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IFN γ : the Dr. Jekyll and Mr. Hyde of immunology?

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IFN γ is a pleiotropic cytokine that plays a central role in the immune system. It is mostly produced by activated T and NK cells but its effects can be detected in most cell types. Although both pro- and anti-inflammatory properties have been ascribed to IFN γ in different settings, a manuscript by Cunnusamy and colleagues in this issue (1) exposes in the same study the dual antagonistic roles of IFN γ in seemingly similar corneal transplant models.

IFN γ is well-known to be essential to establish Th1-type responses and is most commonly associated with their immunostimulatory and pro-inflammatory effects (Figure 1). Indeed, IFN γ -mediated signaling induces or increases MHC expression on most cell types thereby facilitating antigen presentation, drives expression of co-stimulatory molecules on macrophages, recruits and activates lymphocytes and macrophages, increases the release of inflammatory mediators (2) and can antagonize the differentiation of inducible T regulatory cells (iTregs). Analysis of immune responses in IFN γ - or IFN γ R-deficient mice, or in animals treated with IFN γ -neutralizing antibodies highlights its importance in promoting immune-mediated tumor rejection, resistance to pathogens and acute rejection of MHC class II-disparate skin and pancreatic islet allografts.

However, in addition to the pro-inflammatory properties of IFN γ , additional studies have demonstrated another set of IFN γ attributes that highlight the dual personality of this cytokine (Figure 1). For instance, impairing IFN γ signaling prevented the induction of long-term skin and cardiac allograft survival by costimulation blockade therapies (3) and precipitated the rejection of corneal allografts (1). Thus, IFN γ can have a protective rather than detrimental effect on allografts. At least 2 mechanisms have been reported that may explain the inhibitory properties of IFN γ . First, IFN γ may promote the contraction phase of CD8⁺ T cells during a primary immune response, as has been described following *Listeria* infection, although this effect remains controversial (4). A second property of IFN γ that may play a role in the ability of IFN γ to contribute to the induction of transplantation tolerance is its capacity to induce expression and activation of the enzyme indoleamine 2,3-dioxygenase (IDO) in antigen presenting cells (APCs) and other cell types (5). IDO's activity leads to the catabolism of the essential amino acid L-tryptophan and accumulation of its metabolites, including kynurenine. Tryptophan degradation results in reduced availability of this substrate both for pathogens (which contributes to the antimicrobial response), and for cellular consumption which results in reduced T cell proliferation. In addition, production of kynurenine can lead to T cell apoptosis and clonal deletion, effectively limiting antigen-specific T-cell responses. For instance, IDO is known to participate in maintaining maternal tolerance during pregnancy and in suppressing T-cell responses to major histocompatibility complex (MHC)-mismatched liver allografts and to self-antigens in a type I diabetes model.

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It is appealing to postulate that the net outcome of the apparent paradoxical effects triggered by IFN γ might be dictated by context-dependent triggers. For example, the abundance of pathogen-derived molecules in infectious models can be recognized by pattern-recognition receptors, and lead to activation of an IFN γ -induced pro-inflammatory response by innate immune cells. On the other hand, the tissue injury and/or neoangiogenesis that occur after solid organ transplantation may result in a local increase in tissue-repair molecules, such as TGF β and chemotactic recruitment of monocytes. In this context, IFN γ produced by alloreactive NK and T cells may drive differentiation of such monocytes into immunosuppressive IDO-producing macrophages.

The new findings reported by Cunnusamy and colleagues (1) highlight that IFN γ can have fundamentally opposite roles on the immune response in very similar experimental settings. Disrupting IFN γ signaling prevented generation of allospecific Tregs and precipitated the rejection of fully allogeneic corneal allografts when both MHC and minor histocompatibility (mHC) *loci* were mismatched (C57BL/6 into BALB/c), suggesting a predominantly immunosuppressive role for IFN γ in this context. However, when donors and recipients were mismatched only at MHC (but not mHC) or only at mHC (but not MHC) *loci* (BALB.B into BALB/c, or NZB into BALB/c), IFN γ -impairment promoted graft survival and enhanced antigen-specific Treg immunosuppressive activity, demonstrating the deleterious effect of IFN γ on these grafts. These dichotomous results on regulation and corneal graft outcome suggest that IFN γ signaling may have opposing consequences as a result of very subtle differences in the conditions that initiate the immune response, although the molecular mechanisms driving one pathway versus the other still need to be clarified. Can the seemingly paradoxical role of IFN γ in such only subtly different settings be explained by the recruitment of different innate immune cells, or the cooperation between a different set of cytokines? Is there a threshold in the number of antigen-specific T cell precursors beyond which IFN γ mediates immunosuppression instead of immunopotentialization? The answer to these and other pertinent questions should provide valuable insights into the benefits of IFN γ modulation in clinical setting and transplantation immunology in particular.

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Figure 1.

Antagonistic consequences of IFN γ on immune responses. IFN γ -mediated signaling leads to recruitment and activation of lymphocytes and macrophages, release of inflammatory mediators such as reactive oxygen species and nitric oxide and increased expression of MHC and co-stimulatory molecules on APCs (green arrow 1). Th1 and CTL differentiation is favored in the presence of IFN γ (green arrow 2). On the other hand, IFN γ is a strong inducer of IDO expression which degrades tryptophan and limits T cell proliferation (red arrow 3). Finally, IFN γ has been implicated in promoting the contraction phase of CD8⁺ T cells, which would contribute to suppress the immune response (red arrow 4).