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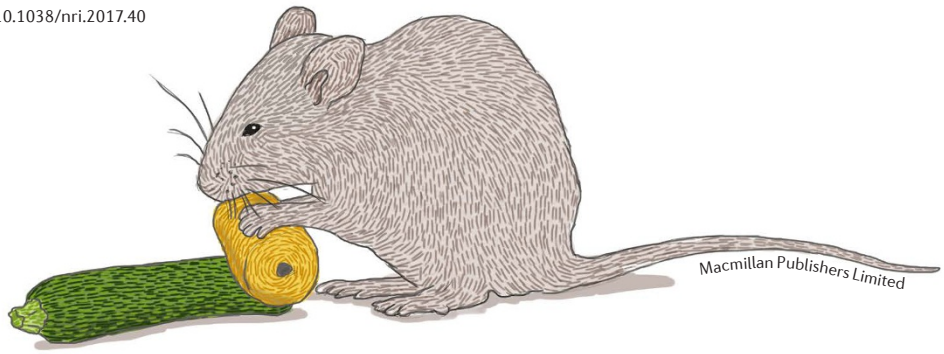

MICROBIOTA

Diet can protect against type 1 diabetes

> ...diet provided complete protection from diabetes

Type 1 diabetes (T1D) is an autoimmune disease with a strong genetic basis, but a progressive rise in its incidence indicates that environmental factors also contribute to the disease. Now, Mariño *et al.* report that mice fed diets that release high levels of either acetate or butyrate have enhanced protection from T1D, and this is mediated by a decreased frequency of autoreactive T cells or an increased number of regulatory T (T_{reg}) cells, respectively.

Patients with T1D have impaired gut barrier function, and the microbiota has been implicated in disease progression. To investigate the role of gut dysbiosis in the development of T1D, the authors used non-obese diabetic (NOD) mice, which develop diabetes by autoimmune destruction of pancreatic β-cells.

It had been shown previously that NOD mice that lack the innate immune signalling molecule MYD88 (*Myd88*$^{-/-}$ NOD mice) are protected from T1D development. These mice have an overrepresentation of the bacterial phylum Bacteroidetes in their gut and lose protection when housed under germ-free conditions, leading to the hypothesis that protection from T1D is mediated by an immunomodulatory bacterial product.

The authors now show that *Myd88*$^{-/-}$ NOD mice have higher blood levels of the short-chain fatty acids (SCFAs) acetate and butyrate than NOD mice. To investigate a potentially protective effect of these SCFAs, NOD mice were fed special diets that release large amounts of either acetate or butyrate after bacterial fermentation in the colon — high amylose maize starch (HAMS) that had been acetylated (HAMSA) or butyrylated (HAMSB). Indeed, mice fed either the HAMSA or the HAMSB diet had a reduced incidence of diabetes compared with those given the HAMS diet, and a combination of the HAMSA and HAMSB diet provided complete protection from diabetes, indicating that acetate and butyrate may act through different mechanisms.

The authors first investigated whether the different diets influence the number of autoreactive T cells and found that mice fed the HAMSA diet had less T1D autoantigen-reactive T cells. Moreover, these mice had a marked reduction in the number of B cells in the spleen and Peyer's patches, and their B cells expressed lower levels of MHC class I and CD86 costimulatory molecules. This indicates that acetate alters the number and surface phenotype of B cells and thereby impairs the ability of B cells to expand autoreactive T cell populations. Of note, the protective effect of the HAMSA diet was associated with an increase in *Bacteroides*, and transfer of microbiota from HAMSA-fed mice to germ-free NOD mice fed a normal diet protected against diabetes for 30 weeks.

The protective effect of the HAMSB diet was examined by transferring T cells from NOD mice fed various diets into mice of the NOD–severe combined immunodeficiency (SCID) strain, which lack B and T cells. T cells from NOD mice fed the HAMS diet rapidly transferred diabetes to the recipient mice. By contrast, NOD–SCID mice that received T cells from NOD mice fed a HAMSB diet were protected from diabetes, which correlated with an increased number of T_{reg} cells in the spleen. Further cell-transfer experiments and single-cell transcriptome analysis showed that the HAMSB diet promoted the conversion of naive T cells into T_{reg} cells by affecting histone acetylation, leading to the upregulation of the lineage-specifying transcription factor FOXP3.

In summary, acetate- and butyrate-yielding diets provide protection from diabetes, suggesting that dietary supplements could be an effective treatment for T1D.

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ORIGINAL ARTICLE Mariño, E. *et al.* Gut microbial metabolites limit the frequency of autoimmune T cells and protect against type 1 diabetes. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3713 (2017)
FURTHER READING Levy, M. *et al.* Dysbiosis and the immune system. *Nat. Rev. Immunol.* **17**, 219–232 (2017)