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Induction of endogenous virogenes and oncogenes in the pathogenesis of leukemia

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Introduction

Oncogenic retroviruses fall into two classes, those with slow and those with acute transforming ability. The former are termed leukemia viruses; they induce leukemia after about 3–12 months following virus inoculation. The latter are termed sarcoma- or acute leukemia viruses. Their effect becomes obvious after 1–2 weeks after inoculation. They transform fibroblasts and other suitable target cells *in vitro*. This is in contrast to the leukemia viruses which do not display transforming activities *in vitro*. The important difference between the two classes of viruses is that the sarcoma viruses, but not the leukemia viruses, carry additional genes, called oncogenes, which control neoplastic transformation. Interestingly, these oncogenes are normal cellular host genes which have found their way into the viral genome via recombination. In other words, sarcoma viruses have evolved from non-transforming retroviruses by recombination with host oncogenes. It is the "picked up" oncogene which controls and directs the malignant phenotype (for references and review see Weiss et al., 1982). In vertebrate cells, the oncogenes are thought to carry out normal functions of still unknown nature, while under the control of the viral genome they cause transformation.

The first mammalian leukemia virus was isolated by Gross from AKR mice (Gross, 1951). It was only 20 years later that it was realized that all mice carry in their genomes multiple copies of integrated retroviral genomes, collectively called endogenous viruses. Nucleic acid hybridisation ("Southern blot") analyses shows that mice carry about 15–25 viral copies related to the Gross leukemia virus. They are inherited as normal cellular genes, following Mendel's laws and appear to be subject to normal gene regulation by the host (Aaronson and Stephenson, 1977). They offer a model to study gene expression in eukaryotic cells.

There is heterogeneity amongst endogenous viruses. (In this article, we deal only with the endogenous viruses related to leukemia viruses). Many copies show deletions and are therefore defective. When expressed, they may lead to production of viral proteins, but not to infectious virus. The complete infectious viruses of inbred mice fall into two groups, distinguishable by their host range. Xenotropic viruses replicate in non-mouse, e.g. rabbit cells, but not in mouse cells (Levy, 1973; Levy, 1978), while ecotropic viruses show the reciprocal behaviour (Pincus et al., 1971). There is recombination amongst endogenous viruses. In leukemogenesis, an ecotropic virus recombines with a (presumably defective) virus related to the xenotropic group to generate a dual-tropic virus which replicates both in mouse- and non-mouse cells (Hartley et al., 1977).

In retroviral leukemogenesis the following steps can be distinguished: First, there is expression and high-titer replication of ecotropic viruses. This can be achieved by spontaneous induction of the ecotropic viral loci as in AKR mice, or, when these loci are silent or absent, by passive inoculation of an ecotropic viral stock. In AKR mice, later in life, the endogenous xenotropic virus becomes expressed, and with the onset of the characteristic T-cells thymoma the dual-tropic virus appears (Rowe et al., 1980). It may be that only this latter virus has the ability to infect the target cell for neoplastic transformation. It is thought that the long latency of this disease is related to the time required to generate the dual-tropic virus and to infect the appropriate target cell. How does a virus lacking known transforming genes induce transformation? From work with avian leukosis virus, which also lacks

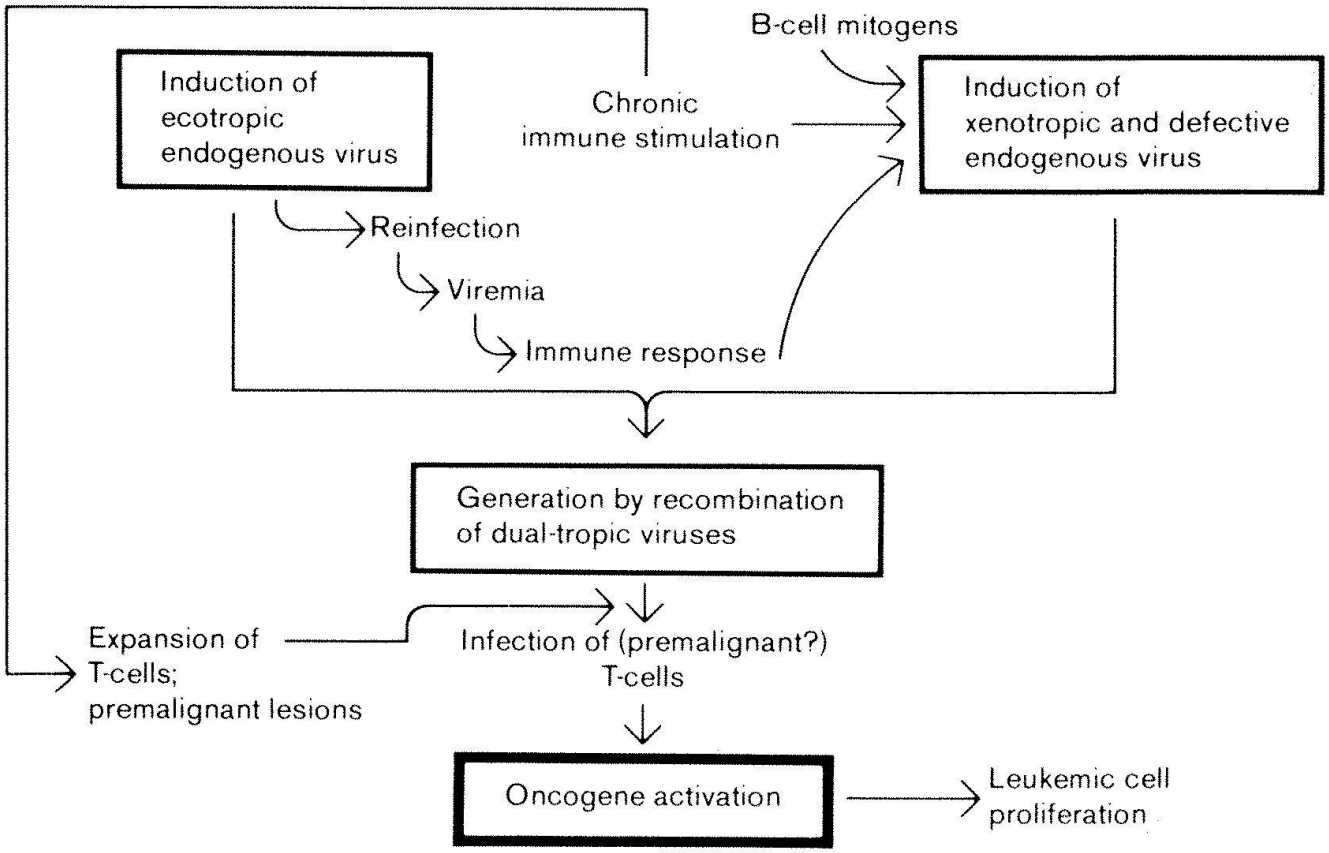

Fig. 1. Minimum model of retroviral leukemogenesis

oncogenes, we know that following infection viral DNA can integrate next to a cellular *onc* gene, in this case the *myc* gene (Hayward et al., 1981). Viral control elements called LTR (see Diggelmann, this volume) containing promoter sequences can then induce the transcription of the neighbouring *myc* gene. It may be that in murine leukemia, the dual tropic virus induces an oncogene in a T-cell in the way avian leukosis virus does in the B-cell tumor of the chicken. Figure 1 shows a "minimum model" of leukemogenesis. According to this model, the critical steps are: induction of at least two different endogenous viruses; the recombinational generation of dual-tropic viruses; and, the activation of oncogenes. Chronic immune-stimulation, known to favor leukemogenesis, may affect this process by two ways: by inducing endogenous viruses, and by triggering pre-malignant changes in T-lymphocytes. There is some evidence that such changes are even required to allow T-cell infection to take place; normal T-cells which grow *in vitro* cannot be infected by retroviruses (Horak et al., 1981; Stoye and Moroni, unpublished results).

Induction of endogenous viruses

The multiple copies of endogenous viruses are integrated at different sites and apparently in many chromosomes. It appears that they have been acquired by exogenous infection, and have succeeded in maintaining themselves in the genome of the species. Over time, they have duplicated, changed their position in the genome (perhaps by reinfection of the germ line) and have given rise to the heterogeneity observed to date. It is not known why they have been maintained for long periods of time. Either they offered to their host a selective advantage of unknown nature, or they found an ecological niche as "harmless" molecular parasites, causing rare leukemias and sarcomas but not affecting the viability of the species as such. As expected, the host has evolved protection mechanisms to prevent reinfection of spontaneously induced viruses. Two such mechanisms are known: First, there is a serum lipoprotein which is highly and selectively active in neutralizing xenotropic virus. Second, mouse cells lack receptors for xenotropic virus and therefore cannot be rein-

fected once virus has become activated (Levy et al., 1975; Levy, 1978). Reinfection by ecotropic virus is restricted by an intracellular mechanism which prevents integration of viral DNA into the host genome and is controlled by the host Fv-1 locus (Lilly and Pincus, 1973).

The induction of endogenous viruses is important for two reasons. First, it corresponds to one step in the development of retroviral leukemia. Second, it is of interest in the general context of induction and function of eukaryotic genes. The analysis of virus-induction is complicated by the heterogeneity mentioned above. If one wishes to make statements about the induction of a single provirus, care must be taken to exclude the induction of additional loci. This heterogeneity also has its merits: viruses integrated at different sitey may serve as guides and probes to chromosomal regions for which no marker yet exists.

In the following sections some pertinent facts about induction of xenotropic, ecotropic and defective viruses are being summarized.

a. Xenotropic viruses

Some strains of mice (prototype NZB) spontaneously produce high titers of xenotropic viruses. A genetic analysis revealed that they carry two non-linked loci, Nzv-1 and Nzv-2, which control virus production (Datta and Schwarz, 1977). It is not known whether the lack of virus-repression results from a specific integration site, or from sequences present in the viral genome. Genetic information for a different type of xenotropic virus is present in most strains of mice, but expression is repressed. When fibroblasts from such strains, e.g. BALB/c, are treated with IrdU or BrdU, production of the repressed xenotropic virus is induced in some of the cells (Lowy et al., 1971; Aaronson et al., 1971). The mechanism for this induction is still poorly understood. Suboptimal doses of IrdU followed by UV treatment lead to virus induction, suggesting that chromosome brakes may be involved (Teich et al., 1973). Other agents which have been found to be virus-inducers in fibroblast cultures include inhibition of protein synthesis (Aaronson and Dunn, 1974), L-canavanine (Aksamit and Long, 1977), hydroxyurea (Rascati and Tennant, 1978) and 5-azacytidine (Groudine et al., 1981; Niwa and Sugahara, 1981). We have been interested in the induction mechanisms operating in lymphocytes which are the target cells of leukemogenesis. We found that induction of xenotropic virus occurs in cells during B-cell differentiation (Moroni and Schumann, 1975; Moroni et al., 1978). This can be shown by culturing spleen-of lymphnode cells *in vitro* with B-cell mitogens, such as bacterial lipopolysaccharides, lipoprotein or tuberculin, which all trigger B-cell differentiation. Induction was enhanced by BrdU (Moroni et al., 1975). There is evidence that virus induction is linked to the process of differentiation itself: 1. When B-cell mitogens, such as dextran sulfate, lacking the capacity to induce terminal differentiation are used, no induction is seen (Moroni and Schumann, 1978). 2. CBA/N mice show a recessive sex-linked defect in B-cell differentiation. When F_1 animals in a cross with wild type mice are examined individually, only the male animals exhibit B-cell differentiation and virus-induction (Phillips et al., 1977). 3. LPS-induced B-cell differentiation can be blocked by prior treatment of B-cells with anti-μ serum. When this is done, virus induction is also impaired (Stoye and Moroni, in preparation). In a genetic cross (Stoye and Moroni, 1983) involving inducible BALB/c mice and non-inducible 129 mice, induction by mitogen as well as the BrdU-amplification effect segregated as a single trait, closely linked if not identical to the locus Bxv-1 which controls virus-induction by fibroblasts, and was discovered by Kozak and

Table 1. Cell type specificity of the induction of xenotropic and ecotropic endogenous viruses

	Xenotropic virus			Ecotropic virus		
	B-cell	T-cell	Fibro-blast	B-cell	T-cell	Fibro-blast
B-cell mitogen	ind.	—	—	—	—	—
T-cell mitogen	—	—	—	—	—	—
BrdU	ampl.	—	ind.	—	—	ind.

ind.: induction
ampl.: amplification
—: no effect

Rowe (1980). In our cross, we indentified a second inducible locus (Bdv-1), unlinked to Bxv-1, which controls the induction of a defective virus (see below), and is also induced by LPS (Stoye and Moroni, 1983). We view Bxv-1 and Bdv-1 genes as viral markers integrated in those regions of the chromosome active in B-cell differentiation. It will be interesting to learn what cellular functions are encoded in the DNA adjacent to these viral loci.

b. Ecotropic viruses

Mice carrying ecotropic viruses fall into two groups. Some (AKR, C58) produce virus spontaneously, which leads later in life to leukemia. Other mice (BALB/c, C57Bl/6) do not express virus, but can be induced to do so by *in vitro* treatment of their fibroblasts by IrdU. Induction is controlled by a single dominant locus (Stephenson and Aaronson, 1972) mapping on chromosome 5 (Kozak and Rowe, 1979). Interestingly, no ecotropic virus is induced in B-cells under conditions that induce xenotropic virus. Table 1 summarizes the induction pattern for ecotropic and xenotropic viruses. Virus production appears to be virus type- and cell typespecific and the observed patterns raise interesting questions on the relationship between the differentiation stage of a cell and virus expression.

c. Defective viruses

Most endogenous viruses are defective and their analysis is difficult in the absence of provirus-specific assays. Eventually, monoclonal antibodies or specific DNA-probes may provide the necessary tools. The most challenging question at present is to identify and induce the (presumably defective) virus which is involved in the recombinational event which generates the leukemogenic dual-tropic virus. We have demonstrated the induction of a defective virus from strain-129 mice which lack inducible replicating viruses. With BALB/c mice, we have shown that viruses can be induced from B-cells. The first is the xenotropic virus mentioned above, the second is a defective but reverse transcriptase-positive virus. In a genetic analysis, the two loci were found to segregate (Stoye and Moroni, 1983).

While T-cells cannot be induced to produce complete virus, incomplete virus expression from what appears to be defective endogenous genomes has been observed. Thymus T-cells, for example, express constitutively an antigen (G_{IX}), which corresponds to the retroviral gp70 protein (Tung et al., 1975). When mature T-cells are activated by concanavalin A, viral gp70 antigen becomes induced and inserted into the cellular membrane. This can be demonstrated by the fact that activated, but not resting T-cells can be killed by anti-gp70 antibody in the presence of complement. Interestingly, gp70-induction was shown on different subpopulations of T-cells, namely T-helper, T-suppressor, and cytotoxic T-cells (Wecker et al., 1977; Wecker and Horak, 1982; Klenner et al., 1982). As argued above for B-cells, it appears that the induced provirus in activated T-cells lies in a chromosomal region important and perhaps specific for T-cell maturation.

Using a fluorescence-activated cell sorter, Morse et al. (1979) found a gp70 molecule related to the xenotropic virus on lymphocytes of all the strains they tested. The relative amounts in different organs varied in a strain-specific way; induction of this defective virus is under host control. In conclusion, different proviral loci become expressed during the different phases of lymphocyte differentiation. This in turn may favor the recombinational event generating the leukemogenic variants and explain the observed association between leukemogenesis and hyperblastic dysfunctioning of the immune system as observed following graft-versus-host reactions (Schwartz and Beldotti, 1965).

Oncogene activation

Following infection by sarcoma- and acute leukemia viruses, the viral oncogene becomes expressed and directs malignancy. After it was realized that viral oncogenes are transduced host genes, the question arose wheter these cellular host "oncogenes" – more appropriately called proto-oncogenes – might also become activated and play a role

in non-viral malignancies. Recent evidence suggests that this may be the case.

The oncogenes known at present fall into two, partially overlapping groups. The first group contains the oncogenes present in sarcoma or acute leukemia viruses. Examples are the *src* gene of Rous sarcoma virus, *myc* of avian myelocytomatosis virus, *mos* of mouse Moloney sarcoma virus. The second group contains genes which have been identified by their ability to induce foci of transformed cells following transfection into suitable fibroblast cells (NIH 3T3 cells). Many human tumor lines, but also primary human tumors contained oncogenes, as revealed by transfection experiments, amongst them lung-, colon-, bladder-mammary-tumors and leukemias (Shih et al., 1981; Murray et al., 1981; Lane et al., 1981; Lane et al., 1982; Perucho et al., 1981; Pulciani et al., 1982). The human oncogenes derived from bladder carcinomas have been cloned. They were found to be homologous to the oncogene from the Harvey sarcoma virus (Parada et al., 1982; Goldfarb et al., 1982; Santos et al., 1982).

In the following section I will summarize the evidence that cellular oncogenes become activated in cancer, and concentrate on the *myc* gene, one of the best studied examples.

The activation of the cellular *myc* gene was first shown in experiments involving avian leukosis virus (ALV). This virus, lacking an oncogene, induces B-cell lymphomas after a long latency. It turned out that the ALV genome is integrated in the tumor DNA near the cellular *myc*-gene. The integrated virus contains promoter sequences at its 3' end, which can direct transcription into flanking host sequences (Hayward et al., 1981). This induction of *myc* by nearby ALV genes is called promoter insertion. The viral promoter forms part of a larger sequence, which occurs at both ends of the integrated virus and resembles the insertion-like elements (IS) identified in prokaryotes (see Diggelmann, this volume). This suggests that integration of IS-like elements near an oncogene may trigger its expression. Indeed, Rechavi et al. (1982) recently found that one allele of the *mos* gene in a murine plasma-cytoma carried at the 5' end an insertion with direct and indirect repeats typical for IS-elements. It will be interesting to see if this observation is a general one. Evidence suggesting a possible role of the *myc* gene in human B-cell tumors has recently been presented. In man, the *myc* gen is located on chromosome 8. In Burkitt's lymphoma, as well as in other B-cell neoplasias, there is a typical translocation involving chromosomes 8 and 14, or, more rarely 8 and 22. Part of the long arm of 8 is translocated to chromosomes 14 (see Müller, this volume). Molecular cloning experiments show that in this translocation the *myc* gene, located on chromosome 8, becomes joined to the H-chain locus which is active in immunoglobulin-producing B-cells. In the more rare t (8; 22) translocation *myc* appears to become translocated to the lambda L-locus (Dalla-Favera et al., 1982; Taub et al., 1982; Nell et al., 1982). The translocation of the *myc* gene to the H-chain locus is also observed in plasmacytomas of mice which show a typical t (15; 12) translocation. In mice, *myc* is located on chromosomes 15 and the H-chain gene on chromosome 12 (Taub et al., 1982; Shen-Ong et al., 1982). In conclusion, the *myc* oncogene, known to cause experimental myelocytomatosis following MC29 virus infection is involved in a specific and virtually pathognomonic chromosome translocation in human and murine leukemias.

Activated oncogenes in human leukemias have also been detected using the NIH-3T3 transfection technique. Lane et al. (1981) described 5 oncogenes derived from human and murine T- and B-cell leukemias and lymphomas. Interestingly, different oncogenes were associated with pre-B, intermediate-B, mature-B, intermediate-T and mature-T cell tumors. It remains to be seen whether these genes are actually contributing to the malignant phenotype of these leukemias and lymphomas, or whether their activation occurs normally in differentiation and becomes "frozen" if the cell is immortalized by the transforming event.

In conclusion, the study of retroviruses and the development of suitable transfection techniques has led to the discovery of a fascinating family of genes, the oncogenes. There is hope that the elucidation of their function both in normal cells and experimental tumors will contribute to the understanding of some pathogenetic mechanisms underlying human cancer as well.

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