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Comment on Ye et al, page 2021

Induced senescence: a cunning Fox's new trick

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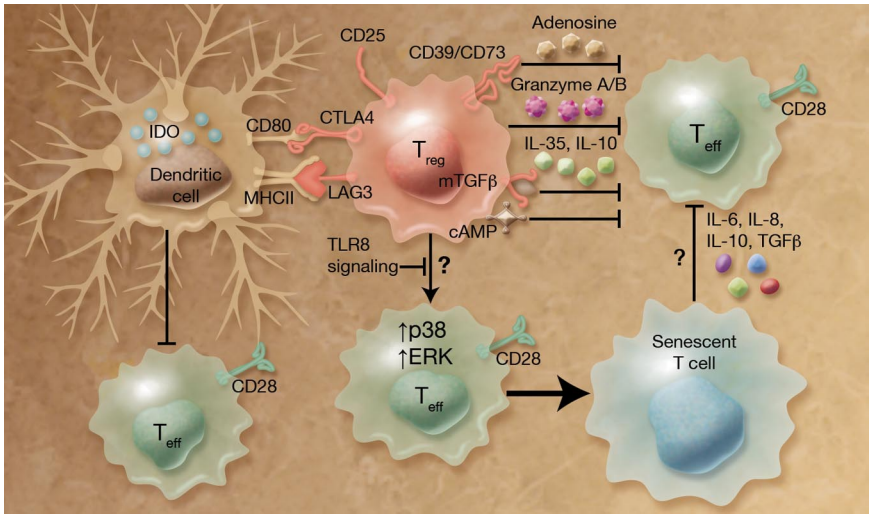
In this issue of *Blood*, Ye and colleagues demonstrate that human Foxp3$^+$ regulatory T (Treg) cells suppress target T cells by inducing senescence, and this endows them with suppressive functions.[1]



Treg cells use multiple mechanisms to suppress effector T (Teff) cells, including the newly identified process that involves induction of target cell senescence. Treg cells produce inhibitory cytokines (such as TGFβ, IL-10, and IL-35), cytolytic enzymes (such as granzyme A/B), and suppressive molecules (such as cAMP). They also express surface receptors, including CD25 (IL-2R), CD39, CD73, CTLA4, and LAG3, important for immune regulation. Treg cells induce senescence of responder cells by up-regulation of p38 and ERK1/2 activities, and this in turn endows them with suppressive functions, thereby reinforcing Treg-mediated suppression. Stimulation with TLR8 ligands abrogates the ability of Treg cells to induce senescence. Professional illustration by Alice Y. Chen.

Treg cells are pivotal in maintaining self-tolerance and immune homeostasis, but can also inhibit immune responses against cancer and infection.[2] To tap the potential of Treg cells in clinical application, it is crucial to understand the effector mechanisms by which Treg cells exert their suppressive functions. Many molecular mechanisms have been proposed (see figure and reviewed in Shevach[3] and Vignali et al[4]). Briefly, suppression can be carried out by: (1) inhibitory cytokines, such as TGFβ (including membrane-tethered mTGFβ), IL-10, and IL-35; (2) cytolytic enzymes, such as granzyme A/B; (3) metabolic disruption including consumption of local IL-2 by CD25, generation of pericellular adenosine by ectoenzyme CD39 and CD73, and generation of cyclic adenosine monophosphate (cAMP); and (4) targeting antigen presenting cells, particularly dendritic cells (DCs). For example, interaction of CTLA4, which is highly expressed on Treg cells, with CD80/CD86 on DCs leads to the induction of indoleamine 2, 3-dioxygenase (IDO), an immunosuppressive molecule.

Despite these proposed molecular mechanisms, relatively little is known about the cellular events during Treg-mediated suppression. In particular, the fate of responder T cells is not fully understood, although apoptosis has been observed in these cells.[5] Another unresolved question is how the responder cells interact with Treg cells and other immune cells. Indeed, there have been publications showing that naive T cells can be turned into suppressor cells by Treg cells and therefore amplify Treg-mediated suppression, a phenomenon called infectious tolerance.[6,7] Lastly, many of these proposed mechanisms are derived from studies in the murine systems, and it is not clear whether human Treg cells use the same mechanisms.

Ye et al examined the fate of suppressed T cells using human Treg cells and responder (both naive and memory) T cells. Interestingly, they show that responder T cells do not undergo apoptosis, but instead become senescent, which is characterized by permanent cell cycle arrest and loss of surface CD27 and CD28 expression.[1] Loss of CD28 is a hallmark of T cells from elderly people or patients with chronic viral infection and inflammatory diseases. Notably, this effect only occurs in primates, but not in laboratory mice.[8] Hence it is possible that this Treg-enforced senescence is a novel mechanism used by human Treg cells, but not murine Treg cells. Another important conclusion from Ye et al is that the Treg-induced senescent cells can in turn suppress naive T-cell proliferation.[1] These data therefore provide new insight into infectious tolerance, which could play an important role in human physiology.[9]

Ye and colleagues further investigated the molecular pathways involved in Treg-induced senescence. They demonstrate that p38 and ERK1/2 MAP kinases, but not JNK, are activated in responder cells. Blocking p38 or ERK1/2 by pharmacologic inhibitors or

siRNA knockdown prevents Treg-induced senescence. On the Treg side, continuing the authors' previous findings,[10] they now show that stimulation with TLR8 ligands, but not other TLR ligands, abrogates the ability of Treg cells to induce target cell senescence. These results suggest that human Treg-mediated suppression can be manipulated pharmacologically either on Treg cells or on responder cells, which could have important clinical implications.

This elegant study also raises several interesting questions. What is the mechanism through which human Treg cells exert their senescence-inducing function, and is it through soluble factors or cell contact dependent processes? Similarly, although the data suggest that cytokines produced by Treg-induced senescent T cells might be responsible for their suppressive functions, the detailed mechanism remains to be identified. Further, it will be interesting to ascertain whether alterations of Treg-enforced senescence contribute to human autoimmune disorders and other immune-mediated diseases. No matter what is found in future studies, the present work reveals new territory that will undoubtedly provide more insight into the potentially lifesaving field of human Treg cells.

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Comment on Brown et al, page 2055

Has the T cell bitten off more than it can chew?

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In this issue of *Blood*, Brown et al demonstrate that T cells acquire antigens through intercellular protein transfer from malignant plasma cells rendering them novel regulators of T-cell proliferation.[1]

Intercellular protein transfer has been recognized as a mode of communication within the immune system for nearly 30 years, yet only with the advent of recent technology has our understanding of how this happens really expanded. One such mechanism of intercellular protein transfer is trogocytosis (from the Greek trogo, meaning gnaw), a process whereby a direct and rapid exchange of membrane fragments between APCs and T cells results in the transfer of immune-modulatory surface proteins. The formation of an immune synapse through cell surface ligand/receptor interaction (MHC-TCR, CD28-B7, CD54-LFA, MHC-I–KIR) facilitates the rapid transfer (within minutes) of cell-surface, transmembrane, and intracellular molecules encompassed in a membrane patch, resulting in a modification of the immune response.[2] Research to date (both murine and human) has demonstrated that intercellular transfer is more efficient in activated T cells, underpinning the central role of TCR-MHC engagement in the facilitation of trogocytosis. However, the exact mechanism or mechanisms involved in trogocytosis remain unclear. It may represent the physical disruption of the immune synaptic membrane as cells attempt to dissociate, especially where there is a high avidity ligand/receptor interaction.[3]

What is the physiologic purpose of trogocytosis? The immune response is the orchestration of multiple cell types with complex specific functions in the pursuit of target eradication, for example, viral infected cells. The effectiveness of the immune response not only rests with recognition of the target with resulting initiation of the response, but the balance between expansion and limitation of such a response to ensure target eradication without overzealous collateral damage. Numerous studies to date have indicated a role for trogocytosis in the evolution of the immune response. The process of intercellular protein transfer can augment the immune response through transfer of stimulatory membrane portions, in particular acquired MHC class II/peptide ($MHCIIp^{acq}$) and co-stimulatory molecules ("presentasomes"), resulting in the generation of APC-like T cells. Such APC-like T cells can amplify the response through sustained T-cell activation and cytokine production.[4] By contrast, trogocytosis can also play a role in regulating the immune response. $MHCp^{acq+}$ $CD4^+$ T cells have been shown to induce neighboring $CD4^+$ T-cell anergy or apoptosis and $CD8^+$ T cells that have captured cognate MHC class I/peptide complexes can become susceptible to antigen-specific cytolysis by neighboring $CD8^+$ T cells ("fratricide") resulting in a dampening of the antigen-driven clonal response.

What is the role that intercellular protein transfer plays in limiting the extent of the immune response? It has previously been shown that HLA-G, a nonclassical MHC molecule characterized by strong immunosuppressive function and highly restricted tissue expression under physiologic conditions (mediating immune tolerance at the maternal-fetal interface), can be acquired from APCs by both $CD4^+$ and $CD8^+$ T cells.[5] The transfer of HLA-G (along with CD86, CD54, and ILT-3) to primarily activated T cells results in hyporesponsive T cells that acquire regulatory function. As such, trogocytosis provides a mechanistic explanation of how the immune system may regulate the extent of the immune response under physiologic conditions, which was previously assumed to only occur through cytokine-driven lineage commitment of the peripheral immune compartment to generate regulatory T cells.