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Interactions between Exogenous and Endogenous Retroviruses

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Abstract

Retroviruses are distinguished from other viruses by several features. Notably, some retroviruses are present as normal elements in the genomes of virtually all vertebrates (endogenous proviruses). Others are exogenous, i.e. horizontally transmitted agents, many of which cause fatal diseases. The endogenous retroviruses are genetically transmitted and to a large extent their significance is uncertain. However, there is evidence suggesting that they contribute to the development of diseases in several animal species. Most importantly, some endogenous retroviruses are capable of interacting with exogenous counterparts through a variety of different mechanisms with serious consequences to the host. Conversely, others are advantageous in that they protect against exogenous retroviruses. In this review various types of interactions between endogenous and exogenous retroviruses are discussed, including receptor interference, recombination, phenotypic mixing, immunological interactions and heterologous *trans*-activation.

Retroviruses are single-stranded RNA viruses with a DNA intermediate form. During infections with retroviruses their genomes are incorporated into the chromosomes of the infected cells. If integration takes place in germ line cells (oocytes) or early embryos, the retroviral genes are 'endogenized', i.e. they have become a part of the host genome [for more comprehensive information on endogenous retroviruses, see for example 12, 77, 87]. Most likely, endogenous retroviruses in this way are the footprints of ancient retroviral infections. Alternatively, endogenous as well as exogenous retroviruses derive from a common genomic ancestor [17, 19].

The genomes of retroviruses contain a regulatory region in both ends, i.e. the upstream and downstream long terminal repeats (LTRs). In between the LTRs there are at least three major genes, designated *gag*, *pol*, and *env*,

encoding for internal structural proteins, reverse transcriptase and envelope proteins, respectively [11]. Some retroviruses, such as the human T cell leukemia viruses (HTLVs), are more complex in their composition allowing for the production of additional proteins [14].

Endogenous retroviruses are inherited in a classical Mendelian fashion. They are present in virtually all vertebrates and retroviral-like elements have even been detected in lower animals such as *Drosophila* [20]. Although most endogenous retroviruses probably have been normal genomic constituents for millions of years, the acquisition of new endogenous retroviral sequences is an ongoing phenomenon as suggested by observations of *de novo* integration in germ line cells of mice [52, 79]. Most endogenous retroviruses contain stop codons in the reading frames or they are truncated, precluding their expression

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as viral particles. However, several animal species such as chickens [12], mice [12] and baboons [81] harbor endogenous retroviruses which can produce infectious particles.

To a large extent, the possible significance of endogenous retroviruses in the development of diseases is obscure but there is increasing evidence that they are capable of inducing diseases or modifying disease courses [43, 67, 77]. Most importantly, they can interact with exogenous counterparts through a number of different mechanisms. In the following, the nature of these interactions and their consequences are discussed. The aim of this review is to focus attention upon endogenous retroviruses as factors playing decisive roles in the development and outcome of infections with exogenous retroviruses and if possible indicate new lines of research within the field of human retroviral diseases.

Receptor Interference and Host Resistance Factors

Receptor interference refers to the inability of a virus to infect cells which already are infected by a virus with the same specificity of the outer surface envelope glycoprotein [86]. Of note, endogenous proviruses are able to protect against infections with exogenous retroviruses carrying related or identical envelope glycoproteins. Findings that preincubation of cells with viral glycoproteins impedes or blocks infection by a virus with a corresponding glycoprotein suggest that competition for receptors is involved in receptor interference [86]. However, this is not the only mechanism of importance. Thus, an avian retrovirus seems to prevent superinfection with related viruses through binding of its glycoproteins to the corresponding receptors in the endoplasmic reticulum [15]. This interferes with the normal translocation of the receptors resulting in their absence on the surfaces of infected cells.

Inherited resistance to retroviral infections, associated with receptor-interfering endogenous retroviruses, has been reported in mice [6–8, 21, 22] and cats [58]. Also chickens harbor endogenous retroviruses involved in receptor interference [65, 69, 75]. Most likely, the primary function of these avian endogenous retroviruses is to prevent reintegration of replication-competent endogenous retroviruses into the host chromosomes [69, 75].

In mice endogenous retroviruses which confer protection against the ecotropic and the polytropic classes of murine leukemia viruses (MuLVs), respectively, have been detected. The ecotropic class of MuLVs is character-

ized by an inability to replicate in cells from other animal species than mouse while the polytropic MuLVs, also known as MCF MuLVs (mink cell focus-forming MuLVs), are recombinant viruses with a broader host cell range [42].

The *Fv-4* gene, detected in populations of wild mice, controls the susceptibility to infections with ecotropic MuLVs [21, 22]. The dominant resistance allele at the *Fv-4* locus is a truncated endogenous retrovirus which encodes for a glycoprotein closely related to ecotropic MuLV gp70 [35]. This glycoprotein seems to be the protective factor acting by receptor interference as suggested by observations with mice transgenic for the *Fv-4 env* gene [50].

Another gene in mice, namely *Rmcf*, has been associated with a restriction in the replication of the polytropic MuLVs [6–8]. The *Rmcf* resistance allele is presumably also an endogenous retrovirus encoding for a glycoprotein which confers protection by competition for retroviral receptors [6, 7]. Alternatively, it is a nonretroviral gene regulating the transcription of a protecting endogenous retrovirus [8].

The degree of resistance against a retroviral infection conferred by receptor interference seems to be correlated with the level of expression of the protecting endogenous retroviral gene [41, 50]. Consequently, information about the transcriptional regulation of these genes would be valuable to have. Of importance, there is no upstream LTR associated with the *Fv-4* resistance allele, implying that its transcription is determined by nonretroviral *cis*-acting sequences [35]. This also seems to be the case with an avian endogenous retrovirus acting by receptor interference [12].

Perhaps protection based upon receptor-interfering endogenous *env* gene products represents an antiretroviral defense mechanism utilized by a wide variety of different vertebrate species. Previous observations have suggested that the human genome contains a variety of sequences related with the human immunodeficiency virus type 1 (HIV-1) *rev* and *env* genes [31]. However, the sequences characterized thus far do not seem to be part of endogenous proviruses; instead they most likely represent the exons of hitherto unknown genes. The possibility that these HIV-related endogenous sequences are involved in receptor interference is unlikely since their relationship with the region of the HIV genome, encoding the surface glycoprotein, is limited.

Whether receptor interference can be utilized as a new concept in the treatment of retroviral diseases is an interesting question. So far, observations with mice offer ther-

apeutic prospects in that grafting of bone marrow cells bearing the *Fv-4* resistance allele into susceptible individuals can protect against the disease induced by Friend leukemia virus [40, 41]. Moreover, evidence has been provided that susceptible cells are able to take up the *Fv-4* antigen from serum resulting in a reduced attachment of Friend virions to these cells [41]. Consequently, there is no need for the *Fv-4* resistance allele to be expressed in all susceptible cells.

Recently, the possibility that other defense mechanisms against retroviral infections also involve endogenous retroviral genes has become more likely with the cloning and sequencing of the murine *Fv-1* gene [5]. This gene confers resistance to MuLV infections by a mechanism different from receptor interference in that its alleles encode the ability to block the replication cycle of certain subclasses of MuLVs at a stage after entry of the invading virus into the target cell. Of interest, there is evidence to suggest that *Fv-1* is derived from the *gag* gene of an endogenous retrovirus. Hopefully, studies of the mechanism by which the *Fv-1* gene product acts will provide clues to the understanding of natural resistance to other retroviruses. So far, there are observations suggesting a significant degree of genetic variation in the susceptibility to infection with HIV [88]. Whether an *Fv-1*-like resistance mechanism is involved in this is an interesting possibility.

Recombination

Retroviruses are characterized by a high frequency of recombination [51]. Accordingly, this mechanism of combining genetic information is believed to play an important role in the evolution of retroviruses although the repair of defects probably is the most important function of retroviral recombination [80]. Normally, virions of retroviruses contain two identical genomes attached to each other in the 5' end. Recombination is dependent upon the copackaging of two different genomes into the same virion. The exchange of genetic information between such two retroviral genomes takes place during reverse transcription after uncoating of the retroviral RNAs [for mechanisms of retroviral recombination, see 32, 78]. Recombinations with single as well as multiple crossovers in different regions of the retroviral genomes have been detected but not all crossovers are functionally compatible. Probably, recombination is a dynamic process resulting in the appearance of new variants with a preferential replication of some recombinants over that of others.

Recombination is important in the pathogenesis of several retroviral diseases. A classical example concerns the development of leukemia by the MCF viruses in certain mouse strains. These transforming viruses arise as a result of recombinations between various endogenous retroviruses, i.e. ecotropic and MCF-like MuLV sequences [42 and references therein]. In addition polytropic MuLVs have been isolated from mice inoculated with exogenous MuLVs [42]. In cats recombinants between feline leukemia virus (FeLV) and endogenous FeLV-like sequences seem to be the proximal pathogens in the development of FeLV-associated diseases [64, 71, 72]. Moreover, recent findings that a considerable number of tumors induced by mouse mammary tumor viruses (MMTVs) contain recombinants of the invading virus and an endogenous MMTV suggest a role of these recombinants in the development of mammary tumors [26].

Apparently, an invading retrovirus can acquire enhanced growth and survival capabilities through recombination with endogenous partners. Most importantly, recombinations involving the *env* gene may result in the appearance of a progeny with a new host cell tropism. For example, a recent study reported the detection of in vitro recombinants of exogenous and endogenous FeLV sequences with tropism for brain capillary endothelial cells and potential neuropathogenic properties [10]. This is of interest given that neurological disease sporadically develops in FeLV-infected cats [60].

Recombination between exogenous and endogenous retroviruses could have significant immunological consequences. Of note, studies in mice [66, 83] as well as cats [71] have indicated that viral progenies lacking neutralizing epitopes emerge upon recombination between an invading retrovirus and endogenous counterparts. Perhaps this helps an infecting retrovirus to escape the immune surveillance of the host and establish a persistent infection.

Recently, recombinations have been detected between endogenous retroviral sequences and the defective MuLV associated with the murine acquired immunodeficiency syndrome (MAIDS) [23]. These recombinations involved the MAIDS virus *gag* gene which encodes for a component with a superantigen activity [33], and their detection raises the question of whether the generation of new superantigen specificities by recombination is implicated in the pathogenesis of MAIDS.

Another aspect is that endogenous retroviruses are capable of repairing defects in exogenous retroviruses by recombination. This can result in the rescue of a defective retrovirus [57, 70]. However, the ease and rapidity of such

a recombinational repair probably depends upon the degree of relationship between the retroviral sequences in question.

Retroviral recombination is also a phenomenon of relevance in other contexts. Regarding gene therapy with retroviral vectors, one of the major safety aspects concerns the risk of formation of replication-competent viruses by recombinational events between the vector and the helper virus [for review, see 13, 30]. However, also endogenous retroviruses of the packaging cell line are of importance as possible participants in recombinational events [30]. Furthermore, recombinations between contaminating replication-competent viruses in the vector preparation and endogenous retroviruses of the recipient are a possibility [16]. Another safety aspect, although of minor importance, concerns the possibility of recombination between endogenous retroviruses of the target cells and the vector [13].

A lack in human organs for transplantations has focused interest upon the possibility of using xenografts from primates and pigs. However, xenotransplantation involves introduction of 'foreign' endogenous retroviruses into a new host. This entails a risk of recombination between these retroviruses and the 'native' endogenous retroviruses of the recipient [74]. Of note, several animal species, including baboons and their close relatives, carry endogenous retroviruses which have the potential of being expressed as particles [81], i.e. a prerequisite for recombinations to take place.

A wide spectrum of endogenous retroviruses are transcriptionally active. For example, several human endogenous retroviruses are transcribed in peripheral blood mononuclear cells [44, 68] as well as brain tissue [68]. Obviously, the expression of a variety of different endogenous retroviral transcripts provides a rich and diverse source for recombinational exchange of genetic information with exogenous retroviruses.

Phenotypic Mixing

Phenotypic mixing refers to the formation of virions containing proteins which are not encoded by the encapsidated viral genomes [89]. In the extreme, viral genomes are packaged into particles consisting of structural proteins entirely encoded by another virus. By phenotypic mixing helper viruses may supply a defective virus with proteins necessary for replication and particle formation [27]. This is also known as complementation. The initial step of a retroviral infection involves interactions be-

tween the envelope glycoproteins of the invading virus and the corresponding cell surface receptors. Consequently, the formation of viral particles containing envelope glycoproteins encoded by another virus may provide these particles with a novel host cell tropism.

Phenotypic mixing between distantly related retroviruses is usually confined to envelope glycoproteins [51]. There are several observations of phenotypic mixing between endogenous and exogenous retroviruses. For example, HIV is capable of utilizing surface glycoproteins from endogenous MuLVs resulting in the appearance of pseudotypes with a novel host cell range, including CD4⁻ cells and various animal cells [9, 47, 55, 76]. There is also an accelerated replication of HIV in CD4⁺ cells coinfecting with MuLVs, perhaps reflecting a more efficient adsorption of HIV pseudotypes to the target cells [9, 55, 76]. Obviously, the potential of human exogenous retroviruses to form pseudotypes with envelope glycoproteins of endogenous retroviruses raises questions with regard to the value of animals as model systems for studies of human retroviral infections. Whether human exogenous retroviruses also participate in phenotypic mixing with endogenous counterparts from the human genome is not known. By analogy with the above observations, this possibility can certainly not be dismissed.

Since phenotypic mixing does not involve exchange of genetic information, permanently modified viral progenies are not produced. Nevertheless, phenotypic mixing between exogenous and endogenous retroviruses might have important consequences through the formation of virions with an expanded host cell range, perhaps allowing for the transmission to other species. Moreover, an invading retrovirus, which has acquired envelope proteins encoded by an endogenous retrovirus, may escape attack by the host immune system. Finally, the rescue of a replication-defective provirus by phenotypic mixing may provide this provirus with an opportunity to recombine with the helper virus.

Immunological Self-Tolerance, Epitope Restriction and Antigenic Mimicry

Antibodies against various endogenous type C retroviruses are naturally occurring in various inbred mouse strains [1, 49, 62]. Natural antibodies against retroviral components are also common in higher primates [18]. The specificity of these antibodies are restricted to epitopes on the surface glycoprotein and the transmembrane protein [18, 34] while there seems to be self-tolerance to

other endogenous retroviral gene products. Since some of the naturally occurring retroviral antibodies in mice and primates have neutralizing capacity they could be acting as a defense mechanism against exogenous retroviruses [18, 34].

Reactivity against one or a few of the major antigens of HTLV [46] and HIV [37, 82], most frequently *gag* gene products, is detectable in a relatively small fraction of sera from healthy humans with no other evidence of having a retroviral infection. Most likely, some of these seroindeterminate reactivities are due to autoantibodies directed against endogenous retroviruses [46, 82]. This assumption is supported by observations that a protein, encoded by an HTLV-related human endogenous retrovirus, may act as an autoantigen [4].

The genomes of retroviruses contain conserved stretches. In particular, certain stretches within the *pol* gene are conserved [38, 61] but also a stretch in the transmembrane protein seems to be subjected to a limited degree of variation between different retroviruses [61]. There is evidence that the occurrence of identical or related epitopes between endogenous and exogenous retroviruses results in a restricted ability to raise an immune response against the exogenous retrovirus in question [59]. Observations with avian leukosis viruses indicate that endogenous retroviruses interfere with the ability of the immune system to eliminate invading retroviruses [75, 85]. Briefly, the envelope glycoproteins of endogenous avian leukosis viruses contain epitopes which are also present in the exogenous avian leukosis/sarcoma viruses. Chickens carrying these endogenous retroviruses do not respond with the production of antibodies to the common epitopes upon infection with the exogenous retroviruses. This is opposed to chickens lacking the endogenous *env* loci in question. Consequently, there is a lower susceptibility to infections with the avian leukosis/sarcoma viruses in the latter group of chickens.

A restriction in the number of available epitopes of an invading retrovirus could also have implications for the development of vaccines against that virus. Moreover, the occurrence of shared or cross-reactive epitopes between endogenous and exogenous retroviruses represents a potential source of false-positive or indeterminate reactivities in the serodiagnosis of retroviral infections [46, 82].

A breakdown of self-tolerance through antigenic mimicry may occur if an infectious agent is distinct from but sufficiently related to host epitopes to induce a cross-reacting immune response. A number of different infectious agents possess stretches of amino acid homologies with host cell components suggesting a potential for

induction of autoimmunity [63]. Whether exogenous retroviruses are capable of inducing autoimmunity as a result of an antigenic relationship with endogenous counterparts is not known. Recently, this possibility was examined by immunization of rats with MuLV [29]. Autoimmune diseases were not observed in these rats, but they responded with the production of antibodies possessing a reactivity to proteins encoded by their own endogenous retroviruses. Interestingly, HIV-1 infections are accompanied by the appearance of autoantibodies. These autoantibodies are primarily reactive with regulatory molecules of the immune system [73]. Future studies might reveal whether autoimmune responses against endogenous retroviral antigens can also be detected during retroviral infections.

Superantigens

Superantigens are substances characterized by an ability to stimulate and/or delete T cells with particular V β chains [2, 56]. They are subdivided according to their origin. The exogenous (microbial) superantigens include various bacterial substances but also several viruses such as infectious MMTV [2, 56], the defective MuLV strain associated with MAIDS [33] and HIV [48] have been linked with the production of factors possessing superantigen activity. So far, endogenous superantigens have only been detected in mice. The murine self superantigens are encoded by an open reading frame in the 3' LTR of endogenous MMTV. The human genome does not seem to encode homologues of the murine endogenous superantigens [3] although human T cells respond to MMTV superantigens [45]. Recently, isolation of a human endogenous retroviral sequence perhaps encoding for a superantigen was reported [36], but confirmation of its biological activity is needed.

Exogenous MMTVs are transmitted by the milk. After having crossed the gut of the suckling mouse, they infect susceptible target cells, presumably B cells in the Peyer patches [28, 39]. Most likely, the next steps in the establishment of the infection involve expression of viral superantigen on the surface of the infected cells resulting in stimulation and activation of T cells with the appropriate V β chains. These stimulated T cells are believed to cause a local expansion of infected B cells followed by spreading of the infection to other lymphocyte subsets and finally to the mammary glands [84]. A different scenario with superantigen-stimulated T cell subsets serving as the proximal targets of MMTV has also been proposed [25].

Irrespective of the exact nature of the initial steps of the infection, mouse strains in which T cell V β subsets have been depleted by self superantigens are resistant to infections with MMTVs encoding superantigens of the same specificities as those of the self superantigens [25, 28]. Whether such a mechanism protects against infections with other retroviruses than MMTV is still uncertain. Future findings that human retroviruses utilize superantigens might serve to stimulate research into new therapies based upon specific depletion of the proximal target cells.

Heterologous *Trans*-Activation and Possible Interactions on the Posttranscriptional Level

Heterologous *trans*-activation may occur in cells harboring two different viruses, i.e. the transcription of one of the viruses is activated by transcriptional factors produced by the other one. Whether the transcriptional factors encoded by various exogenous retroviruses *trans*-activate endogenous retroviruses is not known. However, exogenous retroviruses may indirectly cause activation of endogenous retroviruses through activation of various cellular genes. Notably, the HTLV *tax* protein *trans*-activates genes encoding cellular transcription factors [24].

Apparently, the human genome does not contain endogenous homologues of *tax* [cited in 43]. On the other hand, a recent study reported the detection of a double-spliced human endogenous retroviral transcript, encoding a protein related with *rev* of the lentiviruses and *rex* of HTLV-I [53, 54]. Further studies are needed to reveal the activities of this endogenous factor, including possible modulating effects on the nuclear export and processing of transcripts of human exogenous retroviruses.

Concluding Remarks and Perspectives

Endogenous and exogenous retroviruses may interact through a variety of different mechanisms. There is evidence that endogenous retroviruses affect the susceptibility to retroviral infections and the courses of the retroviral diseases. That is, some endogenous retroviruses are capable of enhancing the pathogenicity of exogenous retroviruses while others confer protection against infections with highly pathogenic exogenous counterparts. Most strikingly, envelope glycoproteins of endogenous retroviruses can confer protection against retroviral infections, but they have also been associated with a restriction in the ability of the immune system to combat such infections. Further, there are examples that individual variations in the susceptibility to retroviral infections reflect genetic variation at certain endogenous retroviral loci.

To a large extent, the issues of this review have been based upon observations with animal retroviruses, in particular murine retroviruses. Still the question of corresponding interactions between endogenous and exogenous retroviruses taking place in man essentially remains unexplored. A complicating aspect concerns the large number of human endogenous retroviruses and their diverse nature.

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