

Therapeutic IL-10R blockade

with

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What is known about interleukin (IL)-10?

CM Filippi & MG von Herrath: IL-10 is a cytokine that can be produced by a number of cell types in response to stimulation (1). Among those are antigen-presenting cells (APCs), such as dendritic cells and macrophages, but also T and B lymphocytes. IL-10 inhibits a broad spectrum of cellular immune responses. IL-10 can suppress T cell proliferation and cytokine production, regulate B cell isotype switching, and impair the function of APCs by inhibiting pro-inflammatory cytokine production, co-stim-

ulation, MHC class II expression and chemokine secretion (1-3). The consequence is an impairment of CD4⁺ and CD8⁺ T cell responses. IL-10 has been associated with immunopathology in various immune-mediated and inflammatory diseases. For example, treatment with a combination of anti-IL-10 receptor (anti-IL-10R) monoclonal antibody and toll-like receptor 9 (TLR9) ligands was reported to have potent therapeutic anti-tumor effects (4,5), indicating a role for IL-10 in the pathogenesis of cancer.

Why is IL-10 increased during some viral infections and what are the consequences?

CM Filippi & MG von Herrath: Viruses utilize a variety of strategies, such as the active induction of immune suppression, in order to avoid recognition by the host immune system and establish persistent infection (6-9). Impairment of T cell immunity is a common feature of chronic infections, raising the possibility that mechanisms of immune suppression may be conserved from one virus to the next. Indeed, systemic production of IL-10 is associated with various chronic infections, such as hepatitis C virus (HCV) (10,11), Epstein-Barr virus (EBV) (2,12) and, although more controversial, human immunodeficiency virus (HIV) (13-17). Interestingly, certain

viral genomes such as that of EBV or cytomegalovirus (CMV) can directly encode an IL-10 homologue. A mechanistic explanation why IL-10 is increased during certain viral infections could be the selective elimination of cell types that normally favor the production of antiviral cytokines such as IFN- γ . In this respect, we have recently found that persistent lymphocytic choriomeningitis virus (LCMV) infection was linked to a decline in the number of CD8 α^+ dendritic cells (DCs), which efficiently primed IFN- γ responses by virus-specific CD4⁺ T cells (18). DCs from the CD8 α subset primed IL-10 secretion, preventing viral clearance and therefore enabling viral persistence.

Do you believe that blockade of IL-10R is a good therapeutic approach to treat persistent infections?

CM Filippi & MG von Herrath: Numerous strategies have been developed to increase immunity in chronic viral infections. The goal is to eliminate the persisting virus, or at least reduce the immunopathological consequences of viral persistence. Such vaccination strategies have been combined with direct

antiviral drug treatments, such as protease inhibitors and highly active antiretroviral therapy (HAART) in the case of HIV infection, and interferon administration or ribavirin in the case HCV infection. Although this approach may be effective in some scenarios, it has mostly failed to affect the outcome

of chronic viral infections, as complete elimination of the pathogen has not been established so far.

We and others recently observed that mice chronically infected with LCMV produce high levels of IL-10, which led to the development of a new intervention (18,19). In our study, persistent infection was resolved in the majority of mice treated with a blocking antibody to IL-10R.

What are the next steps for treatment of chronic infections?

CM Filippi & MG von Herrath: Chronic viral infections afflict more than 500 million humans worldwide and can pose severe health problems (20-22). We believe that comparable therapy in humans should primarily target HCV infection, which affects 180 million people worldwide, the majority of whom are chronic carriers susceptible to develop liver cancer. Systemic IL-10 production is increased in persistent HCV infection and is most dramatic compared to other chronic virus infections (10,11). It should thus be determined whether blockade of the IL-10 signaling pathway can restore antiviral immunity in HCV patients, first *in vitro* and then in clinical trials. The next steps would be to combine viral vaccines, antiviral drugs or other antibodies to blocking anti-IL-10R and determine whether synergy can be achieved in eliminating the virus in the absence of unwanted side effects. For example, the IL-10 signaling pathway could be targeted along with that of Programmed Death (PD)-1, a surface molecule whose expression on T cells has been associated with T cell exhaustion and viral persistence in HCV and LCMV infections (23,24). We propose that combination ther-

These mice developed a normal antiviral immune response and returned to a healthy state as a consequence of neutralization of the IL-10 signaling pathway. Furthermore, anti-IL-10R therapy aborted the capacity of CD8 α^+ DCs to induce IL-10 secretion by CD4⁺ T cells, in this way enhancing T_H1/T_C1 immunity. Whether IL-10 affects the outcome of infection, the extent of immunopathology, the occurrence of further complications, or indeed whether it could be the actual cause of persistence is unclear. Regardless, conventional immunotherapy has mostly failed to affect the outcome of chronic viral infections so far, and this work suggests that addressing the problem from a different angle may be a critical step toward successful treatment of persistent infections in humans.

apy using blocking antibodies to IL-10R and PD-L1, the ligand for PD-1, holds great promise for the treatment of persistent viral infections in humans. Such an innovative approach to treating persistent viral infections constitutes a departure from classical vaccine strategies that have been unsuccessful so far. Importantly, targeting host factors that do not directly interact with the virus will limit the possibility that mutated resistant viral strains emerge, as has been the case with certain antiviral drugs.

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