PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE **188,** 235–242 (1988)

MINIREVIEW

Abelson Virus: Current Status of a Viral Oncogene (42732)

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Since its isolation from an unusual mouse lymphoid tumor (1) the Abelson murine leukemia virus (A-MuLV) and the viral oncogene that it encodes, i.e., v-*abl,* have been used to investigate the mechanisms by which viral gene products bring about the oncogenic transformation of cells and interact with signal transduction pathways involved in hematopoietic cell growth control. The value of this model system for the study of human cancer has been established by the observation that the human homolog of the cellular gene from which the v-*abl* oncogene was derived is a partner in the Philadelphia chromosomal translocation found in chronic myelogenous leukemia (CML) (2). Alterations of human *abl*-related sequences presumably play a role in the development of this form of human cancer (2–6). This review emphasizes recent developments in the study of A-MuLV and what these discoveries indicate about the mechanism of cell transformation and tumorigenesis.

A-MuLV: A Brief Overview. *Structure of the viral genome.* The earliest studies of A-MuLV focused on the elucidation of the structure of the viral genome, the identification of the proteins encoded by the virus, and the determination of the biochemical and biological functions of those proteins. Like most other rapidly oncogenic retroviruses (7), A-MuLV is defective for its own replication and, therefore, is dependent on a helper virus to supply necessary replication functions (8). The recombination event that generated A-MuLV from the replication-competent Moloney MuLV resulted in the deletion of a portion of the *gag* gene, all of the *pol* gene, and most of the *env* gene and the insertion of a portion of the murine c-*abl* proto-oncogene (9–11). The A-MuLV viral genome contains from 5′ to 3′ a 68-base sequence R, a 75-base sequence U5, 477 bases of viral *cis*-acting sequences, 709 bases of *gag* structural gene sequences, 3879 bases of processed c-*abl* sequences, 211 bases of 3′ viral sequences, 449 bases of U3 sequences, the 68-base R region, and a poly(A) tail (Fig. 1) (12, 13).

The recombination event that generated A-MuLV from Mo-MuLV and c-*abl* fused *gag* coding sequences in-frame with c-*abl* protein coding sequences to generate a novel open reading frame encoding a 136.30-kDa protein, i.e., the v-*abl* oncogene product (14, 15). An additional open reading frame of 489 bases is present in the A-MuLV genome; however, no corresponding protein has ever been identified. The c-*abl*-derived sequences inserted into A-MuLV lack the two 5′-most exons of the proto-oncogene (114 codons), c-*abl* introns, and 765 bp of 3′ noncoding sequences (10, 16, 17). Interestingly, a recent feline sarcoma virus isolate encoding an activated *abl* viral oncogene also lacks the 5′-most c-*abl* exons (18, 19). Also, the novel c-*abl*-derived genes found in human CML, i.e., the *bcr–abl* fusion genes, lack 26 codons of 5′ c-*abl* sequences (20–22). The transforming activity of *bcr/abl* genes is less efficient than that of the v-*abl* oncogene. These results suggest that the 5′ deletions may play an important role in the oncogenic activation of c-*abl.* The nucleotide sequence of mouse c-*abl* cDNA also differs from that of v-*abl* in several positions, and these mutations in v-*abl* may also contribute to its transforming activity (17).

The v-abl oncogene product. The original isolate of A-MuLV most likely encoded a v-*abl* oncogene product of 160 kDa as identified on SDS–polyacrylamide gels, and cloned derivatives of that virus are in use in many laboratories. A common variant of the P160 strain of A-MuLV arose by deletion of a portion of the c-*abl*-derived sequences and encodes a 120-kDa protein (14, 15, 23). The

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0037-9727/88 $1.50

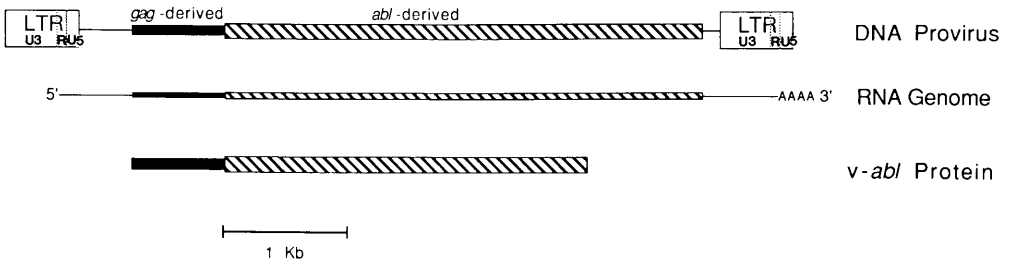

FIG. 1. The boxes labeled LTR (long terminal repeat) and the thin lines indicate Moloney MuLV-derived sequences. The thick black lines indicate Moloney *gag* structural-derived sequences. The hatched boxes indicate c-*abl*-derived sequences. The direction of transcription is indicated 5′ to 3′ and AAAA indicates the poly(A) tail. Drawing is to scale.

v-*abl* product is a tyrosine-specific kinase which phosphorylates both itself and several cellular proteins (24–26). Although several cellular substrates for v-*abl* kinase have been demonstrated none has yet been linked to crucial events in cell transformation (27, 28). The v-*abl* oncogene is classified as a member of the *src*-related family of viral oncogenes on the basis of its enzymatic activity and its nucleotide sequence similarity to these other retroviral oncogenes (7, 12, 29). Molecularly constructed and naturally occurring mutants of A-MuLV established that the kinase activity of the protein was necessary to establish transformation, and that this activity mapped to the amino half of the v-*abl* protein (12, 25, 30). The recent isolation of a variant of A-MuLV that is temperature-sensitive in its kinase activity has demonstrated that expression of the v-*abl* kinase is necessary to maintain transformation (31). A-MuLV grown in retroviral packaging lines and thus free of contaminating helper virus has been used to demonstrate that expression of v-*abl* is sufficient for cell transformation and tumor induction in susceptible animals (32). Thus the critical viral contribution to the biological responses induced by A-MuLV is the v-*abl* protein.

Pathogenesis in vivo. The predominant form of tumor induced by the virus is a nonthymic lymphoma that appears as a monoclonal or oligoclonal lymphoproliferative disease. The latent period is very short and disseminated tumors appear approximately 30 days after intraperitoneal or intravenous inoculation of susceptible mice with virus (1, 33, 34). The most susceptible mouse strain for tumor induction is BALB/c. Several mouse strains are resistant to tumor induction, and at least two mouse genes have been shown to control these patterns of resistance and susceptibility (35). Characterization of the primary tumor cells or lines derived from A-MuLV tumors using cell-surface markers indicates that the tumor cells are pre-B cell in phenotype (36, 37). They express early markers of the B-cell pathway of differentiation and show rearrangement of the joining (J) region of the immunoglobulin (Ig) heavy-chain locus (32). Inoculation of pristane-primed mice with A-MuLV results in the appearance of both lymphomas and plasmacytomas (38). A-MuLV-induced plasmacytomas contain clonally integrated A-MuLV proviruses that express the v-*abl* product and Ig:c-*myc* chromosomal translocations that result in elevated levels of c-*myc* expression (39). Intrathymic inoculation of A-MuLV results in thymic lymphomas (40, 41). A variety of phenotypes have been reported for cell lines derived from A-MuLV-induced thymic lymphomas including pre-B, pre-T, and L3T4 + Lyt2+, L3T4 − Lyt2+, and L3T4 + Lyt2− T-cell subsets (42–45). In one study the genotype of the helper virus was found to influence the phenotype of the resulting thymic tumor (43).

Transformation in vitro. Infection of several established rodent cell lines, e.g., BALB 3T3, NIH 3T3, and Rat 1, results in focal morphological transformation of cells, and this has provided a standard biological assay to titer the virus (8). Infection of primary bone marrow cells or fetal liver cells with A-MuLV in tissue culture results in the pro-

liferation of lymphoid cells (46, 47) and when these infected cultures are seeded in semisolid agarose, macroscopic colonies of proliferating lymphocytes appear 10–12 days later (48). Under appropriate culture conditions lymphoid colonies can be established into cell lines. In contrast, retroviruses coding for the *bcr/abl* gene product do not transform NIH 3T3 cells (49) and partially transform primary bone marrow cells *in vitro* (50). Examination of the status of cell-surface markers and immunoglobulin genes in cell lines transformed by A-MuLV indicates that they are of the pre-B cell phenotype (51, 52). Also, detailed examination of A-MuLV-transformed cell lines has been instrumental in unraveling many aspects of immunoglobulin gene rearrangement (53–55).

Functional Domains of the v-*abl* Oncogene and Viral Determinants of Pathogenicity. One unusual feature of A-MuLV is its apparent plasticity when grown in established cell lines such as NIH 3T3. The first molecularly characterized form of the v-*abl* protein was a 120-kDa protein (14, 15) rather than the larger 160-kDa protein encoded by virus strains cloned from earlier pools of virus. Subsequently many variant viruses have been isolated, and the size of the v-*abl* products encoded by them range from 85 up to 160 kDa (56, 57). This variation in part results from the deletion of sequences in the 3′ half of the v-*abl* protein that are toxic to established fibroblastoid lines. Deletion of the terminal 70–80 kDa from the v-*abl* product appears to abrogate this toxic effect (58). To date there is no convincing evidence to indicate that the toxic effect is seen in normal cells such as primary lymphocytes.

Using site-directed deletions it has been possible to map the sequences necessary for the kinase activity and transforming capacity of the protein. These lie 360 bases 3′ of the junction with *gag* sequences and encode 252 amino acids in the v-*abl* protein (12). As predicted these are the sequences that bear homology to v-*src* and other tyrosine kinase oncogenes. v-*abl* proteins that contain these sequences and as little as 34 amino acids of *gag* origin are competent to transform fibroblastoid lines. Additional *gag* sequences are apparently necessary for stability of the protein and efficient transformation of lymphoid cells (59). The *gag* amino terminus of the protein also plays a crucial role in transformation because it encodes sequences necessary for myristylation of the protein and hence a subcellular localization at the plasma membrane (60).

Although attempts to alter the tissue specificity of A-MuLV have not succeeded, these experiments have provided evidence that the tissue tropism of A-MuLV is a function of the v-*abl* oncogene and not the viral vector (61, 62). Construction of v-*src*/v-*abl* chimeric viruses demonstrated that when the kinase domain of the virus was derived from v-*src,* lymphoid cell transformation was abolished, consistent with the phenotype of the parental v-*src*-containing virus. Substitution of the lymphotropic A-MuLV long terminal repeat (LTR) with that of the erythrotropic Friend MuLV or the erythrotropic/fibrotropic Harvey MuSV did not alter the *in vivo* tissue tropism of the recombinant viruses. The *in vitro* transforming activity for primary bone marrow cells of the Friend LTR recombinant was abolished, however, a result which suggests that different levels of v-*abl* protein are necessary for *in vitro* cell transformation and *in vivo* tumorigenesis, or the two processes have different target cells (62).

Infection of Factor-Dependent Hematopoietic Cell Lines. Several different lineages of hematopoietic cells have been shown to be dependent on the presence of the growth factor interleukin 3 (IL-3) for continued proliferation *in vitro.* These cells include mast cells, early stages of erythroid differentiation (BFU-E), and some myeloid cells. Continuous cell lines with phenotypes characteristic of mast, early myeloid, granulocytic, or primitive lymphoid cells have been established using medium supplemented with IL-3 (63–66). Infection of these cells with A-MuLV results in the generation of IL-3-independent lines (67–71). In several studies A-MuLV-infected IL-3-independent cell lines expressed the v-*abl* protein and showed no evidence of autologous production of IL-3 factor or mRNA. From these results it has been concluded that expression of v-*abl* is sufficient to overcome IL-3 dependence by a nonautocrine mechanism. In those cases where it has been examined, the A-MuLV-

induced IL-3-independent lines were tumorigenic unlike the parental lines (68, 70, 71). In one study it was also shown that further differentiation of a granuloid line was blocked following A-MuLV infection (70).

Experiments from several laboratories with several different IL-3-dependent lines and other oncogenic viruses would lead one to think that the v-*abl* oncogene is more efficient than other oncogenes at rendering cells independent of IL-3. Thus decreased dependence on IL-3 has been reported following infection with viruses that encode v-*src,* or v-*myc* oncogenes, and high-copy numbers are needed for v-*fms*-encoding viruses to render cells IL-3 independent (71–76). No effect on IL-3 dependence has been seen following infection with viruses that encode v-Ha-*ras,* v-*mos,* or v-*fps* oncogenes (69, 71, 76). It remains to be determined if that ability of v-*abl* to render cells factor independent is related to its function in cell transformation.

Progression of Malignancy during Tumorigenesis by v-*abl*. An early study to examine the question of progression during A-MuLV transformation employed bone marrow cells cultured on feeder layers that support B-cell lymphopoiesis. Following infection with A-MuLV the majority of cells that grew continued to be dependent on the feeder layers for a period of 3 months (77). During that period clones could be isolated and the levels of v-*abl* protein were not found to change significantly (78). These clones also were less tumorigenic than clones which grew in the absence of growth factors. Subsequent work has focused on isolation of clonal cell lines that produce factors that would replace the feeder layer effect and three laboratories have reported success (79–81). To date characterization of the relevant factor(s) is preliminary. Indirect support for the role of progressive changes during *in vitro* transformation by A-MuLV comes from the general protocol used to establish cell lines from colonies directly induced by A-MuLV infection. During the initial stages of these cultures high cell density must be maintained and attempts to subdivide the cultures or clone them in the absence of feeder layers usually have proved unsuccessful. The caveat that must be added to these results is that they may solely reflect conditions of tissue culture selection.

Examination of primary tumors induced by A-MuLV supports the idea that expression of v-*abl* is not sufficient in most cells of an infected clone to induce tumorigenicity. Primary tumors induced by A-MuLV are oligoclonal in origin despite the fact that up to 20% of the bone marrow cells become infected during the course of the disease (34). Moreover cells capable of forming colonies in *in vitro* transformation assays can be isolated during the preleukemic phase of the disease, and the majority of these cells clone significantly better on feeder layers than in the absence of feeder layers. Because of the presence of replicating virus in these cultures it was not possible to analyze the fate of individual clones and thereby determine directly if progressive changes could be documented in individual cell clones.

Recently it has been possible to prepare A-MuLV free of helper virus using retroviral packaging lines (32). When helper-free A-MuLV was used to infect weanling mice of the susceptible strain, i.e., BALB/c, tumors developed with a latent period of about 30 days. Tumors were of monoclonal origin and did not express any viral proteins other than v-*abl.* Using an *in vitro* transformation assay it was possible to isolate preleukemic cells from helper-free A-MuLV-infected mice. Examination of the proviral integration patterns in several individual colonies isolated from preleukemic mice indicated that within each mouse all colonies were derived from a single infected cell. Therefore colonies within a given infected mouse could be compared with each other for their tumorigenic phenotypes. The results of that experiment indicated that only about 5% of the preleukemic cells were tumorigenic *in vivo,* whereas 85% of the leukemic clones were tumorigenic. The levels of v-*abl* protein present in leukemic and preleukemic clones were not significantly different (P. L. Green, D. A. Kaehler, and R. Risser, unpublished observations). These results indicate that expression of v-*abl* is not sufficient within an infected clone to lead to tumorigenicity but must be accompanied by a secondary event or the selection of a stem cell subclone.

Summary and Directions. A key area of research on the structure and function of

v-*abl* will be the search for the substrates critical to cell transformation. As we have seen the mechanism of activation of v-*abl* depends upon truncation of the normal c-*abl* protein to generate a protein with detectable tyrosine kinase activity. Why this means of activation should result in a transforming protein with tropism for the lymphoid lineage in mice is unclear, particularly when we consider that a similar mechanism of activation of *abl* genes is involved in the stem cell disease CML in humans. It is also not clear why v-*abl* is more efficient than other tyrosine kinase oncogenes in relieving cells of their requirements for the growth factor IL-3. The mechanism and significance of that activity will be a focus of future efforts. Finally understanding of the role of v-*abl* in tumorigenesis will require identification and analysis of other cellular genes that may play essential roles in progression in A-MuLV disease.

The authors' support is provided by National Cancer Institute Grant CA-41302 and Training Grant CA-09135.

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