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T CELL RESPONSES

Autophagy maintains metabolic order

Autophagy is the process through which intracellular components are targeted to lysosomes for degradation and recycling — it is essential for maintaining cellular homeostasis, particularly during infection or metabolic stress. Two complementary studies describe a crucial role for autophagy in regulating cellular metabolism in regulatory T (T_{Reg}) cells and T helper 2 (T_H2) cells. Interestingly, defective autophagy impairs survival and lineage stability in peripheral T_{Reg} cells but leads to expansion of T_H2 cell populations in a cell-intrinsic manner.

Wei *et al.* found that peripheral T_{Reg} cells show higher autophagy activity compared with naive $CD4^+$ T cells. They generated mice with a T_{Reg} cell-specific deletion of the essential autophagy-related 7 (*Atg7*) gene (*Foxp3*^{Cre}*Atg7*$^{fl/fl}$ mice) and found that these animals developed lymphoid hyperplasia by ~3 months of age and had increased proportions of effector/memory T cells compared with controls. Effector/memory T cells from *Foxp3*^{Cre}*Atg7*$^{fl/fl}$ mice produced aberrantly high levels of interferon-γ (IFNγ) and interleukin-17 (IL-17), and the animals developed severe systemic inflammation by ~5 months of age. Compared with controls, *Foxp3*^{Cre}*Atg7*$^{fl/fl}$ mice had lower proportions of T_{Reg} cells in the spleen, lymph nodes and, in particular, the colon but normal proportions of thymic T_{Reg} cells. Similar phenotypes were observed in mice with a T_{Reg} cell-specific deletion of *Atg5*, another essential autophagy gene.

> “drugs targeting autophagy could be useful for manipulating peripheral $CD4^+$ T cell responses in the clinic”

Further analyses showed that ATG7 is not essential for T_{Reg} cell proliferation but instead promotes their survival and lineage stability. ATG7-deficient T_{Reg} cells showed higher rates of apoptosis and a failure to maintain FOXP3 expression, which was associated with the upregulation of IFNγ and other inflammatory cytokines. Autophagy maintained T_{Reg} cell stability and survival partly by restraining mTOR complex 1 (mTORC1) activity following T_{Reg} cell activation through T cell receptors or other stimulatory pathways. Aberrant mTORC1 activity in ATG7-deficient T_{Reg} cells was associated with increased MYC expression and heightened glycolytic metabolism; pharmacological blockade of MYC or glycolysis partially restored lineage stability in these cells. Furthermore, activated T_{Reg} cells were more sensitive to apoptosis than quiescent T_{Reg} cells in response to autophagy deficiency. Therefore, autophagy preferentially supports the survival and lineage stability of activated T_{Reg} cells.

Kabat *et al.* examined how the inflammatory bowel disease (IBD)-associated gene autophagy-related 16-like 1 (*Atg16l1*) affects intestinal T cell responses. They generated mice with a $CD4^+$ T cell-specific deletion of *Atg16l1* (*Atg16l1*$^{\Delta CD4}$ mice) and found that these animals developed splenomegaly, lymphadenopathy and chronic intestinal pathology by ~ 5 months of age. Younger *Atg16l1*$^{\Delta CD4}$ mice had lower T cell counts in peripheral lymphoid organs and the intestine compared with controls, but developed exacerbated disease in a model of IBD. Closer analysis showed that young *Atg16l1*$^{\Delta CD4}$ mice had decreased numbers of T_H1 and T_H17 cells, and reduced peripheral T_{Reg} cell counts (particularly in the intestine) but had higher T_H2 cell numbers. In keeping with this, ageing *Atg16l1*$^{\Delta CD4}$ mice developed an aberrant type 2 antibody response against dietary antigens and commensal bacteria.

The authors found that T_{Reg} cells from *Atg16l1*$^{\Delta CD4}$ mice showed intrinsic survival defects, whereas T_H2 cells from these animals showed comparable or improved survival in relation to wild-type controls. Experiments in which *Atg16l1*$^{\Delta CD4}$ mice were reconstituted with wild-type T_{Reg} cells indicated that ATG16L1 regulates T_H2 cell expansion through a cell-intrinsic mechanism, rather than indirectly through T_{Reg} cell loss. Kabat *et al.* next generated mice with a T_{Reg} cell-specific deletion of *Atg16l1* (*Foxp3*^{Cre}*Atg16l1*$^{fl/fl}$ mice); in agreement with the findings by Wei *et al.*, these animals developed a severe spontaneous systemic inflammation by 5 months of age that was associated with impaired survival and lineage stability of peripheral T_{Reg} cells. Also in keeping with the study by Wei *et al.*, Kabat *et al.* found that ATG16L1-deficient T_{Reg} cells showed augmented glycolytic activity; this was most apparent in intestinal T_{Reg} cells. The authors noted that T_H2 cells have enhanced glycolytic metabolism compared with T_{Reg} cells under homeostatic conditions and propose that this accounts for why T_H2 cells are more resistant to the metabolic consequences of blocking autophagy.

These studies suggest that drugs targeting autophagy could be useful for manipulating peripheral $CD4^+$ T cell responses in the clinic — indeed, in a mouse tumour model, Wei *et al.* observed that *Foxp3*^{Cre}*Atg7*$^{fl/fl}$ mice have reduced tumour cell growth owing to defective T_{Reg} cell function at the tumour site.

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ORIGINAL ARTICLES Wei, J. *et al.* Autophagy enforces functional integrity of regulatory T cells by coupling environmental cues and metabolic homeostasis. *Nat. Immunol.* **17**, 277–285 (2016) | Kabat, A. M. *et al.* The autophagy gene *Atg16l1* differentially regulates T_{Reg} and T_H2 cells to control intestinal inflammation. *eLife* http://dx.doi.org/10.7554/eLife.12444 (2016)