terminal kinase (JNK/SAPK) pathways at TNF receptor–associated factor 2. Proc Natl Acad Sci U S A **94**:9792–9796, 1997.
59. Yeh WC, Shahinian A, Speiser D, Kraunus J, Billia F, Wakeham A, de la Pompa JL, Ferrick D, Hum B, Iscove N, Ohashi P, Rothe M, Goeddel DV, Mak TW. Early lethality, functional NF-κB activation, and increased sensitivity to TNF-induced cell death in TRAF2-deficient mice. Immunity **7**:715–725, 1997.
60. Lee SY, Reichlin A, Santana A, Sokol KA, Nussenzweig MC, Choi Y. TRAF2 is essential for JNK but not NF-κB activation and regulates lymphocyte proliferation and survival. Immunity **7**:703–713, 1997.
61. Kelliher MA, Grimm S, Ishida Y, Kuo F, Stanger BZ, Leder P. The death domain kinase RIP mediates the TNF-induced NF-κB signal. Immunity **8**:297–303, 1998.
62. Shu HB, Takeuchi M, Goeddel DV. The tumor necrosis factor receptor 2 signal transducers TRAF2 and c-IAP1 are components of the tumor necrosis factor receptor 1 signaling complex. Proc Natl Acad Sci U S A **93**:13973–13978, 1996.
63. Yeh WC, Pompa JL, McCurrach ME, Shu HB, Elia AJ, Shahinian A, Ng M, Wakeham A, Khoo W, Mitchell K, El-Deiry WS, Lowe SW, Goeddel DV, Mak TW. FADD: Essential for embryo development and signaling from some, but not all, inducers of apoptosis. Science **279**:1954–1958, 1998.
64. Duan H, Dixit VM. RAIDD is a new "death" adapter molecule. Nature **385**:86–89, 1997.
65. Jiang Y, Woronicz JD, Liu W, Goeddel DV. Prevention of constitutive TNF receptor 1 signaling by silencer of death domains. Science **283**:543–546, 1999.
66. Sing A, Ni J, Aggarwal BB. Death domain receptors and their role in cell demise. J Interferon Cytokine Res **18**:439–450, 1998.
67. Salvesen GS, Dixit VM. Caspases: Intracellular signaling by proteolysis. Cell **91**:443–446, 1997.
68. Slee EA, Harte MT, Kluck RM, Wolf BB, Casiano CA, Newmeyer DD, Wang HG, Reed JC, Nicholson DW, Alnemri ES, Green DR, Martin SJ. Ordering the cytochrome-c–initiated caspase cascade: Hierarchical activation of caspases-2, -3, -6, -7, -8, and -10 in a caspase-9–dependent manner. J Cell Biol **144**:281–292, 1999.
69. Green DR, Reed JC. Mitochondria and apoptosis. Science **281**:1309–1312, 1998.
70. Thornberry NA, Lazebnik Y. Caspases: Enemies within. Science **281**:1312–1316, 1998.
71. Prendergast GC. Mechanisms of apoptosis by c-*Myc*. Oncogene **18**:2967–2987, 1999.
72. Schreiber M, Rajarathnam K, McFadden G. Myxoma virus T2 protein, a tumor necrosis factor (TNF) receptor homolog, is secreted as a monomer and dimer that each bind rabbit TNF-α, but the dimer is a more potent TNF inhibitor. J Biol Chem **271**:13333–13341, 1996.
73. Schreiber M, Sedger L, McFadden G. Distinct domains of M-T2, the myxoma virus tumor necrosis factor (TNF) receptor homolog, me-

diate extracellular TNF binding and intracellular apoptosis inhibition. J Virol **71**:2171–2181, 1997.
74. Zhou Q, Snipas S, Orth K, Muzio M, Dixit VM, Salvesen GS. Target protease specificity of the viral serpin CrmA: Analysis of five caspases. J Biol Chem **272**:7797–7800, 1997.
75. Kettle S, Alcami A, Khanna A, Ehret R, Jassoy C, Smith GL. Vaccinia virus serpin B13R (SPI-2) inhibits interleukin-1β–converting enzyme and protects virus-infected cells from TNF- and Fas-mediated apoptosis, but does not prevent IL-1β–induced fever. J Gen Virol **78**:677–685, 1997.
76. Paulose M, Bennett BL, Manning AM, Essani K. Selective inhibition of TNF-α induced cell adhesion molecule gene expression by tanapox virus. Microb Pathog **25**:33–41, 1998.
77. Izumi KM, Kaye KM, Kieff ED. The Epstein-Barr virus LMP1 amino acid sequence that engages tumor necrosis factor receptor associated factors is critical for primary B lymphocyte growth transformation. Proc Natl Acad Sci U S A **94**:1447–1452, 1997.
78. Sylla BS, Hung SC, Davidson DM, Hatzivassiliou E, Malinin NL, Wallach D, Gilmore TD, Kieff E, Mosialos G. Epstein-Barr virus-transforming protein latent infection membrane protein 1 activates transcription factor NF-κB through a pathway that includes the NF-κB–inducing kinase and the I-κB kinases IKK-α and IKK-β. Proc Natl Acad Sci U S A **95**:10106–10111, 1998.
79. Devergne O, McFarland EC, Mosialos G, Izumi KM, Ware CF, Kieff E. Role of the TRAF binding site and NF-κB activation in Epstein-Barr virus latent membrane protein 1-induced cell gene expression. J Virol **72**:7900–7908, 1998.
80. Mosialos G, Birkenbach M, Yalamanchili R, VanArsdale T, Ware C, Kieff E. The Epstein-Barr virus transforming protein LMP1 engages signaling proteins for the tumor necrosis factor receptor family. Cell **80**:389–399, 1995.
81. Sandberg M, Hammerschmidt W, Sugden B. Characterization of LMP-1's association with TRAF1, TRAF2, and TRAF3. J Virol **71**:4649–4656, 1997.
82. Kaye KM, Devergne O, Harada JN, Izumi KM, Yalamanchili R, Kieff E, Mosialos G. Tumor necrosis factor receptor associated factor 2 is a mediator of NF-κB activation by latent infection membrane protein 1, the Epstein-Barr virus transforming protein. Proc Natl Acad Sci U S A **93**:11085–11090, 1996.
83. Kilger E, Kieser A, Baumann M, Hammerschmidt W. Epstein-Barr virus-mediated B-cell proliferation is dependent upon latent membrane protein 1, which simulates an activated CD40 receptor. EMBO J **17**:1700–1709, 1998.
84. Liebowitz D. Epstein-Barr virus and a cellular signaling pathway in lymphomas from immunosuppressed patients. N Engl J Med **338**:1413–1421, 1998.
85. Kawanishi M. Epstein-Barr virus BHRF1 protein protects intestine 407 epithelial cells from apoptosis induced by tumor necrosis factor–α and anti-Fas antibody. J Virol **71**:3319–3322, 1997.
86. Lay JD, Tsao CJ, Chen JY, Kadin ME, Su IJ. Upregulation of tumor necrosis factor-α gene by Epstein-Barr virus-infected T cells in the pathogenesis of hemophagocytic syndrome. J Clin Invest **100**:1969–1979, 1997.
87. Rossol-Voth R, Rossol S, Schutt KH, Corridori S, de Cian W, Falke D. *In vivo* protective effect of tumour necrosis factor–α against experimental infection with herpes simplex virus type 1. J Gen Virol **72**:143–147, 1991.
88. Delero GC, Marcatili A, Folgore A, Donnarumma G, Petrillo G. TNF-α expression and herpes simplex infection in human monocytes treated with growth hormone, prolactin, and insulin. Microbiologica **21**:213–220, 1998.
89. Galvan V, Brandimarti R, Roizman B. Herpes simplex virus 1 blocks caspase-3–independent and caspase-dependent pathways to cell death. J Virol **73**:3219–3226, 1999.
90. Montgomery RI, Warner MS, Lum BJ, Spear PG. Herpes simplex virus-1 entry into cells mediated by a novel member of the TNF/NGF receptor family. Cell **87**:427–436, 1996.
91. Whitbeck JC, Peng C, Lou H, Xu R, Willis SH, Ponce de Leon M, Peng T, Nicola AV, Montgomery RI, Warner MS, Soulika AM, Spruce LA, Moore WT, Lambris JD, Spear PG, Cohen GH, Eisenberg RJ. Glycoprotein D of herpes simplex virus (HSV) binds directly to HVEM, a member of the tumor necrosis factor receptor superfamily and a mediator of HSV entry. J Virol **71**:6083–6093, 1997.
92. Terry-Allison T, Montgomery RI, Whitbeck JC, Xu R, Cohen GH, Eisenberg RJ, Spear PG. HveA (herpesvirus entry mediator A), a co-receptor for herpes simplex virus entry, also participates in virus-induced cell fusion. J Virol **72**:5802–5810, 1998.
93. Marsters SA, Ayres TM, Skubatch M, Gray CL, Rothe M, Ashkenazi A. Herpesvirus entry mediator, a member of the tumor necrosis factor receptor (TNFR) family, interacts with members of the TNFR-associated factor family and activates the transcription factors NF-κB and AP-1. J Biol Chem **272**:14029–14032, 1997.
94. Mauri DN, Ebner R, Montgomery RI, Kochel KD, Cheung TC, Yu GL, Ruben S, Murphy M, Eisenberg RJ, Cohen GH, Spear PG, Ware CF. LIGHT, a new member of the TNF superfamily, and lymphotoxin-α are ligands for herpesvirus entry mediator. Immunity **8**:21–30, 1998.
95. Stein J, Volk HD, Liebenthal C, Kruger DH, Prosch S. Tumour necrosis factor–α stimulates the activity of the human cytomegalovirus major immediate early enhancer/promoter in immature monocytic cells. J Gen Virol **74**:2333–2338, 1993.
96. Geist LJ, Monick MM, Stinski MF, Hunninghake GW. The immediate early genes of human cytomegalovirus upregulate tumor necrosis factor-α gene expression. J Clin Invest **93**:474–478, 1994.
97. Smith PD, Saini SS, Raffeld M, Manischewitz JF, Wahl SM. Cytomegalovirus induction of tumor necrosis factor-α by human monocytes and mucosal macrophages. J Clin Invest **90**:1642–1648, 1992.
98. Davignon JL, Castanie P, Yorke JA, Gautier N, Clement D, Davrinche C. Anti-human cytomegalovirus activity of cytokines produced by $CD4^+$ T-cell clones specifically activated by IE1 peptides *in vitro*. J Virol **70**:2162–2169, 1996.
99. Lucin P, Jonjic S, Messerle M, Polic B, Hengel H, Koszinowski UH. Late phase inhibition of murine cytomegalovirus replication by synergistic action of interferon-γ and tumour necrosis factor. J Gen Virol **75**:101–110, 1994.
100. Yerkovich ST, Olver SD, Lenzo JC, Peacock CD, Price P. The roles of tumour necrosis factor–α, interleukin-1, and interleukin-12 in murine cytomegalovirus infection. Immunology **91**:45–52, 1997.
101. Pavic I, Polic B, Crnkovic I, Lucin P, Jonjic S, Koszinowski UH. Participation of endogenous tumour necrosis factor–α in host resistance to cytomegalovirus infection. J Gen Virol **74**:2215–2223, 1993.
102. Orange JS, Salazar-Mather TP, Opal SM, Biron CA. Mechanisms for virus-induced liver disease: Tumor necrosis factor–mediated pathology independent of natural killer and T cells during murine cytomegalovirus infection. J Virol **71**:9248–9258, 1997.
103. Lee H, Choi JK, Li MT, Kaye K, Kieff E, Jung JU. Role of cellular tumor necrosis factor receptor-associated factors in NF-κB activation and lymphocyte transformation by herpesvirus Saimiri STP. J Virol **73**:3913–3919, 1999.
104. Su F, Schneider RJ. Hepatitis B virus HBx protein sensitizes cells to apoptotic killing by tumor necrosis factor–α. Proc Natl Acad Sci U S A **94**:8744–8749, 1997.
105. Lara-Pezzi E, Mesilla AL, Majano PL, Redondo JM, Lopez-Cabrera M. The hepatitis B virus X protein activates nuclear factor of activated T cells (NF-AT) by a cyclosporin A-sensitive pathway. EMBO J **17**:7066–7077, 1998.
106. Fang JW, Shen WW, Meager A, Lau JY. Activation of the tumor necrosis factor–α system in the liver in chronic hepatitis B virus infection. Am J Gastroenterol **91**:748–753, 1996.
107. Guidotti LG, Borrow P, Hobbs MV, Matzke B, Gresser I, Oldstone MB, Chisari FV. Viral cross talk: Intracellular activation of the hepatitis B virus during an unrelated viral infection of the liver. Proc Natl Acad Sci U S A **93**:4589–4594, 1996.
108. Guidotti LG, Borrow P, Brown A, McClary H, Koch R, Chisari FV. Noncytopathic clearance of lymphocytic choriomeningitis virus from the hepatocyte. J Exp Med **189**:1555–1564, 1999.
109. Guidotti LG, Rochford R, Chung J, Shapiro M, Purcell R, Chisari FV. Viral clearance without destruction of infected cells during acute HBV infection. Science **284**:825–829, 1999.
110. Hohler T, Kruger A, Gerken G, Schneider PM, Meyer zum Buschenefelde KH, Rittner C. A tumor necrosis factor–α (TNF-α) promoter polymorphism is associated with chronic hepatitis B infection. Clin Exp Immunol **111**:579–582, 1998.
111. Lopez-Guerrero JA, Rayet B, Tuynder M, Rommelaere J, Dinsart C. Constitutive activation of U937 promonocytic cell clones selected for their resistance to parvovirus H-1 infection. Blood **89**:1642–1653, 1997.

112. Rayet B, Lopez-Guerrero JA, Rommelaere J, Dinsart C. Induction of programmed cell death by parvovirus H-1 in U937 cells: Connection with the tumor necrosis factor–α signaling pathway. J Virol **72**:8893–8903, 1998.
113. Gomez del Moral M, Ortuno E, Fernandez-Zapatero P, Alonso F, Alonso C, Ezquerre A, Dominguez J. African swine fever virus infection induces tumor necrosis factor–α production: Implications in pathogenesis. J Virol **73**:2173–2180, 1999.
114. Fauci AS. Multifactorial nature of human immunodeficiency virus disease: Implications for therapy. Science **262**:1011–1018, 1993.
115. Lahdevirta J, Maury CP, Teppo AM, Repo H. Elevated levels of circulating cachectin/tumor necrosis factor in patients with acquired immunodeficiency syndrome. Am J Med **85**:289–291, 1988.
116. Herbein G, Montaner LJ, Gordon S. Tumor necrosis factor–α inhibits entry of human immunodeficiency virus type 1 into primary human macrophages: A selective role for the 75-kDa receptor. J Virol **70**:7388–7397, 1996.
117. Karsten V, Gordon S, Kim A, Herbein G. HIV-1 envelope glycoprotein gp120 downregulates CD4 expression in primary human macrophages through induction of endogenous tumour necrosis factor–α. Immunology **88**:55–60, 1996.
118. Herbein G, Doyle AG, Montaner LJ, Gordon S. Lipopolysaccharide (LPS) downregulates CD4 expression in primary human macrophages through induction of endogenous tumor necrosis factor (TNF) and IL-1β. Clin Exp Immunol **102**:430–437, 1995.
119. Sallusto F, Lenig D, Mackay CR, Lanzavecchia A. Flexible programs of chemokine receptor expression on human polarized T helper 1 and 2 lymphocytes. J Exp Med **187**:875–883, 1998.
120. Schmidtmayerova H, Nottet HS, Nuovo G, Raabe T, Flanagan CR, Dubrovsky L, Gendelman HE, Cerami A, Bukrinsky M, Sherry B. Human immunodeficiency virus type 1 infection alters chemokine-β peptide expression in human monocytes: Implications for recruitment of leukocytes into brain and lymph nodes. Proc Natl Acad Sci U S A **93**:700–704, 1996.
121. DiMarzio P, Tse J, Landau NR. Chemokine receptor regulation and HIV type 1 tropism in monocyte-macrophages. AIDS Res Hum Retroviruses **14**:129–138, 1998.
122. Loetscher H, Stueber D, Banner D, Mackay F, Lesslauer W. Human tumor necrosis factor–α (TNF-α) mutants with exclusive specificity for the 55-kDa or 75-kDa TNF receptors. J Biol Chem **268**:26350–26357, 1993.
123. Duh EJ, Maury WJ, Folks TM, Fauci AS, Rabson AB. Tumor necrosis factor–α activates human immunodeficiency virus type 1 through induction of nuclear factor binding to the NF-κB sites in the long terminal repeat. Proc Natl Acad Sci U S A **86**:5974–5978, 1989.
124. Osborn L, Kunkel S, Nabel GJ. Tumor necrosis factor–α and interleukin 1 stimulate the human immunodeficiency virus enhancer by activation of the nuclear factor-κB. Proc Natl Acad Sci U S A **86**:2336–2340, 1989.
125. Poli G, Kinter A, Justement S, Kebrl JH, Bressler P, Stanley S, Fauci AS. Tumor necrosis factor–α functions in an autocrine manner in the induction of human immunodeficiency virus expression. Proc Natl Acad Sci U S A **87**:782–785, 1990.
126. Butera ST, Roberts BD, Leung K, Nabel GJ, Folks TM. Tumor necrosis factor receptor expression and signal transduction in HIV-1 infected cells. AIDS **7**:911–918, 1993.
127. Herbein G, Gordon S. 55- and 75-kDa tumor necrosis factor receptors mediate distinct actions in regard to human immunodeficiency virus type 1 replication in primary human macrophages. J Virol **71**:4150–4156, 1997.
128. Orenstein JM, Fox C, Wahl SM. Macrophages as a source of HIV during opportunistic infections. Science **276**:1857–1861, 1997.
129. Zybarth G, Reiling N, Schmidtmayerova H, Sherry B, Bukrinsky M. Activation-induced resistance of human macrophages to HIV-1 infection *in vitro*. J Immunol **162**:400–406, 1999.
130. Alfano M, Schmidtmayerova H, Bukrinsky M. Bacterial lipopolysaccharide is a potent inhibitor of HIV-1 replication in T lymphocytes and macrophages. AIDS **12**:1724–1726, 1998.
131. Margolick JB, Munoz A, Donnenberg AD, Park LP, Galai N, Giorgi JV, O'Gorman MR, Ferbas J. Failure of T-cell homeostasis preceding AIDS in HIV-1 infection: The Multiple AIDS Cohort Study. Nat Med **1**:674–680, 1995.
132. Herbein G, Mahlknecht U, Batliwalla F, Gregersen P, Pappas T, Butler J, O'Brien WA, Verdin E. Apoptosis of $CD8^+$ T cells is mediated by macrophages through interaction of HIV gp120 with chemokine receptor CXCR4. Nature **395**:189–194, 1998.
133. Herbein G, Van Lint C, Lovett JL, Verdin E. Distinct mechanisms trigger apoptosis in human immunodeficiency virus type 1-infected and in uninfected bystander T lymphocytes. J Virol **72**:660–670, 1998.
134. Yu XF, Wang Z, Vlahov D, Markham RB, Farzadegan H, Margolick JB. Infection with dual-tropic human immunodeficiency virus type 1 variants associated with rapid total T-cell decline and disease progression in injection drug users. J Infect Dis **178**:388–396, 1998.
135. Somasundaran M, Robinson HL. A major mechanism of human immunodeficiency virus-induced cell killing does not involve cell fusion. J Virol **61**:3114–3119, 1987.
136. Gandhi RT, Chen BK, Straus SE, Dale JK, Lenardo MJ, Baltimore D. HIV-1 directly kills $CD4^+$ T cells by a Fas-independent mechanism. J Exp Med **187**:1113–1122, 1998.
137. Lifson JD, Reyes GR, McGrath MS, Stein BS, Engleman EG. AIDS retrovirus induced cytopathology: Giant cell formation and involvement of CD4 antigen. Science **232**:1123–1127, 1986.
138. Sodroski J, Goh WC, Rosen C, Tartar A, Portetelle D, Burny A, Haseltine W. Replicative and cytopathic potential of HTLV-III/LAV with *sor* gene deletions. Science **231**:1549–1553, 1986.
139. Yoffe B, Lewis DE, Petrie BL, Noonan CA, Melnick JL, Hollinger FB. Fusion as a mediator of cytolysis in mixtures of uninfected $CD4^+$ lymphocytes and cells infected by human immunodeficiency virus. Proc Natl Acad Sci U S A **84**:1429–1433, 1987.
140. Golding H, Robey FA, Gates FT III, Linder W, Beining PR, Hoffman T, Golding B. Identification of homologous regions in human immunodeficiency virus 1 gp41 and human MHC class II β1 domain. I. Monoclonal antibodies against the gp41-derived peptide and patients' sera react with native HLA class II antigens, suggesting a role for autoimmunity in the pathogenesis of acquired immune deficiency syndrome. J Exp Med **167**:914–923, 1988.
141. Zinkernagel RM, Hengartner H. T-cell–mediated immunopathology versus direct cytolysis by virus: Implications for HIV and AIDS. Immunol Today **15**:262–268, 1994.
142. Imberti L, Sottini A, Bettinardi A, Puoti M, Primi D. Selective depletion in HIV infection of T cells that bear specific T-cell receptor Vβ sequences. Science **254**:860–862, 1991.
143. Ameisen JC, Capron A. Cell dysfunction and depletion in AIDS: The programmed cell death hypothesis. Immunol Today **12**:102–105, 1991.
144. Laurent-Crawford AG, Krust B, Muller S, Riviere Y, Rey-Cuille MA, Bechet JM, Montagnier L, Hovanessian AG. The cytopathic effect of HIV is associated with apoptosis. Virology **185**:829–839, 1991.
145. Martin SJ, Matear PM, Vyakarnam A. HIV-1 infection of human $CD4^+$ T cells *in vitro*: Differential induction of apoptosis in these cells. J Immunol **152**:330–342, 1994.
146. Terai C, Kornbluth RS, Pauza CD, Richman DD, Carson DA. Apoptosis as a mechanism of cell death in culture T lymphoblasts acutely infected with HIV-1. J Clin Invest **87**:1710–1715, 1991.
147. Gougeon ML, Garcia S, Heeney J, Tschopp R, Lecoeur H, Guetard D, Rame V, Dauguet C, Montagnier L. Programmed cell death in AIDS-related HIV and SIV infections. AIDS Res Hum Retroviruses **9**:553–563, 1993.
148. Groux H, Torpier G, Monte D, Mouton Y, Capron A, Ameisen JC. Activation-induced death by apoptosis in $CD4^+$ T cells from human immunodeficiency virus–infected asymptomatic individuals. J Exp Med **175**:331–340, 1992.
149. Lewis DE, Tang DS, Adu-Oppong A, Schober W, Rodgers JR. Anergy and apoptosis in $CD8^+$ T cells from HIV-infected persons. J Immunol **153**:412–420, 1994.
150. Oyaizu N, McCloskey TW, Coronesi M, Chirmule N, Kalyanaraman VS, Pahwa S. Accelerated apoptosis in peripheral blood mononuclear cells (PBMCs) from human immunodeficiency virus type 1-infected patients and in CD4 cross-linked PBMCs from normal individuals. Blood **82**:3392–3400, 1993.
151. Finkel TH, Tudor-Williams G, Banda NK, Cotton MF, Curiel T, Monks C, Baba TW, Ruprecht RM, Kupfer A. Apoptosis occurs predominantly in bystander cells and not in productively infected cells of HIV- and SIV-infected lymph nodes. Nat Med **1**:129–134, 1995.

152. Badley AD, McEhlinny JA, Leibson PJ, Lynch DH, Alderson MR, Paya CV. Upregulation of Fas ligand expression by human immunodeficiency virus in human macrophages mediates apoptosis of uninfected T lymphocytes. J Virol **70**:199–206, 1996.
153. Badley AD, Dockrell D, Simpson M, Schut R, Lynch DH, Leibson P, Paya CV. Macrophage-dependent apoptosis of $CD4^+$ T lymphocytes from HIV-infected individuals is mediated by FasL and tumor necrosis factor. J Exp Med **185**:55–64, 1997.
154. Oyaizu N, McCloskey TW, Than S, Hu R, Kalyanaraman VS, Pahwa S. Cross-linking of CD4 molecules upregulates Fas antigen expression in lymphocytes by inducing interferon-γ and tumor necrosis factor-α secretion. Blood **84**:2622–2631, 1994.
155. Wiley SR, Schooley K, Smolak PJ, Din WS, Huang CP, Nicholl JK, Sutherland GR, Smith TD, Rauch C, Smith CA, Goodwin RG. Identification and characterization of a new member of the TNF family that induces apoptosis. Immunity **3**:673–682, 1995.
156. Pitti RM, Marsters SA, Ruppert S, Donahue CJ, Moore A, Ashkenazi A. Induction of apoptosis by Apo-2 ligand, a new member of the tumor necrosis factor cytokine family. J Biol Chem **271**:12687–12690, 1996.
157. Lewis DE, Ng Tang DS, Wang X, Kozinetz C. Co-stimulatory pathways mediate monocyte-dependent lymphocyte apoptosis in HIV. Clin Immunol **90**:302–312, 1999.
158. Ameisen JC. Setting death in motion. Nature **395**:117–119, 1998.
159. Ray RB, Meyer K, Steele R, Shrivastava A, Aggarwal BB, Ray R. Inhibition of tumor necrosis factor (TNF-α)–mediated apoptosis by hepatitis C virus core protein. J Biol Chem **273**:2256–2259, 1998.
160. Marusawa H, Hijikata M, Chiba T, Shimotohno K. Hepatitis C virus core protein inhibits Fas- and tumor necrosis factor α-mediated apoptosis *via* NF-kB activation. J Virol **73**:4713–4720, 1999.
161. You LR, Chen CM, Lee YHW. Hepatitis C virus core protein enhances NF-κB signal pathway triggering by lymphotoxin-β receptor ligand and tumor necrosis factor–α. J Virol **73**:1672–1681, 1999.
162. Zhu N, Khoshnan A, Schneider R, Matsumoto M, Dennert G, Ware C, Lai MM. Hepatitis C virus core protein binds to the cytoplasmic domain of tumor necrosis factor (TNF) receptor 1 and enhances TNF-induced apoptosis. J Virol **72**:3691–3697, 1998.
163. Nelson DR, Lim HL, Marousis CG, Fang JW, Davis GL, Shen L, Urdea MS, Kolberg JA, Lau JY. Activation of tumor necrosis factor-α system in chronic hepatitis C virus infection. Digestive Dis Sci **42**:2487–2494, 1997.
164. Kallinowski B, Haseroth K, Marinos G, Hanck C, Stremmel W, Theilmann L, Singer MW, Rossol S. Induction of tumour necrosis factor (TNF) receptor type p55 and p75 in patients with chronic hepatitis C virus (HCV) infection. Clin Exp Immunol **111**:269–277, 1998.
165. Hohler T, Kruger A, Gerken G, Schneider PM, Meyer zum Buschenfelde KH, Rittner C. Tumor necrosis factor–α promoter polymorphism at position 238 is associated with chronic active hepatitis C infection. J Med Virol **54**:173–177, 1998.
166. Roberts NJ Jr., Nichols JE. Regulation of lymphocyte proliferation after influenza virus infection of human mononuclear leukocytes. J Med Virol **27**:179–187, 1989.
167. Mock DJ, Roberts NJ Jr. Role of the monocyte-macrophage in influenza virus infection of lymphocytes: Implication for HIV infection. AIDS Res Hum Retroviruses **6**:965–966, 1990.
168. Hofmann P, Sprenger H, Kaufmann A, Bender A, Hasse C, Nain M, Gemsa D. Susceptibility of mononuclear phagocytes to influenza A virus infection and possible role in the antiviral response. J Leukoc Biol **61**:408–414, 1997.
169. Sareneva T, Matikainen S, Kurimoto M, Julkunen I. Influenza A virus-induced IFN-α/β and IL-18 synergistically enhance IFN-γ gene expression in human T cells. J Immunol **160**:6032–6038, 1998.
170. Gong JH, Sprenger H, Hinder F, Bender A, Schmidt A, Horch S, Nain M, Gemsa D. Influenza A virus infection of macrophages: Enhanced tumor necrosis factor–α (TNF-α) gene expression and lipopolysaccharide-triggered TNF-α release. J Immunol **147**:3507–3513, 1991.
171. Lehmann C, Sprenger H, Nain M, Bacher M, Gemsa D. Infection of macrophages by influenza A virus: Characteristics of tumour necrosis factor–α (TNF-α) gene expression. Res Virol **147**:123–130, 1996.
172. Nain M, Hinder F, Gong JH, Schmidt A, Bender A, Sprenger H, Gemsa D. Tumor necrosis factor–α production of influenza A virus-infected macrophages and potentiating effect of lipopolysaccharide. J Immunol **145**:1921–1928, 1990.
173. Bender A, Amann U, Jager R, Nain M, Gemsa D. Effect of granulocyte/macrophage colony-stimulating factor on human monocytes infected with influenza A virus: Enhancement of virus replication, cytokine release, and cytotoxicity. J Immunol **151**:5416–5424, 1993.
174. Brown EL, Wooters JL, Ferenz CR, O'Brien CM, Hewick RM, Herrmann SH. Characterization of peptide binding to the murine MHC class I H-2Kk molecule: Sequencing of the bound peptides and direct binding of synthetic peptides to isolated class I molecules. J Immunol **153**:3079–3092, 1994.
175. Kuwano K, Kawashima T, Arai S. Antiviral effect of TNF-α and IFN-γ secreted from a $CD8^+$ influenza virus-specific CTL clone. Viral Immunol **6**:1–11, 1993.
176. Van Campen H. Influenza A virus replication is inhibited by tumor necrosis factor–α *in vitro*. Arch Virol **136**:439–446, 1994.
177. Pahl HL, Baeuerle PA. Expression of influenza virus hemagglutinin activates transcription factor NF-κB. J Virol **69**:1480–1484, 1995.
178. Becker S, Quay J, Soukup J. Cytokine (tumor necrosis factor, IL-6, and IL-8) production by respiratory syncytial virus-infected human alveolar macrophages. J Immunol **147**:4307–4312, 1991.
179. Cirino NM, Panuska JR, Villani A, Taraf H, Rebert NA, Merolla R, Tsivitse P, Gilbert IA. Restricted replication of respiratory syncytial virus in human alveolar macrophages. J Gen Virol **74**:1527–1537, 1993.
180. Arnold R, Konig B, Galatti H, Werchau H, Konig W. Cytokine (IL-8, IL-6, TNF-α) and soluble TNF receptor-1 release from human peripheral blood mononuclear cells after respiratory syncytial virus infection. Immunology **85**:364–372, 1995.
181. Patel JA, Jiang Z, Nakajima N, Kunimoto M. Autocrine regulation of interleukin-8 by interleukin-1α in respiratory syncytial virus-infected pulmonary epithelial cells *in vitro*. Immunology **95**:501–506, 1998.
182. Jiang Z, Kunimoto M, Patel JA. Autocrine regulation and experimental modulation of interleukin-6 expression by human pulmonary epithelial cells infected with respiratory syncytial virus. J Virol **72**:2496–2499, 1998.
183. Panuska JR, Merolla R, Rebert NA, Hoffmann SP, Tsivitse P, Cirino NM, Silverman RH, Rankin JA. Respiratory syncytial virus induces interleukin-10 by human alveolar macrophages: Suppression of early cytokine production and implications for incomplete immunity. J Clin Invest **96**:2445–2453, 1995.
184. Fiedler MA, Wernke-Dollries K. Incomplete regulation of NF-κB by I-κBα during respiratory syncytial virus infection in A549 cells. J Virol **73**:4502–4507, 1999.
185. Jamaluddin M, Casola A, Garofalo RP, Han Y, Elliott T, Ogra PL, Brasier AR. The major component of I-κBα proteolysis occurs independently of the proteosome pathway in respiratory syncytial virus–infected pulmonary epithelial cells. J Virol **72**:4849–4857, 1998.
186. Langedijk JP, de Groot BL, Berendsen HJ, van Oirschot JT. Structural homology of the central conserved region of the attachment protein G of respiratory syncytial virus with the fourth subdomain of 55-kDa tumor necrosis factor receptor. Virology **243**:293–302, 1998.
187. Finke D, Brinckmann UG, ter Meulen V, Liebert UG. γ-Interferon is a major mediator of antiviral defense in experimental measles virus–induced encephalitis. J Virol **69**:5469–5474, 1995.
188. Massa PT, Schimpl A, Wecker E, ter Meulen V. Tumor necrosis factor amplifies measles virus–mediated Ia induction on astrocytes. Proc Natl Acad Sci U S A **84**:7242–7245, 1987.
189. Dhib-Jalbut SS, Cowan EP. Direct evidence that interferon-β mediates enhanced HLA-class I expression in measles virus–infected cells. J Immunol **151**:6248–6258, 1993.
190. Dhib-Jalbut SS, Xia Q, Drew PD, Swoveland PT. Differential upregulation of HLA class I molecules on neuronal and glial cell lines by virus infection correlates with differential induction of IFN-β. J Immunol **155**:2096–2108, 1995.
191. Dhib-Jalbut S, Xia J, Rangaviggula H, Fang YY, Lee T. Failure of measles virus to activate nuclear factor-κB in neuronal cells: Implications on the immune response to viral infections in the central nervous system. J Immunol **162**:4024–4029, 1999.
192. Wong GHW, Goeddel DV. Tumour necrosis factor–α and β inhibit

virus replication and synergize with interferons. Nature **323**:819–822, 1986.
193. Koyama AH, Arakawa T, Adachi A. Acceleration of virus-induced apoptosis by tumor necrosis factor. FEBS Lett **426**:179–182, 1998.
194. Gagnon SJ, Ennis FA, Rothman AL. Bystander target cell lysis and cytokine production by dengue virus–specific human $CD4^+$ cytotoxic T lymphocyte clones. J Virol **73**:3623–3629, 1999.
195. Villinger F, Rollin PE, Brar SS, Chikkala NF, Winter J, Sundstrom JB, Zaki SR, Swanepoel R, Ansari AA, Peters CJ. Markedly elevated levels of interferon (IFN)-γ, IFN-α, interleukin (IL)-2, IL-10, and tumor necrosis factor–α associated with fatal Ebola virus infection. J Infect Dis **179**:S188–S191, 1999.
196. Ryabchikova E, Kolesnikova L, Smolina M, Tkachev V, Pereboeva L, Baranova S, Grazhdantseva A, Rassadkin Y. Ebola virus infection in guinea pigs: Presumable role of granulomatous inflammation in pathogenesis. Arch Virol **141**:909–921, 1996.