Research Highlights

Highlights from the latest articles in immunotherapy

Gut microbes and regulatory Th17 cells in Type 1 diabetes

Evaluations of: Kriegel MA, Sefik E, Hill JA *et al.* Naturally transmitted segmented filamentous bacteria segregate with diabetes protection in nonobese diabetic mice. *Proc. Natl Acad. Sci. USA* 108, 11548–11553 (2011); King C, Sarvetnick N. The incidence of Type-1 diabetes in NOD mice is modulated by restricted flora not germ-free conditions. *PLoS One* 6, e17049 (2011).

Microbes play a central role in human health, not just as pathogens or as benign communities, but also as contributors to a number of chronic health conditions. The microbes that reside in the gut are of particular significance in autoimmunity and immune health. Until recently, the goal of this type of research was to define a healthy versus disease-associated intestinal flora. Fortunately this trend is now changing towards a better understanding of the fundamental immunological mechanisms that may be driven by gut microbial flora. This information is critical for providing a direct link between specific components of the gut microbial flora and a prevalent autoimmune disease such as Type 1 diabetes (T1D), as well as indicate rationale therapeutic opportunities. The ultimate goal of this research is to determine how to adapt the intestinal flora towards a healthier composition of gut microbiota. This will hopefully lead to new treatments with benign modalities such as diet and nutrition.

Gut microbiota has a major influence on the development and function of the host's immune system. The poorly developed immune system in germ-free mice and human neonates (who develop in the germ-free womb) argues that gut microbes drive the normal maturation of

the immune system, particularly adaptive immunity. It is becoming increasingly evident that the gut microbiota is a major environmental factor that can predispose to T1D. In 2008, Wen *et al.* [1] reported that the composition of gut microbes can alter disease development in T1D-prone non-obese diabetic (NOD) mice where normal intestinal microbiota could alleviate T1D. Children delivered by cesarean section have a 20% increased risk of developing T1D [2], which might be explained by differences in the intestinal microbiota acquired from the mother during different delivery modes [3]. The role of gut microbes in the maturation of the immune system and its associated disease risk is extremely complex and poorly understood.

Two recent papers provide important insight into the regulation of T1D etiology by gut microbes. Kriegel *et al.* [4] showed that gut-resident commensal microbes of restricted heterogeneity can alter diabetes progression in NOD mice from different mouse colonies. In these studies, there was a clear discrimination of diabetes prevalence in female NOD mice from the same colony that was based on their segmented filamentous bacteria (SFB) gut flora. The vast majority (91%) of NOD mice lacking SFB developed T1D, while mice colonized with this flora had a greatly reduced disease incidence. Interestingly, the presence of SFB in both female and male NOD mice corresponded to increased numbers of Th17 cells, but not conventional Tregs in the small intestinal lamina propria. Intestinal SFB are commensal *Clostridia*-related bacteria shown to be potent inducers of protective Th17 cells in the small intestinal lamina propria of B6 mice [5]. Th17 cells have been implicated in both the prevention and induction of T1D, which may reflect altered Th17 immunity according to the condition of tissue

**Kelly L Summers*
& Bhagirath Singh**

Centre for Human Immunology, Department of Microbiology & Immunology, Lawson Health Research Institute and Robarts Research Institute, Western University, London, Ontario, N6A 5C1, Canada

*Author for correspondence:

Tel.: +1 519 661 3432

ksummers@uwo.ca

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Future
Medicine

fsg
part of

(intestine, pancreatic lymph node or islet) or peripheral environments. In the context of Kriegel's study, SFB contributes to the generation of protective intestinal Th17 cells that likely regulate immunological tolerance. These findings are supported by the gut flora-mediated protective Th17 responses reported in T1D-prone bio-breeding-diabetes prone rats [6]. Likewise, children with established T1D have a low frequency of small intestinal Th17 cells [7], which may reflect alterations in gut flora. Kriegel's study also showed that SFB colonization in NOD mice did not alter the initial inflammatory processes causing insulinitis, but instead modulated downstream mechanisms that mediate destruction of the insulin-producing beta cells. From these studies we can speculate that SFB colonization promotes immune tolerance in NOD mice by stimulating regulatory Th17 cell populations in the gut that may inhibit the development or response of effector diabetogenic T cells. The protective effect of regulatory Th17 cells may also be mediated by their secretion of IL-22, which augments epithelial barrier integrity.

Another interesting and related study by King and Sarvetnick [8] challenges the current assumption that germ-free female NOD mice have increased diabetes incidence. This paper supports the idea that

modulation of intestinal microbiota can be used to influence disease outcomes in autoimmune diabetes. A critical role for gut flora in the development of T1D was clearly evident by a delayed onset and reduced incidence of diabetes observed in germ-free NOD mice having spontaneous monocolonization with *Bacillus cereus*. This study further suggests that well-defined commensal gut microflora may attenuate T1D development, and offers noninvasive diet-mediated immunoregulatory potential for treating T1D.

In conclusion, these two papers provide interesting new insight into the complex relationship between the intestinal microbiome and the immune system in T1D. They both emphasize that future studies must consider variations in the gut microbiota of individual human or animal subjects. In addition, these studies open up the area of molecular mimicry between host autoantigens and microbial antigens. This could induce or prevent T1D through cross-stimulation, immunological tolerance or cross-priming of autoreactive T cells by the microbial antigens in the gut. Given the load of microbes in the gut this could have significant impact on the development of autoimmune diseases and in designing appropriate therapeutic regimens.

References

- 1 Wen L, Ley RE, Volchkov PY *et al*. Innate immunity and intestinal microbiota in the development of Type 1 diabetes. *Nature* 455, 1109–1113 (2008).
- 2 Cardwell CR, Stene LC, Joner G *et al*. Caesarean section is associated with an increased risk of childhood-onset Type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia* 51, 726–735 (2008).
- 3 Dominguez-Bello MG, Costello EK, Contreras M *et al*. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc. Natl Acad. Sci. USA* 107, 11971–11975 (2010).
- 4 Kriegel MA, Sefik E, Hill JA *et al*. Naturally transmitted segmented filamentous bacteria segregate with diabetes protection in nonobese diabetic mice. *Proc. Natl Acad. Sci. USA* 108, 11548–11553 (2011).
- 5 Iwaylo I, Ivanov II, Atarashi K *et al*. Induction of intestinal th17 cells by segmented filamentous bacteria. *Cell* 139, 485–498 (2009).
- 6 Lau K, Benitez P, Ardisson A *et al*. Inhibition of Type 1 diabetes correlated to a *Lactobacillus johnsonii* N6.2-mediated Th17 bias. *J. Immunol.* 186, 3538–3546 (2011).
- 7 Lahdenperä A, Hölttä V, Ruotula T *et al*. Up-regulation of small intestinal IL-17 immunity in untreated celiac disease but not in potential celiac disease or in Type 1 diabetes. *Clin. Exp. Immunol.* 167, 226–234 (2012).
- 8 King C, Sarvetnick N. The incidence of Type-1 diabetes in NOD mice is modulated by restricted flora not germ-free conditions. *PLoS One* 6, e17049 (2011).