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Recent updates of immune tolerance

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In general, immunological tolerance refers to mechanisms that prevent an immune response from being mounted against host' own tissues, that is self-tolerance. This self-tolerance is achieved during development of immature B and T lymphocytes, and after maturation and emigration into peripheral tissue via apoptotic purging of the cells with reactivity to self-antigens, processes known as central and peripheral tolerance, respectively. Anergy is non-apoptotic form of T cell non-responsiveness to self-antigens. T cells activated in the absence of danger signals to induce co-stimulatory molecules required to fully activate immune response become anergic. Tolerance achieved by regulatory T cells (Treg) is distinguished from such forms of self-tolerance, in that Treg have the potential to suppress immune responses, maintaining self-tolerance, and contribute to tissue and vascular repair. Natural Treg cells are programmed in the thymus to express the transcription factor FxoP3 in response to self-antigens. When activated by the same antigens in peripheral tissues, nTregs cells inhibit other self-reactive T cells that recognize antigens in the same tissue to prevent their differentiation into effector T cells or prevent their effector function. Induced Treg (iTreg) cells also express FoxP3 but develop in peripheral immune tissues in response to antigens recognized in the presence of TGF-b but in the absence of pro-inflammatory cytokines. Tregs express CD3, CD4, CD25 (IL2R) and Foxp3. Treg can inhibit the proliferation of T cells via call-call direct contact, through granzyme B and perforin-mediated, or through reducing costimulatory signals and inhibiting antigen presentation. Demethylation of FOXP3 determines stable FoxP3 expression in Tregs. During an alloimmune inflammation, hypoxia inducible factor 1 subunit alpha (HIF-1a) expression upregulates Th17 cells while downregulates Tregs through the binding to Foxp3. IL2 plays an important role in stabilizing Foxp3 gene expression, a high expression of the IL2 receptor correspond the effective immunosuppressive functions of Tregs. In response to IL-2 receptor signaling, Janus kinases (JAKs) initiate phosphorylation of STAT5 (signal transducer and activator of transcription 5) and an activated STAT5 bindings to the Foxp3 promoter and conserved non-coding sequence2 (CNS2), signaling Treg activation. IL6 induces CNS2 methylation to suppress Foxp3 expression, and IL21 activates STAT3 to suppress Foxp3 expression, whereas TNF-a dephosphorylates and restores Treg function. FoxP3-negaitve regulatory T cells characterized b their production of IL10 are also identified to be a type of

regulatory lymphocytes. IL-10 is an anti-inflammatory cytokine, and helps to suppress the production of pro-inflammatory cytokines such as IFN-r, IL-2, IL-2 and TNF-a by Th1 cell, mast cells, NK cells, endothelial cells, and macrophages. IL10 helps maintain the regulatory microenvironment by upregulating M2 macrophages, and tolerogenic dendritic cells, and antigen-specific T regulatory type 1 (Tr1), while suppressing Th1/Th17 effector immunity. M2 macrophages generally inhibit inflammation and promote tissue repair through IL10 and TGF-b. Peripheral blood monocyte-derived dendritic cells that express higher levels of indoleamine dioxigenase (IDO) which converts tryptophan to kynurenine are capable of expanding regulatory T cells. When activated in the allograft, alloreactive CD8 T cells can be eliminated by apoptosis or functional exhaustion. The load of the antigen exposure primarily determines CD8 + T cells' fate. High loads lead to cell exhaustion and lower loads to effector response. The presence of peripheral cell signatures such as high proportion of FoxP3+ Treg cells, Treg/Th17 subpopulation, tolerogenic DC2/DC1 subset ratio have been identified as potential biomarkers predicting tolerance after transplantation. Serum signatures of immune exhaustion such as high Eomes+ T cells and PD-1+ T cells hold promise as potential non-invasive biomarkers. High levels of ferritin, hepdicin-25 (in serum), intrahepatocytic iron accumulation, allograft expression of genes associated with iron metabolism predicted tolerance in cases of liver transplantation. Anti-thymoglobulin (ATG) has been described in the management of steroid-resistant cute rejection. A combination of ATG and donor-derived mesenchymal stem cells, ex vivo-expanded Treg cells can be candidate trials for induction of tolerance.