are capable of killing IDO-expressing cells. Given that IDO expression is induced in physiologic and pathologic immune responses, and that IDO-expressing cells may temper immune activation, this work suggests an important role for IDO-specific CD8 T cells in immune-regulatory networks.

Sorensen and colleagues have described a population of IDO-specific CD8 T cells that may function as regulators of immune responses. IDO has long been examined as an enzyme critical in immune suppression: it cleaves the pyrrole ring of L-tryptophan, an essential amino acid consumed (not synthesized) by humans. IDO exerts its suppressive effects via reduction of the local tryptophan concentration and the creation of tryptophan metabolites capable of immune modulation. Cell types known to express this molecule in humans include certain dendritic cell (DC) subsets, macrophages, endothelial cells, fibroblasts, and tumor cells. Interestingly, IDO expression may be induced by several stimuli, including type I and type II interferons (IFN), interleukin 2 (IL-2), bacterial lipopolysaccharide, and ligation of B7 family members. It is noteworthy that IFNγ, a cytokine perceived as predominantly immunostimulatory, can serve suppressive functions as well by inducing expression of IDO, arginase, and the inhibitory B7-H1 molecule. IDO biology has been examined by multiple groups in the contexts of immune privilege, organ transplantation, and tumor immunity. In situations of transplantation, the tolerance-inducing function of IDO is desirable. Administration of intermediates involved in tryptophan metabolism or induction of IDO in grafted tissue via genetic manipulation in animal studies has resulted in prolonged graft acceptance compared with control animals not receiving treatment. As for graft-versus-host disease, IDO up-regulation in mice lessens colonic injury and delays death due to disease.

IDO function is of special interest to the field of cancer immunology because tumor cell expression of IDO allows it to escape from immune control and because IDO expression in DC subsets both increases tumor-associated regulatory T-cell (Treg) populations and induces tumor-specific T-cell anergy. The laboratory of Drs Munn (Medical College of Georgia Cancer Center), Prendergast (Lankenau Institute for Medical Research), and Mellor (Medical College of Georgia Cancer Center) have been instrumental in increasing our knowledge base of role(s) for IDO in malignancy. Experiments with tumor-bearing mice have shown that IDO-expressing DCs can activate Tregs to induce B7-H1 (PD-L1) on target DCs, thereby inhibiting tumor-specific T-cell responses.2 Tumor-associated DCs mediate immune suppression partially through the B7-H1/PD-1 pathway.3,4 Fallarino et al demonstrated that Tregs, either resting or induced via anti-CD3 stimulation to up-regulate CTLA-4, could induce tryptophan consumption in dendritic cells in a CTLA-4-dependent manner.5 The investigators also observed that release of autocrine IFNγ by DCs was the principal mechanism whereby CD3-activated Tregs mediated IDO induction in those cells, but that Treg-derived IFNγ could also contribute to their tryptophan catabolism. Perhaps not surprisingly, this phenomenon additionally required signaling through B7 family members.6 Interestingly, IDO expression has been shown to be under genetic control of the gene Bin1, the expression of which is down-regulated in many cancers. The loss of Bin1 elevates expression of IDO in a signal transducer and activator of transcription 1– and nuclear factor κB–dependent manner, driving the escape of transformed cells from antitumor immunity.7 The results of this study and others have suggested the use of IDO inhibitors to decrease immune suppression and increase tumor-specific T-cell immunity.8

Sorensen et al observe a functional indoleamine 2,3-dioxygenase (IDO)–specific CD8+ T-cell population in humans.1 IDO-specific CD8+ T cells are capable of killing IDO+ cells. Given that IDO expression is induced in physiologic and pathologic immune responses, and that IDO-expressing cells may temper immune activation, this work suggests an important role for IDO-specific CD8+ T cells in immune-regulatory networks.
tumors, and that Th17 cells may promote protective immunity in advanced human tumors. Interestingly, the authors have shown that IDO-specific CD8+ T cells tilt the balance between Treg and Th17 cells toward Th17 cells. IDO-specific CD8+ T cell target killing may impede the proliferation of Tregs while also allowing them exposure to IL-6, which aids in their conversion to Th17-like cells. In vivo, this phenomenon may be promoted by the inflammatory milieu that typically accompanies viral infection and certain instances of tumor development. However, although the presence of these IDO-specific CD8+ T cells has been established in humans, it will be essential to generate direct in vivo evidence of their biologic activity. These cells may indeed be physiologically and pathologically important. They may be induced during immune reactions and serve to fine-tune T-cell responses. Like many interesting works, this report raises more questions than it answers. Can IDO-specific CD8+ T cells in fact kill IDO+ tumor and DCs in a host? What is the functional relevance of this killing? In addition, do IDO-specific CD4+ T cells (or Treg cells) exist? If so, what are their support functions? It will be interesting to see whether future work from Sørensen et al and others can address these questions and establish IDO-specific T cells as an important regulatory component of immune responses.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES

Platelet Syk is a HIT target

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In his issue of Blood, Reilly and colleagues report a novel inhibitor (PRT-060318) of the tyrosine kinase Syk, expressed in platelets, as a new approach to the management of heparin–induced thrombocytopenia (HIT), using a mouse model of the disease.

Heparin-induced thrombocytopenia (HIT) is a common form of drug-induced immune reaction, with life-threatening potential, initiated by treatment of patients with unfractionated heparin or low molecular weight heparin. Heparin is widely used in the prevention and management of thromboembolic complications in surgery and trauma, in venous thrombotic disease, and in intravenous and intra-arterial lines to maintain patency. Although HIT is a product of immune reaction to the administered heparin, the immunogen is not heparin itself, but a complex of heparin bound to platelet factor 4 (PF4), an abundant platelet protein member of the CXC family of chemokines, alternatively known as CXCL4. PF4 is stored in platelet α-granules, and is released by exocytosis on platelet activation, whereupon it is rapidly bound to negatively charged glycosaminoglycans expressed on the surface of endothelial cells. Heparin, however, also highly negatively charged, binds directly to the activated platelet, leading to platelet shape change, aggregation, and secretion of granule contents, including ADP. Platelet aggregates form thrombi, which lead to ischemic disease complications characteristic of HIT. (Professional illustration by Marie Dauenheimer.)

Role of Syk tyrosine kinase in the mechanism of platelet activation and thrombosis in heparin-induced thrombocytopenia (HIT). Platelet factor 4 (PF4) released from platelet α-granules binds with high affinity to heparin through a charge-charge interaction. The heparin-PF4 complex acts as an immunogen, and exposure to heparin after an initial sensitization will lead to the formation of immune complexes, in which the heparin-PF4 aggregates are coated with IgG. These circulating immune complexes activate blood cells expressing Fcγ receptors, including human platelets that express FcγRIIA. After binding to the immune complex, this receptor signals through Syk and activation of phospholipase Cγ2, leading to platelet shape change, aggregation and secretion of granule contents, including ADP. Platelet aggregates form thrombi, which lead to ischemic disease complications characteristic of HIT. (Professional illustration by Marie Dauenheimer.)
T lymphocytes to IDO+ cells: check

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