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MINIREVIEW

The Abelson Murine Leukemia Virus Oncogene (42115)

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Abelson murine leukemia virus (A-MuLV) is an acute transforming retrovirus which induces a rapid lymphosarcoma in mice. The virus arose in one of a series of mice that were treated with prednisolone and infected with the replication-competent retrovirus Moloney murine leukemia virus (M-MuLV) (1, 2). One such mouse developed a non-thymic tumor; the cause was shown to be a virus when it was demonstrated that filtered extracts from this tumor were capable of inducing similar tumors in animals. These tumors were quite distinct from the thymic tumors normally induced by the parental M-MuLV, suggesting that a new virus had arisen in the course of the infection. This new virus, termed A-MuLV, has been the subject of intensive study in recent years. The analysis of the structure of the viral genome has had profound effects on our thinking about the mechanisms by which oncogenic gene structures can arise. This review will describe the biology of the virus, its genetic structure, current models for the origin of the virus, and the properties of the cellular gene from which it arose. Several other reviews describing these and other aspects of the virus have been published (3–8).

Biology of A-MuLV. Infection of experimental animals with A-MuLV preparations results in the rapid onset of disease. Neonatal mice injected with the virus develop an invariably fatal lymphosarcoma 3 to 5 weeks after injection; the first neoplastic cells appear in the bone marrow as early as 15 to 20 days after infection. The cells spread rapidly to the meninges and to selected lymph nodes, often resulting in localized lymphadenopathy. The tumor cells, exhibiting a characteristic lymphoblastic morphology, can be adapted to growth *in vitro* and cloned. These cultures have allowed a detailed characterization of the tumor cells. More importantly, primary explants from various tissues can be prepared and transformed *in vitro* by infection with the virus (9, 10). The resulting cell lines are clonal in origin. This assay for transformation has made possible determination of the tissues containing target cells for transformation by the virus; the majority of the susceptible cells were found in the fetal liver and in the adult bone marrow and spleen, the major sites of lymphoid cell development.

The tumor cells have been demonstrated to represent immortalized "pre-B" cells by a number of criteria. The most important cell type marker has been the structure and expression of the immunoglobulin genes (11, 12). Examination of the heavy- and light-chain genes from the tumor cells has shown that generally both heavy-chain alleles have undergone some DNA rearrangement preparatory to the expression of these genes, while neither κ nor λ light-chain genes have rearranged. There are exceptional cell lines which have rearranged both heavy- and light-chain genes. Some lines derived from infection of early fetal liver are actually unstable at these loci and continue to rearrange their DNA in culture (13, 14). Most A-MuLV tumors, whether arising *in vivo* or derived by infection *in vitro,* fall into one of two categories with regard to the expression of these genes. Many are "mu-only" cells that express only the mu heavy-chain gene to form a cytoplasmic mu protein, not associated with any light-chain protein. Others are null cells, expressing neither heavy- or light-chain proteins. Some of these latter cells can be induced to differentiate partially by treatment with compounds such as lipopolysaccharides; the cells can be made to express mu or IgM in this way. These properties suggest that the A-MuLV target cells are precursors to the virgin B cell, and represent intermediates in the differentiation pathway of cells which are normally assembling immunoglobulin genes. The A-MuLV cell lines, providing a pure

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population of these intermediates, are currently under intensive study.

An important technical advance was the discovery that the virus could also induce the morphological transformation of the NIH/3T3 fibroblastic mouse line (15). Virions released after infection of these cells showed identical properties to the virus recovered from animals. Analyses revealed that the initial virus preparations were mixtures of two agents: a replication-competent nontransforming helper virus, the parental M-MuLV; and a transforming virus, the oncogenic A-MuLV. By infecting cells at very low multiplicity, transformed cells could be isolated which contained only the A-MuLV, and these cells were found not to release virus. Thus, A-MuLV was shown to be replication-defective virus and dependent on the helper for spread from cell to cell. Superinfection of such transformed nonproducer cells with replication-competent MuLVs resulted in the rescue of the A-MuLV genome, and the formation of new mixed virus preparations containing both A-MuLV and the new helper virus.

Perhaps the most puzzling property of the Abelson oncogene is the extremely narrow tissue specificity for transformation that it exhibits. The murine A-MuLV almost always transforms pre-B lymphocytes *in vivo*. Current efforts to probe the biology of the virus have centered on determining the complete range of cell types that can serve as targets for transformation. Several different cell types have been successfully transformed, either transiently or permanently. These include cells of the erythroid lineage (16), and cells with many of the properties of macrophages (17). The range of target tissues has in a sense been widened enormously; recently a feline sarcoma virus has been isolated which is the feline homolog of the mouse virus (18). This virus induces a completely different disease, a sarcoma, even though the oncogene is very similar to that of A-MuLV. Thus, the details of the virus structure may be responsible for the narrow specificity of the murine virus.

Structure and Expression of the A-MuLV Genome. The genetic organization of the A-MuLV genome and its relationship with the parental M-MuLV genome was determined by analyses of the viral nucleic acid (19, 20). Electron microscopic examination of heteroduplex molecules between A-MuLV RNA and M-MuLV cDNAs showed that the A-MuLV genome was homologous to M-MuLV at the termini, but that a large central region was made up of novel sequences. Digestion of these structures with the single strand-specific nuclease S1, followed by determination of the lengths of the protected DNAs by electrophoresis, revealed the sizes of the regions of homology. The virus was thus shown to be a recombinant, apparently derived from M-MuLV by a substitution that resulted in the loss of most of the genes essential for replication, and in the acquisition of unrelated sequences. The novel sequences are termed *v-abl* sequences.

Large quantities of viral DNA were made available by the molecular cloning of the A-MuLV genome in bacteria (21, 22). Analysis of such cloned DNAs confirmed the overall structures defined previously, and allowed more detailed characterizations. The nucleotide sequence of the entire genome has now been determined (23). The 5′ portion of the genome is indeed homologous to that of M-MuLV, and there is a simple abrupt transition from the sequences of the parental virus to the new sequences. The breakpoint is in the P30 domain of the *gag* gene, and results in the fusion of this gene to the new sequences such that an extremely long open reading frame is created. This reading frame terminates within the new sequences, and is followed by a substantial region which is not capable of encoding a large polypeptide. In what is believed to be the true wild-type A-MuLV genome, the inserted sequences are about 4000 base pairs long. The 3′ junction is as abrupt as the 5′ junction, and joins the new sequences to a very short region of homology to the M-MuLV genome.

The protein product of the A-MuLV genome was first detected by serological tests using antisera directed against the M-MuLV *gag* gene products (24, 25). The virus was shown to encode a single polypeptide consisting of a fusion between *gag* peptides and novel peptides; the structure was nicely explained by the genetic structure of the virus. The protein was found in all A-MuLV-induced tumors, in A-MuLV-induced trans-

formed lymphoid cells, and in A-MuLV transformed 3T3 cells, whether or not the M-MuLV helper virus was present. This protein was shown not to be glycosylated, but the majority of the protein was associated with the cell membrane. Sera specific for the new peptides have been prepared and have proved to be exceedingly important in detecting and manipulating the protein. Sera of this type have been prepared from tumor-bearing animals that are in the process of rejecting A-MuLV-induced tumors; more recently, sera have been prepared by immunizing animals with fusion proteins generated in bacteria. These sera have been used to demonstrate that at least a portion of the A-MuLV protein protrudes outside the cell membrane, and can be detected by immunofluorescence (26).

A key advance in our understanding of the mechanism of transformation by A-MuLV came with the discovery that the A-MuLV protein had tyrosine kinase activity (27, 28). The major activity that could be detected *in vitro* was an autokinase activity: incubation of the protein, after immunoprecipitation, with γ-labeled ATP resulted in the transfer of the phosphate to many tyrosine moieties on the protein. The activity required a divant cation, and was highest in the presence of Mn^{2+}. The enzyme was also capable of transkinase activity, as demonstrated by its ability to kinase other heat-inactivated molecules of the A-MuLV protein, as well as a variety of other substrates such as casein and synthetic copolymers containing tyrosine. Some of the antisera with narrowly defined specificities for various parts of the molecule have been shown to be inactivating sera, presumably blocking the active site of the enzyme (29). The sites of *in vitro* autophosphorylation are apparently quite distinct from the sites of phosphorylation seen *in vivo* (30); the *in vitro* reaction probably does not retain the appropriate target specificity.

Numerous variant strains of the A-MuLV genome have been recovered in many laboratories (31–34), and the structures of the genomes of these viruses have been determined [(35); Fig. 1]. These analyses have been useful because they have given important information about the regions of the viral genome that are essential for transforming activity, and for the *in vitro* kinase activity. The largest, and probably the original virus genome, is about 6.8 kb in length as the integrated provirus (36). This virus encodes a protein product, P160, of about 160,000 Da, with high levels of kinase activity. Another strain used as a wild-type virus by some laboratories has suffered a 789-bp deletion near the center of the genome; the deletion preserves the translational reading frame and allows the synthesis of the P120 protein, an active kinase of 120,000 Da. Other variants express still shorter proteins termed P100 and P90 which differ from the P120 by loss of C-terminal peptides. All these variants are still able to transform cells; all encode proteins that still have kinase activity. These data show that the C-terminal portion of the viral protein is dispensable for kinase activity, and for at least residual transforming activity. The virus encoding the shortest protein, P90, although normal at transformation of 3T3 cells, is inefficient at transformation of lymphoid cells. Thus, the C-terminal sequences may serve some role in lymphoid transformation. Nevertheless, it is striking that so much of the protein is dispensable for its activity. In contrast to these viruses, a variant with a deletion in the N-terminal portion of the *v-abl* sequences is completely

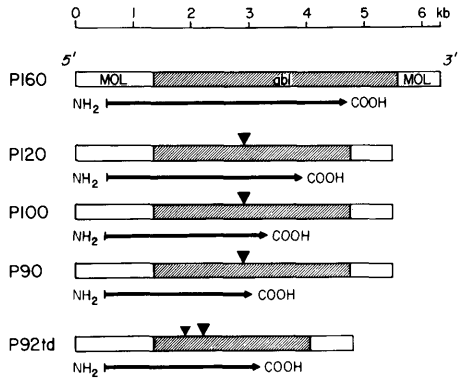

FIG. 1. Structure of various strains of A-MuLV. The genome structures of viruses encoding the designated transforming protein are shown as boxes. The regions homologous to M-MuLV are shown as open boxes, and the *v-abl* sequences are shown as shaded boxes. Closed triangles mark the position of the various deletions in each strain relative to the P160 virus. The protein encoded by each strain is indicated by the solid line. [From Ref. (35).]

defective. The protein synthesized by this variant, termed P92, exhibits no detectable tyrosine kinase activity when assayed *in vitro,* and is apparently unable to induce the transformation of cells. This result suggests that the N-terminal portion of the region is key for biological activity. Comparison of the sequence of this region with the sequence of other tyrosine kinase oncogene products supports this notion: there is close homology in this region between *v-abl* and such oncogenes as *src, fps,* and *fms* (23).

Recent efforts to define more precisely the essential regions of the virus have utilized *in vitro* mutagenesis procedures to introduce defined lesions in the genome (37–39). These studies confirm the deductions based on the natural mutations, and showed that the essential region of the *v-abl* sequences lie near the N-terminal part of the sequences; a region sufficient to encode only about 45,000 Da is required for biological activity. Mutations which alter or even eliminate the *gag* portion of the fusion protein have been constructed, and the effects of these alterations have been determined (39). Mutants lacking virtually all of the *gag* sequences still exhibit kinase activity and can still transform fibroblasts normally; thus, the *gag* region encodes no functions essential for these basic activities. Such mutants, however, show an enormously reduced ability to transform lymphoid cells. Thus, the presence of the *gag* sequences may increase the effectiveness of the kinase; a plausible explanation for the function of these sequences may be the direction of the protein to an important subcellular location, such as to the plasma membrane. In many cases the resulting construct has proven to be highly unstable genetically, and gives rise to rearrangements at a very rapid rate. There may be strong selection for such rearrangements: it may be that the expression of some highly aberrant kinase activities are toxic to cells and that cells carrying variant viruses with reduced activity show selective growth advantage. In support of this idea, the transfection of NIH/3T3 cells with cloned A-MuLV DNA has been demonstrated to be toxic; presumably the high levels of DNA introduced into the cell in these procedures increases the toxicity of the oncogene (40, 41). Mutagenesis of the viral DNA has led to the conclusion that the C-terminal portion of the kinase is responsible for the toxicity (37).

It has been recently shown that the *gag* gene of the parental M-MuLV encodes two proteins, synthesized from one mRNA by the use of either of two alternate translational start codons. The major protein is initiated at an AUG codon, and is a cytosolic nonglycosylated protein; a minor protein is larger, is possibly initiated at a GUG codon 5′ to the major start site, and is a glycosylated membrane protein. Since the A-MuLV protein is a *gag* fusion protein, it was possible that two fusion proteins, corresponding to the two *gag* proteins, would be made by the virus. This prediction has been confirmed (42). The glycosylated version of the protein is apparently not necessary for the virus; the glycosylated protein does not exhibit kinase activity and is not a substrate for an active kinase. Furthermore, variants which lack the glycosylated protein are normal in both kinase and transforming activities. The biologically significant protein seems to be the nonglycosylated one.

Further biochemical studies on the A-MuLV gene product will be facilitated by the successful expression of the protein in bacterial cells [(43); R. Rees-Jones, personal communication]. The cloned genome of the virus has been inserted into a variety of expression vectors, and cross-reactive proteins can be induced by these constructs in bacteria. Importantly, the expressed proteins exhibit functional kinase activity. The essential region for the activity corresponds closely to the region needed for transforming activity as defined in the intact viral genome (44).

It is clear that there is an extremely close correlation between the tyrosine kinase activity, as measured *in vitro,* and fibroblast transformation activity *in vivo.* The implication is that this kinase activity is directly responsible for the alteration of growth control that the virus induces. The significant target of the enzyme in the cell, however, is completely unknown. Examination of the overall pattern of phosphorylated proteins in normal and transformed cells reveals many differences, but it is not apparent which, if any, of the abundant proteins containing elevated phosphotyrosine are the ones responsible for mediating the effect of the oncogene. The avail-

ability of temperature-sensitive mutations in the A-MuLV kinase would facilitate at least a categorization of target proteins. Current efforts in our laboratory are focused on the use of insertional mutagenesis (45) to construct such temperature-sensitive mutations. Probably the definitive approach toward the identification of the significant target will be a genetic one. If mutant cells that are resistant to the effect of an active A-MuLV kinase can be isolated, they would presumably contain an alteration in the chain of command from the kinase to the ultimate proliferative response. A subset of these mutants would exhibit alterations in the immediate target of the kinase. If the levels of any target protein were found to be altered by mutation, and correlated with a resistance to transformation, then the target would be implicated strongly in the response.

The Structure and Expression of the *c-abl* Gene. The cloning of the viral genome has made possible the construction of nucleic acid probes for the detection and isolation of homologous DNAs from uninfected cells. Hybridization experiments with these probes revealed that DNA homologous to *v-abl* could indeed be found in the genome of the uninfected mouse, and confirmed that the source of the *v-abl* gene was the DNA of the host animal (19, 20). A more detailed analysis showed that the relationship between the cellular gene and the viral gene was complex (21, 46). The mouse genome contained only a single locus with homology to the viral DNA, pinpointing this locus as the unequivocal source of the *v-abl* sequences. The structure of the cellular locus, termed *c-abl,* was not colinear with the viral counterpart; rather, the homology was broken into many segments dispersed over at least 30 kb and separated by large intervening sequences. This structure was confirmed by the cloning of the entire region from the mouse (47). The *c-abl* gene seems to be related to the *v-abl* sequences in much the same way that a large mammalian gene is related to its mRNA: *c-abl* contains both exons and introns, while the *v-abl* region contains only the exon portions of the parental gene. This pattern has been found to be common to nearly all transduced oncogenes carried by retroviruses.

The relationship of *c-abl* to *v-abl* has led to a proposed model for the mechanism by which the virus was originally formed (5). It is surmised that an M-MuLV provirus once integrated near the 5′ end of the *c-abl* gene and subsequently suffered a partial deletion which fused the 5′ half of the *gag* gene to the downstream portion of *c-abl.* Sequence analysis of the appropriate portions of the *c-abl* and M-MuLV *gag* gene lends support to this step: there is a four base region of homology between these sites as is often found at the site of deletions in DNA (4). Alternatively, the aberrant integration of an M-MuLV genome could have directly formed the 5′ junction. In either case, a hybrid mRNA would be formed in the cell, initiated at the 5′ end of the M-MuLV genome and elongated through the junction into the *c-abl* gene. The site for the formation of the 3′ end and the polyadenylation of the hybrid mRNA would be the normal 3′ end of the *c-abl* gene. In a key step, this RNA precursor would then be processed and spliced by the cell to form an mRNA; the product mRNA would contain only the exon sequences, joined together at the time of removal of the intron sequences. This mRNA would be translated to form the *abl* protein kinase and would transform the cell. Reconstruction experiments show that a similar structure can indeed act to transform cells (40). The RNA would not be a complete virus genome: the 3′ sequences essential for efficient retroviral transmission would not be present. Thus, the completion of the process requires one more recombination event between the hybrid RNA and the M-MuLV genome. Reconstruction experiments show that this process occurs readily and frequently during retroviral transmission (48); recombination between M-MuLV and A-MuLV genomes lacking 3′ termini can occur as frequently as once every 10^4 or 10^5 transfers. In these reconstructions, the recombination seems to occur between arbitrarily chosen sites on the two parental sequences, and without the benefit of homology (40). As predicted by the model, the 3′ junction of the authentic A-MuLV shows that there was no homology between M-MuLV and *c-abl* at the point of recombination.

The *c-abl* locus is highly conserved. Examination of the DNA of a wide variety of strains of mice has shown an identical pattern

of restriction fragments homologous the *v-abl* probe (21); an extended search of more strains for polymorphic differences in restriction sites at the locus has not detected any such differences (P. D'Eustachio, personal communication). The extent of conservation of the locus and surrounding DNA is quite extraordinary. Although no polymorphisms have been found, the chromosomal assignment of the *c-abl* locus has been determined (49); examination of DNAs from a battery of mouse–hamster hybrid cell lines revealed that the *c-abl* gene is on mouse chromosome 2. Homologous sequences have also been detected in the DNA of a large number of evolutionarily distant species, including man, rodents, and birds. The human *c-abl* locus has been extensively mapped (50) and molecular clones have been isolated (51). The human gene is likely to be functionally related to other tyrosine kinases: sequence analysis of human *c-abl* DNA has shown extensive homology to the sequences of these proteins (52). Recently, a homologous gene has been detected (53) and cloned (54) from *Drosophila.* Thus, the gene is evolutionarily ancient; it must express a rather basic function in the life of multicellular organisms. The data are not consistant with the notion that the gene is responsible for a function specific to mammals or even to vertebrates. The presence of the gene in *Drosophila* will allow at least a partial definition of the function of the gene; techniques are available for the construction of mutations at any known locus in this organism, and the analysis of the phenotype of such mutations should soon give us an important clue as to the time and site of action of the protein.

What can we say about the expression of the normal *c-abl* gene? The gene normally encodes two very large mRNAs (6.5 and 5.5 kb in size), present in approximately equal abundance (55). The exact structure of these RNAs, and the relationship between them, is not yet certain; efforts to clone and characterize them are underway. It is clear that these mRNAs are larger than the novel region present in the A-MuLV genome. The 5′ ends of the RNAs are upstream of the 5′ site of recombination that formed A-MuLV; the 3′ ends are downstream of the 3′ site of recombination. A variety of cell types, from virtually all tissues, contain at least low levels of these mRNAs. Most cell lines also express the gene, and one of the richest sources of these RNAs is the 3T3 cell line. The RNAs are also detected at normal levels in the tumor cells induced by A-MuLV, suggesting that the expression of the viral genome and the transformation of the cell neither turns off nor elevates the expression of the endogenous locus. A surprising finding was the discovery of a third mRNA specifically expressed at very high levels in the testes (56). Examination of spermatogenic cells at various developmental stages has revealed that the bulk of the RNA is present in postmeiotic cells, early and late spermatids (D. Wolgemuth, personal communication). Ultimately this finding may give us a clue to the function of the gene product encoded by the *c-abl* gene.

Antibodies isolated from tumor-bearing animals have been demonstrated to have reactivity to the *v-abl* gene product (26), and these sera have been used to examine uninfected cells for the presence of cross-reactive proteins. A protein can indeed be detected (57): normal cells synthesize a large protein, approximately 150,000 Da in size, which is nonglycosylated but associated with membrane. The level of the protein, termed NCP150, is very low. The cellular gene products homologous to most tyrosine kinase oncogene products are themselves active kinases, but this has not been easy to demonstrate in the case of the *c-abl* protein (58). Recent results suggest that the protein does have weak activity *in vitro,* and that this activity is very labile and sensitive to detergents (O. N. Witte, personal communication). The protein is phosphorylated on serine *in vivo,* presumably by cellular kinases.

The function of the protein in normal cells is currently unknown, and there are very few clues available. The most likely speculations are based on the observed homology between the *v-abl* protein and other tyrosine kinases. It has been shown that the *erbB* oncogene present on the avian erythroblastosis retrovirus, also encoding a tyrosine kinase, was derived from a cellular homolog that encodes the epidermal growth factor receptor. Many other polypeptide hormone receptors, including the insulin receptor, have been shown to contain tyrosine kinase activity. Thus, the

NCP150 protein may be a similar receptor for an unidentified hormone. The tissue distribution of the protein is not so specialized, however, as to immediately suggest a particular receptor. The subcellular location of the protein in the plasma membrane is consistent with this proposed function.

Activation of the *c-abl* Gene. The recombination events which led to the formation of the A-MuLV genome obviously cause a dramatic alteration of the function of the gene. Rather than the normal function mediated by the two alleles of the endogenous *c-abl* gene, the addition of a third version of the gene carries out an extraordinary function of cellular transformation; it acts as a dominant genetic locus for the novel activity. What is the essential difference between the *c-abl* and *v-abl* genes? There are several possibilities. One is that the level of expression of the protein product from the viral gene is enormously higher than that from the cellular homolog. This results in higher levels of phosphoproteins in the cell, and this higher level of some critical phosphorylated substrate could lead to aberrant growth. Alternatively, and perhaps more attractively, the viral protein could be qualitatively distinct from the cellular one by virtue of structural differences. The viral enzyme has much higher kinase activity when assayed *in vitro,* and may exhibit altered substrate specificity. Its activity may be constitutive and not subject to the normal regulatory controls applied by other modulatory proteins. Finally, the site of localization of the viral protein within the cell may be distinct from that of the cellular protein. All these functional differences might be mediated by subtle structural differences such as point mutations, but a much more major difference is inherent in the structure of the A-MuLV genome: the *v-abl* fusion protein is a truncated version of the *c-abl* protein and has lost the normal N-terminus. The removal of this domain of the protein could easily account for the altered properties of the enzyme.

A large number of oncogenes known to be active when incorporated into retroviral genomes can also be mutated in other ways to yield an actively transforming gene. One might therefore expect to find a mutant *c-abl* locus associated with some tumors of nonviral etiology. This expectation has in fact been fulfilled (59–62). A majority of the tumor cells of patients with chronic myelogenous leukemia (CML) exhibit a particular chromosomal abnormality known as the Philadelphia chromosome. The aberrant chromosome is the result of a reciprocal translocation between chromosomes 9 and 22. The chromosomal location of the *c-abl* locus in man has been determined (50) to be on chromosome 9, and cytologically close to the breakpoint of the Philadelphia chromosome (q34-qter). Recently one such breakpoint has been cloned (60), and the breakpoint was shown to lie within the 5′ portion of the *c-abl* gene. The resulting structure is thus strikingly similar to the structure of the *v-abl* genome, and one can hypothesize that the removal of the 5′ exons of the gene and the fusion to another gene results in a similar activation of the gene. A variety of other independent Philadelphia chromosomal breakpoints have been examined and found to be at adjacent but distinct sites; in most cases the breakpoint seems to map far to the 5′ side of the *c-abl* locus. These more distant breakpoints may activate the gene by means of fusions, or may do so by alterations in chromatin structure in the vicinity of the gene. At this time we cannot even be certain that the translocation is causal for the CML tumors, but the direct involvement of the oncogene at the very breakpoint, and the good correlation of the translocation with the tumor, strongly implicates the event as an early causal event.

At least one human cell line has been shown to contain an altered *c-abl* locus. The K562 cell, a CML-derived cell line, has been shown to contain a rearrangement and amplification of the *c-abl* sequences (63). These cells exhibit other oncogene rearrangements as well and the effect of the amplification on the growth of the cell is uncertain. Nevertheless this line provides a clonal population with a defined alteration in the locus, and the expression of the locus has been examined in some detail (64). These cells express a very large mRNA, approximately 8 kb in length, homologous to the *c-abl* gene. Furthermore, the *v-abl*-specific sera detect an aberrantly large *c-abl* protein termed P210 (65) with unrelated sequences at the N-ter-

minus. This new protein, like the viral P160 protein, is an active tyrosine kinase: it exhibits autophosphorylation activity as well as transphosphorylation of exogenous substrates, and these activities are inhibited by the same monospecific sera that inhibit the activity of the P160 protein (66). Preliminary results suggest that other CML cells may encode similar mRNAs and proteins to those of K562 (O. N. Witte, personal communication). The close structural and functional parallels between the *v-abl* gene products and the CML *c-abl* gene products support the idea that the common features of the mutations they have suffered are significant.

The identification and characterization of the oncogene carried by the Abelson virus have lead us a long way toward an understanding of the mechanism of formation of a large class of human tumors. This oncogene takes a prominent place among the roughly 20 analogous genes identified as the transforming genes of retroviruses; it is one of the best characterized of the tyrosine kinase family of oncogenes, and one of the first to be directly implicated in a defined human disease. Our future efforts to understand the *v-abl* gene, and indeed all the oncogenes, must ultimately be directed toward the other components in the cell with which the oncogene products interact. These components are likely to be part of the biochemical pathway that regulates the growth of cells; the oncogenic proteins like the A-MuLV kinase may be the best route to the characterization of this pathway.

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