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T CELLS

Salt promotes pathogenic T_H17 cells

Interleukin-23 (IL-23)-dependent T helper 17 (T_H17) cells have been implicated in the pathogenesis of numerous autoimmune diseases, including multiple sclerosis. The incidence of autoimmune diseases has markedly increased over recent decades, supporting the idea that changes in environmental factors (such as diet) have a role in these diseases. Two studies published in *Nature* now show that a high-salt diet triggers the development of pathogenic T_H17 cells and accelerates a multiple sclerosis-like disease in mice.

Salt (sodium chloride; NaCl) levels in the Western diet have greatly increased with the rise in the consumption of processed foods, so Kleinewietfeld *et al.* examined the effects of salt on human T_H17 cell differentiation. The culture of naive T cells under T_H17-promoting conditions induces only a mild T_H17 cell phenotype. However, the authors found that increasing the NaCl concentrations in the culture medium by 40 mM — which are similar levels to those found in the interstitium of animals on a high-salt diet — resulted in the enhanced and stable production of pathogenic T_H17 signature cytokines and chemokines.

High salt (40 mM NaCl) conditions during cytokine-induced T_H17 cell polarization increased the phosphorylation of p38 mitogen-activated protein kinase (MAPK) and induced the expression of the osmosensitive transcription factor nuclear factor of activated T cells 5 (NFAT5) and its target serum/glucocorticoid-regulated kinase 1 (SGK1). Inhibition of any of these molecules greatly reduced high-salt-induced pathogenic T_H17 cell development.

> “The T_H17 cell transcriptional network is organized into two tightly coupled, self-reinforcing but antagonistic modules”

Mice fed a high-salt diet rapidly developed a more severe form of experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, than mice fed a normal diet. Mice on a high-salt diet had higher numbers of T_H17 cells in the central nervous system, as well as in the periphery.

In another study, Wu *et al.* used transcriptional profiling of differentiating T_H17 cells to construct a model of their signalling network. From this, the authors identified SGK1 as having a central role in IL-23 receptor (IL-23R) signalling, which stabilizes the T_H17 cell phenotype. T cells from mice lacking *Sgk1* specifically in IL-17-producing $CD4^+$ T cells (*Il17f*^{Cre}*Sgk1*$^{flox/flox}$ mice) could not maintain the T_H17 cell phenotype in response to IL-23 *in vitro*. Furthermore, the incidence and severity of EAE was greatly reduced in *Il17f*^{Cre}*Sgk1*$^{flox/flox}$ mice compared with controls, owing to an inability of the T_H17 cells in these mice to maintain IL-17 production.

SGK1 was shown to mediate its effects on T_H17 cells in part through the phosphorylation of the transcription factor forkhead box protein O1 (FOXO1). This phosphorylation abrogated the suppressive effects of FOXO1 on retinoic acid receptor-related orphan receptor-γt (RORγt)-mediated *Il23r* expression, thereby enhancing IL-23R expression and T_H17 cell stability.

As SGK1 has a role in sodium homeostasis, the authors also determined whether increasing NaCl concentrations affected T_H17 cell stability through SGK1. Indeed, increased NaCl concentrations potentiated T_H17 cell differentiation *in vitro* and *in vivo*, and enhanced the induction and severity of EAE in an SGK1-dependent manner.

In an accompanying article, Yosef *et al.* further describe the dynamic regulatory network that controls T_H17 cell differentiation. This network was constructed and validated by combining transcriptional profiling, new computational algorithms and an innovative nanowire-based small interfering RNA delivery system for gene knockdown. The T_H17 cell transcriptional network is organized into two tightly coupled, self-reinforcing but antagonistic modules — a ‘T_H17-positive’ module and a ‘T_H17-negative’ module — which might be essential for maintaining the balance between T_H17 cells and other T cell subsets. In addition, these analyses identified 12 new T_H17 cell regulators, the functions of which were further validated and characterized. These new regulators include three T_H17-positive factors — the chromatin regulator MYC-induced nuclear antigen (MINA), FAS (also known as CD95) and POU domain class 2-associating factor 1 (POU2AF1; also known as OBF1) — and the T_H17-negative factor TSC22 domain family protein 3 (TSC22D3).

So, these studies describe a pathway by which high salt levels can induce pathogenic T_H17 cells and drive autoimmune disease; they also identify several new possible targets for controlling the development of T_H17 cells.

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ORIGINAL RESEARCH PAPERS Kleinewietfeld, M. *et al.* Sodium chloride drives autoimmune disease by the induction of pathogenic T_H17 cells. *Nature* 6 Mar 2013 (doi:10.1038/nature11868) | Wu, C. *et al.* Induction of pathogenic T_H17 cells by inducible salt-sensing kinase SGK1. *Nature* 6 Mar 2013 (doi:10.1038/nature11984) | Yosef, N. *et al.* Dynamic regulatory network controlling T_H17 cell differentiation. *Nature* 6 Mar 2013 (doi:10.1038/nature11981)