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Review

Decoding arenavirus pathogenesis: Essential roles for alpha-dystroglycan-virus interactions and the immune response

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ABSTRACT

Pathogenesis following a virus infection results from interactions between the virus and its host. The outcome is determined by tipping the balance between virulence of the virus or susceptibility/resistance of the host to favor one or the other. This review focuses on two important members of the Old World arenavirus family: Lassa fever virus (LFV), a robust human pathogen that causes a severe acute hemorrhagic disease; and lymphocytic choriomeningitis virus (LCMV), also a human pathogen but better known in the context of its rodent model. Research with this model has uncovered and illuminated many of our current concepts in immunobiology and viral pathogenesis. Presented here are recent advances that form the framework for a better understanding of how viruses induce and maintain persistent infection as well as for the pathogenesis associated with acute LFV infection. A major component for understanding the pathogenesis of these arenaviruses revolves around study of the interaction of virus with its receptor, alpha-dystroglycan (α-DG).
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Contents

Introduction

Viruses are studied for the diseases they cause, and also used as probes for investigating basic biologic mechanism(s). The arenavirus family contains a number of viruses like Lassa fever virus (LFV), Junin, Machupo, Guanarito, and Sabia—important human pathogens that cause hemorrhagic fever and a high incidence of death. Also in this group is lymphocytic choriomeningitis virus (LCMV), which can cause human disease but is best known for its use in research that has successfully uncovered much of our current knowledge of viral pathogenesis, viral persistence and a variety of areas of immunobiology including: immunologic tolerance, major histocompatibility complex (MHC)-based recognition, CD8 and CD4 T cell activity, T cell exhaustion, T and B cell-mediated immune memory, immune-complex disease and virus-induced alteration of cellular differentiation ("luxury") functions.

The arenaviruses were initially subdivided into two major groups based on serologic typing and phylogenetic evidence. This grouping into Old World arenaviruses (LFV and LCMV) and New World arenaviruses (Junin, Machupo, Guanarito, and Sabia) (Fig. 1A) represents a distinction that has held up to study by genome sequencing and monoclonal antibodies. The natural reservoirs of arenaviruses are selected rodent species, in which the viruses are most often maintained as an asymptomatic, persistent infection that is transmitted primarily by vertical/congenital routes. Spread to humans is by contact with excreta from infected rodents or with infected

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blood from patients. In the case of LCMV, transmission has also occurred via laboratory accidents involving infected cell culture material (i.e., LCMV infected cultures fail to exhibit evidence of cytopathology), contact with asymptomatic pets (e.g., hamsters) that are persistently infected with the virus, and by transplant-associated infection (in immunocompromised patients). Indeed, arenaviruses cause little or no toxicity to the cells they infect. The cell and tissue injury–as well as resultant disease–associated with infection are instead caused largely by activity of the immune system of the host, whose antiviral response produces factors that act against and damage virus-infected cells. An additional factor in pathology is the displacement of cellular molecules that are normally attached to cellular receptors by viral proteins; this can result in conformational changes that cause the cell membrane to become fragile as well as interference with normal signaling events.

Interestingly, although the arenaviruses naturally and preferentially exist in a persistent state within their natural rodent hosts, the first arenavirus was isolated from a human (CG) who died of infection during an outbreak of St. Louis encephalitis. Specifically, LCMV was isolated by Charles Armstrong from a monkey that had been used as a vehicle for passaging the infectious agent from this patient. The newly isolated virus passed through a Berkefeld N filter and, when injected intracerebrally (i.c.) into sentinel adult mice, caused rapid onset (within 6 to 9 days) of a central nervous system (CNS) disease that was characterized clinically by seizures and death (Armstrong and Lillie, 1934). The histologic portrait was of lymphocytic infiltration in the leptomeninges and choroid plexus which led to the virus' name lymphocytic choriomeningitis virus (LCMV). On the basis of the clinical incubation course, routes that caused infection, results of non-overlapping antibody neutralization assays, and histopathologic picture of CNS infection, LCMV was swiftly separated from the virus that was responsible for St. Louis encephalitis. Two years later, Eric Traub identified a persistent viral agent dwelling in white mice without causing them apparent harm (Traub, 1935). That virus, isolated by Traub through inoculation of other adult mice which did not previously carry the virus, mimicked Charles Armstrong's isolate. Both the prototype neurotropic LCMV Armstrong virus (ARM 53b) and the prototype viral isolate from persistently infected mice (Cl 13) were cloned and sequenced four decades later (Salvato et al., 1988, 1989).

Arenavirus binding to a cellular receptor and its entry into the cell are initiated by the virus envelope glycoprotein (GP). This protein is first synthesized as a single polypeptide, the GP precursor (GPC), and then undergoes proteolytic processing by the cellular proprotein SKI-1/S1P (convertase subtilisin kexin isozyme-1/site-1 protease) resulting in two proteins: GP1 and GP2. GP1 is located on the GP spikes that surround the virus, and interacts with its receptor on the host cell's plasma membrane (Fig. 1A). GP2 is the transmembrane protein that anchors GP1 to the virus surface. Virus binding to cellular receptors is the key determinant of the physiologic outcome of infection. Alpha-dystroglycan (α-DG) has been identified as the cellular receptor for the Old World arenaviruses (LFV, LCMV, Mopeia, Mobala, and presumably Lujo virus), as well as for the New World Clade C arenaviruses Latino and Oliveros (Fig. 1B) (Cao et al., 1998). The receptor for the New World Clade A and B arenavirus is transferin receptor-1 (Radoshitzky et al., 2007). In this review, we will discuss the mechanisms of infection and pathogenesis of the two best studies of the Old World arenaviruses, LFV and LCMV.

In vivo selection of LCMV variants and molecular and biologic mapping: a single amino acid change in viral GP1 and another in the viral polymerase determine whether the virus causes an acute self-limiting infection or a persistent infection

When LCMV infects its natural murine host, virus variants are generated via organ-specific selection (Fig. 1C) (Ahmed and Oldstone, 1988). Variants selected in the CNS are markedly dissimilar to those selected in lymphoid tissues and cells (spleen, lymph nodes, dendritic cells [DCs], CD4 and CD8 T cells) at both the biological and chemical levels. Inoculation with ARM 53b–the virus cloned from the original Armstrong isolate after multiple mouse-brain passages–into adult immunocompetent mice subcutaneously (s.c.), intraperitoneally (i.p.), or intravascularly (i.v.) leads to rapid emergence of virus-specific MHC-restricted T cell responses in which CD8 T cells attack and remove the virus-infected cells that serve as "factories" that produce infectious virus. This results in rapid purging of the virus and clearance of the infection. The result is quite different when ARM 53b is administered intracerebrally (i.c.). Again, virus-specific CD8 T cells are generated, as i.c. inoculation breaks through the blood–brain-barrier and the virus is thus again introduced peripherally. At the same time, however, brain cells–in particular those of the leptomeningeal and choroid plexus cells–become infected. Ultimately, the virus-specific CD8 T cells migrate to the CNS and interact directly with virus-infected cells (in the leptomeninges, choroid plexus, and endothelium), causing a lethal damage. Specifically, they release cytokines and chemokines that attract polymorphonuclear and mononuclear myeloid cells. The latter cell types can destroy cells and in addition they release cytokines/chemokines, which leads to an increase in intracerebral pressure that kills the host (Kim et al., 2009). In the case of s.c., i.p., and i.v. inoculation of ARM 53b, CNS injury and host death are avoided because the cytotoxic T lymphocytes (CTLs) are generated before the virus can infect CNS cells.

Organ-specific virus variants were generated by injecting cloned ARM 53b into newborn mice less than 24 hours old. This resulted in a life-long persistent infection. Virus variants isolated from the CNS of adult mice, in which the virus persistently infects only neurons, were similar to the wild-type ARM strain biologically. That is, these variants (CTL^+P^- viruses) induced a potent and specific anti-LCMV CTL response in adult mice, and the response cleared this infection within two weeks (Fig. 1C). In contrast, isolates cloned from lymphoid tissues and cells, failed to generate a CTL response that was sufficient to clear the virus when injected i.v. into adult immunocompetent mice, and a persistent infection followed (CTL^-P^+ viruses) (Fig. 1C). Viral clones isolated from the CNS of mice originally infected with CTL^-P^+ virus generated revertants with characteristics of the original ARM 53b virus (CTL^+P^- virus). Thus, tissue- and cell-specific selection is important in the evolution of these viruses, and suggests a mechanism to account for the emergence of viral variants in nature.

An analysis of the sequences of over 50 of the lymphoid and CNS variants revealed that CTL^-P^+ lymphoid variants commonly encode an aliphatic small amino acid (predominantly leucine, but occasionally isoleucine or valine), at position 260 of the GP1 protein. In contrast, CTL^+P^- variants have a bulky aromatic phenylalanine at this position of GP1. In addition, sequencing of the ARM 53b CTL^+P^- and Cl 13 CTL^-P^+ variants revealed a difference in the polymerase gene (L) at residue 1079 with ARM 53b encoding a lysine and Cl 13 a glutamine (Salvato et al., 1991). Although variants other than Cl 13 and ARM 53b were found to encode alternative amino acids at various positions of the GP1 or polymerase protein (Salvato et al., 1989, 1991; Sevilla et al., 2000), these variants consistently featured the residue at GP1 position 260 that are consistent with their CTL response and permissiveness status (i.e., positions GP1 260/L 1079: leucine/glutamine in CTL^-P^+ ; phenylalanine/lysine in CTL^+P^-). Multiple studies, including reverse genetics-based screens (Emonet, Sullivan, de la Torre, and Oldstone, unpublished data), have shown that GP1 residue 260 is required for binding to the α-DG receptor on DCs in order to initiate virus-induced immunosuppression. Our knowledge of how residue 1079 causes persistent infection associated with CTL^-P^+ remains more limited; given that the field still lacks a polymerase assay, it has not been possible to map the domains and functions of the LCMV polymerase protein.

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