LUPUS NEPHRITIS

A CD4$^+$ T cell population provides B cell help in SLE

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Systemic lupus erythematosus (SLE) is characterized by the development of autoantibodies against double-stranded DNA. Virginia Pascual and colleagues previously demonstrated that neutrophils from patients with SLE release an oxidized form of mitochondrial DNA, which induces high levels of type 1 interferon production by plasmacytoid dendritic cells (pDCs). They now show that pDCs activated by oxidized mitochondrial DNA induce the production of a CD4$^+$ memory T cell population — which they term T helper 10 (T_H10) cells — that provides B cell help through the production of IL-10 and succinate. Moreover, the researchers show that T cells with these characteristics are expanded in the blood of patients with SLE and are present in the tubulointerstitium of patients with proliferative lupus nephritis, suggesting that these cells could be a novel therapeutic target.

To assess how oxidized mitochondrial DNA-activated pDCs might shape the adaptive immune response, Pascual and colleagues initially studied the response of naive CD4$^+$ T cells to these pDCs in vitro. "Our in vitro studies showed that oxidized mitochondrial DNA-activated pDCs induce a population of CD4$^+$ T cells that produce IL-10 and IFNγ," explains Pascual.

"These T cells also displayed unique metabolic features leading to the accumulation of reactive oxygen species and the secretion of succinate." Functional studies revealed that these T cells stimulated the activation of B cells in an IL-10 and succinate-dependent manner. "These cells are in fact superb B cell helpers, even though they do not express markers of professional follicular helper T cells," says Pascual. "IL-10 is well known for its immunoregulatory functions, but in humans this cytokine is also a potent inducer of B cell proliferation and differentiation, although interestingly, T regulatory cells that produce high levels of IL-10 are not good B helper cells. On the other hand, succinate has emerged as an important inducer of macrophage and dendritic cell activation, but its role in B cell help was unknown."

To identify the clinical relevance of their in vitro findings, the researchers then assessed whether phenotypically similar cells were present in the blood of patients with SLE. "We found that CXCR5$^-$CXCR3$^+$PD1^{hi}CD4$^+$ T cells, which are distinct from follicular helper T cells but displayed similar phenotypic, functional and metabolic characteristics to T_H10 cells, were expanded in the blood of patients with SLE," notes Pascual. Interestingly, blood levels of these T cells were lowest in children with severe proliferative lupus nephritis, leading the researchers to hypothesize that the cells had migrated from blood to the kidneys of these patients. Indeed, they identified these cells in kidney biopsy samples, where they were located in interstitial areas in close proximity to tubular epithelial cells and B cells. "Although we speculate that these T cells might provide local B cell help in the kidney, it is also important to remember that proximal tubular epithelial cells express the highest density of the succinate receptor, SUCNR1, and that this metabolite has been implicated in the pathogenesis of renovascular hypertension through its capacity to activate the renin–angiotensin system," says Pascual. "Whether T cell-derived succinate directly contributes to kidney damage in patients with proliferative lupus nephritis — the main class of lupus nephritis that is associated with renovascular hypertension — deserves further study."

Given the inverse correlation between blood levels of this T cell population and the presence of proliferative lupus nephritis, Pascual and colleagues suggest that quantification of these cells in blood could be used as a biomarker of lupus nephritis class and, moreover, could represent a new avenue for therapeutic investigation. "In this regard, the use of SUCNR1-specific antagonists, which are being developed to treat diabetic and hypertensive nephropathy, could be explored in early stages of lupus nephritis," she says. "Specific pharmacological regulators of succinate production might also represent a novel niche for therapeutic development in proliferative lupus nephritis."

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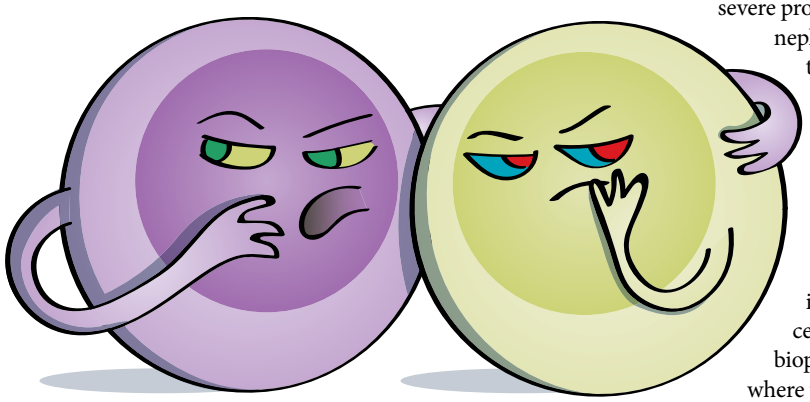

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ORIGINAL ARTICLE Caielli, S. et al. A CD4$^+$ T cell population expanded in lupus blood provides B cell help through interleukin-10 and succinate. *Nat. Med.* https://doi.org/10.1038/s41591-018-0254-9 (2018)
FURTHER READING Caielli, S. et al. Oxidized mitochondrial nucleoids released by neutrophils drive type I interferon production in human lupus. *J. Exp. Med.* **213**, 697–713 (2016)