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Hepatitis A virus binding to its cellular receptor 1 (HAVCR1) blocks T-cell receptor and regulatory T-cell function: A novel viral immune escape mechanism

CD4+ regulatory T cells (Tregs) suppress immune responses and have a crucial role controlling self-tolerance. Pathogens activate Tregs to minimize immune-mediated tissue damage and delay or prevent clearance. For instance, chronic hepatitis C patients have a significant increase in the number of Tregs. In contrast, patients infected with hepatitis A virus (HAV), a Picornaviridae that causes acute hepatitis in humans and enters cells usurping the HAV cellular receptor 1 (HAVCR1), have limited Treg function. HAV-infection induces a poorly understood immunopathogenic processresulting in liver damage and the modulation of allergic and autoimmune responses. HAVCR1 is a significant allergy and autoimmunity determinant in man. Binding of HAV to HAVCR1 expressed on T-cells prevents the activation of the T-cell receptor and the Akt/PI3K pathway. Human Tregs constitutively express HAVCR1, and the HAV-HAVCR1 interaction shuts-off Treg function. Thus HAV infection represents a new paradigm in immune evasion in which the virus functions as an antagonist of HAVCR1 blocking Treg function and inducing a "shock-and-awe" mechanism that overwhelms the immune system with anti-self responses in the presence of low levels of TGF-b, which limits strong T effector responses, and IL-22, which prevents liver damage. We propose that this unique immune evasion mechanism is responsible for the long-lasting modulation of the immune response in HAV-infected individuals, and could serve as a model to develop therapeutic strategies to prevent chronic liver infections, modulate autoimmune and allergic responses, and prevent transplant rejections. Furthermore, a vaccination strategy targeting HAVCR1 to block Treg function may enhance the immune response against problematic antigens.

Biography

Gerardo Kaplan received his doctoral degree from the University of Buenos Aires, Argentina, and performed postdoctoral studies in poliovirus at The College of Physicians and Surgeons of Columbia University. He is a Senior Investigator at CBER, FDA, and his lab is devoted to the understanding of viral cell entry and pathogenesis of hepatitis A virus and Filoviruses. He has published more than 50 papers in peer-reviewed journals and serves in Review Committees at the FDA.

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