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Review Article

Immunosuppression Induced by Avian Leukosis and Sarcoma Virus

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Abstract

Avian Leukosis/Sarcoma Viruses (ALSVs) belong to the genus *Alpha retrovirus* of family Retroviridae. ALSVs that occur in chickens have been divided into 6 envelope subgroups (A–E and J) based on the differences in their viral envelope glycoproteins. ALSV infections usually induce several kinds of neoplasm of infected hosts which lead to severe morbidity and mortality. Most importantly, hosts infected with ALSVs often develop immunosuppression, similar as Acquired Immunodeficiency Syndrome (AIDS) caused by Human Immunodeficiency Virus (HIV) in human. Immunosuppression can be induced by different subgroups of ALSVs in different mechanisms. Some possible mechanisms were reviewed in this short paper.

Keywords: Avian leukosis/Sarcoma virus; Retrovirus; Immunosuppression; Mechanism

Introduction

Immunosuppression means impairment of the immune system that causes a weaker or even no response to antigens in hosts. Studies have demonstrated that many factors cause immunosuppression, including nutritions, diseases, stresses, microbes and so on, in which virus-induced-immunosuppression is most common and especially severe. Immunosuppression associated with a virus infection was first described in patients who lost their tuberculin sensitivity during and after measles about 100 years ago. It was not until the occurrence of Acquired Immunodeficiency Syndrome (AIDS) that virus-induced immunosuppression has attracted a renewed attention and detailed investigation [1-4]. Immunosuppression can be induced through diverse mechanisms, including direct toxicity to target cells, fetal infection leading to tolerance, viral proteins acting on infected cells or uninfected bystander cells leading to cell death and aberrant production of cytokines, and suppressor T lymphocytes.

Avian Leukosis/Sarcoma Viruses (ALSVs) are a group of retroviruses frequently causing immunosuppression [5,6]. Members of this group of viruses have similar physical and molecular characteristics and share a common group-specific antigen envelope glycoprotein. Infection of cells is dependent on the presence, in the cell membrane, of host gene-encoded receptors specific for particular virus envelope subgroups and on fusion of viral and cell membranes [7]. The virion envelope contains 2 glycoproteins encoded by the env gene: SU (surface, gp85), the viral surface knob-like structure, that contains the receptor binding site and determines viral envelope subgroup specificity of the ALSV; and TM (Transmembrane, gp37), harboring functional elements required for fusion with host cells, a fusion peptide, two Heptads Repeats (HR) and a Trans Membrane region (TM) [8,9]. Using interference patterns of different strains of leukosis virus against different strains of Rous Sarcoma Virus (RSV), ALSVs that occur in chickens have been divided into 6 envelope subgroups, designated A, B, C, D, E and J [6,10-12]. A few studies have revealed some possible mechanisms of ALSVs-induced immunosuppression, but detailed mechanisms for immunosuppression induced by these viruses have not been fully understood.

ALSVs-induced immunosuppression

In addition to inducing tumor growth and subsequent mortality, ALSVs impart immunosuppressive effects that lead to decreases in the immunologic function and productivity. Chickens that are infected congenitally with ALV become immunologically tolerant to the virus, that they do not develop immune responses to the virus, but develop a persistent viremia in the absence of neutralizing antibodies [13,14]. The younger the chicken at infections, the longer the duration of a viremia, and the longer for the antibody to develop. Chickens with a tolerant viremic infection are more likely to develop neoplasms because of more virus loads. Infection with ALV can lead to a depression in primary and secondary antibody responses and cell-mediated immunity [15] of hosts to unrelated antigens, making it easy for secondary infections or opportunistic pathogens to develop clinical features. This will result in a severe co-infection phenomenon which increases morbidities and mortalities [16,17]. Decreases in productivity performed as decline in weight gain, egg production, fertility, and hatchability directly cause tremendous economic losses.

Target cells of subgroup J ALV are myeloid cells and immunosuppression induced by ALV-J appears to be associated with both T and B cells [11,18]. Viruses of other subgroups, such as A, B, C, and D, mainly infect B lymphocytes [12]. They are well known potent inducers of wasting disease and anemia, the severity of which, however, appears to be strain dependent. The genetic sequences of the eve loci are related to subgroup E of ALVs and are present as either complete or defective genomes in almost all normal chickens [19-23]. Viruses of subgroup E are of equally important in causing immunosuppression alone and affecting the immunosuppression by exogenous viruses [24-26].

Immunosuppression mechanisms caused by different ALSV subgroups

Acute transforming ALSVs contain viral oncogene in their

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genomes, and they induce neoplastic transformation, in vivo or in vitro, within a few days [27,28]. While slow transforming ALVs do not carry viral oncogenes and they induce tumors by a "promoter insertion" or a related mechanism that activates a cellular oncogene to bring about neoplastic transformation and development of tumors over many weeks or months [8, 29-31]. There are two distinct ways to cause immunosuppression in acute transforming process of tumor genesis different from slow transforming ALVs. One is immunosuppression caused directly by tumor related antigens [32], and another is immunosuppression caused by the induction and activation of suppressor T lymphocytes and macrophages. Suppressor cells play their inhibitory effect via an interaction between suppressor cells and effect cells or through inhibiting factors [32].

Subgroup B and D ALVs are capable of inducing Cytopathic Effects (CPEs) upon infection of cultured avian cells [33,34]. The CPE is explained by use of a death receptor for subgroups B and D, designated TVB^{s3}, as a Tumor Necrosis Factor (TNF) receptor-related death receptor with a cytoplasmic death domain [33, 35-37]. This is most possibly similar to immunosuppression caused directly by tumor related antigens. Symptoms of the disease induced by viruses of ALV subgroup C are most obvious, and a key feature was a depletion of B lymphocytes in the thymus, bursa and spleen within 2 to 3 weeks after hatching. The receptor for the subgroup C ALV, TVC, is related to mammalian butyrophilins, members of the immunoglobulin super family [38]. Although a documented cythopathogenicity of subgroup C to DF-1 cells indicates that some death-promoting activity of the TVC receptor might be stimulated upon binding of the retrovirus, the signaling pathway might be different from those activated by subgroups B and D [39]. However, the direct toxic effect of ALSV to infected cells may not be a principal cause of lymphoid tissue depletion; more probably, uninfected bystander cells are attacked in an indirect way as has been shown in an anther retroviral infection. Studies from HIV indicated that the virus infects CD4+ T helper lymphocyte (Th) and kills infected cells via Cytotoxic T Lymphocyte (CTL)-mediated mechanisms [1,40]. More seriously, viral Env glycoproteins trigger autophagy in uninfected bystander CD4 T cells, leading to apoptosis and thus contributing to a large loss of Th lymphocytes [41-43]. In fact, HIV or SIV infection causes a universal activation of all lymphocyte population (CD4+, CD8+, NK, and B cells) and a high proportion of activated cells undergo rapid apoptosis. Due to the vital role of these cells in regulating and amplifying the immune response, any decline in their number results in deficiencies in both humeral and cell-mediated immunity. Whether ALVs kill uninfected by stander cells via the same manner as HIV still needs further proofs. Binding of HIV-1 Env to both a primary receptor (CD40) and a co-receptor (mainly CCR5 and CXCR4) on the surface of susceptible cells trigger autophagy in uninfected bystander CD4 T cells, which most likely contributes to an immunodeficiency [41]. CD4 is also a member of the immunoglobulin super family. Thus viruses of ALV subgroup C most possibly share the similar mechanism as HIV-1 [41].

Previous studies showed that subgroup A ALV might induce the least immunosuppression in vivo. The receptor for subgroup A ALV, designated TVA, is related to the human low-density lipoprotein receptor [44,45]. Congenital infection with Rous-Associated Viruse-1 (RAV-1) caused no detectable immunodepression during the early and late stages of infections [46], but affected a T cell population during the advanced stage of the disease [47]. Besides, only RAV-1 infection can cause immunodepressions in chickens that lack endogenous virus gene expressions [48,49].

Apoptosis can be induced by binding of a soluble ALV-E Surface envelope protein (SU) to its receptor, at least in quail or turkey cells. Cellular receptors for the noncytopathic subgroup E of ALV (ALV-E), TVB^{T}, a turkey subgroup E-specific ALV receptor, and TVB^{S1}, a chicken receptor for subgroups B, D, and E ALV, are functional death receptors that can trigger cell death by apoptosis [33]. Except cell death induced by subgroup E ALV, the normal presence of ev loci may suppress the immune response to some exogenous ALVs by inducing partial immunological tolerance [25,26,50]. Thus, the presence of the ev loci makes an increased incidence of lymphoid leukosis in the field and experimentally [6]. For example, embryonic infection with Rous-Associated Viruse-0 (RAV-0) causes a more persistent viremia and more neoplasms following infection with exogenous ALV [24]. Similarly, expression of EV21 ALV by the ev21 locus has a tolerating effect on response to exogenous ALV. Besides, there was a strong additive effect between ev6 and ev9 in reducing an antibody response to exogenous ALSVs infection [51]. But a biological value of endogenous viruses is controversial, because in certain circumstances they can be of value as the presence of ev2 or ev3 has been reported to protect birds from a non-neoplastic syndrome caused by infection with subgroup A ALV [48,49]. Because these ev-genes express endogenous viral protein or complete endogenous virus [23], it has been proposed that the induction of immunological tolerance is attributable to common epitomes between endogenous and exogenous virus [48], which is dependent on the expression of viral proteins, and there is possibly synergistic effect between these proteins [51]. Likewise, embryonic infection with any of an exogenous ALSV subgroup may lead to a tolerance to other subgroups.

Subgroup J ALV mainly attacks myeloid cells, causes a malignant growth, interferes synthesis of functional IL-2, influences mature and differentiation of B and T lymphocytes, and thus induces immunosuppression [52,53]. The immunosuppression mechanism induced by subgroup J ALV might distinct from other subgroups because the host cell receptor used by the subgroup J ALV has been identified as the chicken Na(+)/H(+) Exchanger type 1 (chNHE1) protein [54]. Recent studies in immunosuppression mechanisms in cancers revealed that tumor exosomes play an important role in inducing myeloid-derived suppressor cells, which promote a tumor progression [55-57]. Some researchers have sought clues from exosomes secreted by ALV-J infected cells. Their studies suggested that exosomes secreted by ALV-J infected cells contain virus-encoding Env and Gag proteins and showed similar immunosuppression effects in immune cells as subgroup J ALV. Although the role of exosomes in subgroup J ALV induced immunosuppression is still unclear, chicken biliary exosomes were demonstrated to possess a capacity to influence immune responses of lymphocytes and inhibit subgroup J ALV [58].

Other factors playing roles in immunosuppression

Obviously, cell death, either caused by death receptor-mediated CPEs or Env glycoprotein-triggered autophagy, plays an essential role in inducing immunosuppression in slow transforming ALVs. Damage of immune cells will surely cause aberrant responses of cytokines produced by these cells. Since it is cascade reactions to produce

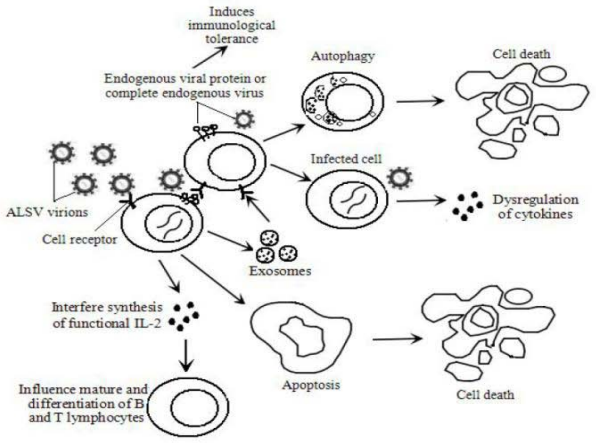

Figure 1: Hypotheses of mechanisms of immunosuppressant caused by ALSVs based on data from the literature.
ALSV visions infect and enter target cells depend on Env-driven fusion of viral and cellular membranes. Immune cells or other cells are affected or killed by the following ways: a: Ev-genes express endogenous viral proteins or complete endogenous viruses that induce immunological tolerance; b: Infected cells express viral proteins or complete viruses trigger autophagy in uninfected bystander; c: Infected immune cells cause aberrant responses of cytokines leading to globe deregulations of cytokines in vivo; d: Exosomes secreted by infected cells show similar immunosuppressant effect in immune cells as visions; e: Cell apoptosis occurs in target cells upon infection by a death receptor; f: The visions attack myeloid cells and cause malignant growth, interfere synthesis of functional IL-2, influence mature and differentiation of B and T lymphocytes.

cytokines and for cytokines to play their role, a globe dysregulation of cytokines in vivo will surely occur. There is also evidence that as AIDS and other retroviruses progress cytokines dysregulation occurs [59,60]. Dysregulation of cytokines in turn aggravate virus-induced immunosuppression. In addition, many DNA viruses produce a number of proteins that act as 'viroceptors', which resemble and compete with cellular receptors of the host, biding the cytokines and reducing its physiological activity. But there is no evidence of such possible manners for ALSVs to perturb cytokine homoeostasis except the damage of immune cells.

Conclusion

Although ALSVs-induced immunosuppression can occur through diverse mechanisms (Figure 1), the virus-encoding Env glycoprotein's play a major role in almost all of the possible mechanisms. Env is not only a key protein for ALSVs to recognize corresponding receptors and enter target cells, but also mediates the death of uninfected bystander immune cells. Further studies on Env-related mechanisms of immunosuppression will be of great value in seeking potential new therapeutic targets direct against immunosuppression. Regulation of autophagy also provided a possible way, but it depends on clear awareness of the role of autophagy in ALSVs infection. Considering the complexity of immunosuppression phenomenon and the complexity of ALSVs group, researches on ALSVs-induced immunosuppression still need much effort. Since ALSV has been intensively used as a model to study retroviruses, there is no doubt that any breakthrough in ALSVs studies will bring new insights into retroviruses.

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