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Time matters: the circadian rhythm in intestinal homeostasis and food allergy

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Abbreviations

SIEC: Small intestinal epithelial cells

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SI: Small intestine

IF: Intermittent fasting

MHC: Major histocompatibility complex

Intestinal immune homeostasis and well-balanced oral tolerance mechanisms are essential for defending the host against pathogens and toxic substances while simultaneously absorbing essential nutrients to nourish the human body. Impaired oral tolerance can lead to development of food allergy, which has a continuously rising prevalence worldwide. Several factors contribute to food allergy development, such as genetic and epigenetic factors, but also environmental stimuli, food composition, allergen stability and the route of food allergen exposure. Moreover, increasing evidence shows that food allergy development is strongly associated with a dysfunctional gastrointestinal barrier ¹. In several studies an impaired allergen digestion induced by e.g., administration of gastric acid suppressive medication, enhanced susceptibility to food allergy development. Support of gastric digestion via use of medication containing gastric enzymes resulted in a reduction of food allergy development and an alleviation of clinical symptoms upon oral allergen exposure in food allergic animals ². Besides impairment of allergen degradation, reduced gastric acidity changes intestinal microbiota composition, which further contributes to allergy development ³.

In a recent study by Tuganbaev et al. (2020), the authors report a change of the immunological activity of small intestinal epithelial cells (SIEC) throughout the day. Modulated by distinct mucosal-adherent commensals in the small intestine (SI), the expression of Major histocompatibility complex (MHC) class II receptors by a subpopulation of SIEC is regulated diurnally with significantly higher expression during the peak of the resorptive activity compared to baseline activity. With regards to the mucosal immune barrier, the MHC class II expressing SIECs seem to be essential for migration and activation of CD4⁺ intraepithelial lymphocytes and consequently for the release of the tolerogenic cytokine IL-10. Not only the tolerance inducing immunological program itself seems to follow a diurnal rhythm; the intestinal barrier function is modulated by circadian influences too. Changes in feeding time and food composition was associated with an inflammatory response ⁴. Thus, we speculate that the timing of allergen intake might contribute to food allergy development and influence the intensity of allergic reactions via the immune-barrier-axis. As the immune response in the SI was now reported to have a specific rhythmicity fluctuating between more or less tolerogenic phases, we suggest a beneficial influence on the immune responses upon food intake during the active, tolerogenic state (Figure 1). The study by Tuganbaev et al. further showed a contribution of the dietary content in the regulation of SIEC MHC class II expression, with the SI microbiome serving as a signaling hub. High fat diet induced lower expression levels of MHC class II on SIEC ⁴. In a previous mouse study, the overall composition of mouse chow was found to be highly relevant for development of food allergy. Mice fed with a soy-containing diet with specific pattern of lipids, vitamins and other

micronutrients showed elevated allergen-specific antibody levels and allergic symptoms upon allergen challenge, while mice on a soy-free diet with a more beneficial fatty acid composition and higher vitamin D levels revealed elevated levels of IL-10 and were protected from food allergy development.⁵

In light of these studies, intermittent fasting (IF), with eating only during a restricted time-period, might represent a novel strategy to prevent food allergy development or adverse food reactions. In context of the data reported by Tuganbaev et al., strict fasting hours might support to establish an intestinal rhythm and food might only be taken up during the active, tolerogenic phase of the day. Several studies report that IF is associated with beneficial outcomes in animal and human studies indicated by positive effects on risk factors for aging, diabetes, autoimmunity, cardiovascular disease, neurodegeneration and cancer. Amongst others, it was observed that IF influences the immune system by “rejuvenation” of immune cells⁶. Age-dependent immunosenescence was reported to alter the ratio of myeloid to lymphoid cells, subsequently leading to reduced counts of B-, T-cells and lymphoid progenitors resulting in a reduced regenerative capacity. Certain dietary restriction rhythms have been demonstrated to partially restore these effects via an increased apoptosis of autoreactive T cells and their partial replacement with newly generated naive T cells. Furthermore, clinical studies reported that after Ramadan fasting, participants had reduced serum levels of the proinflammatory cytokines IL-1 β , IL-6 and TNF α ^{7, 8}. In contrast to these studies, repeated fasting exacerbated food antigen-induced diarrhea in a cholera toxin-driven mouse model for delayed type hypersensitivity to food allergens. The authors suggested an attenuated oral tolerance due to fasting-dependent decreased levels of antigen-specific IgA as the main cause of their result⁹. However, a possible impact of cholera toxin on the commensal microbiota itself was not discussed in this study. As the microbiome plays an important role in oral tolerance, we consider further investigations of this aspect on intestinal barrier function as essential. Although scientific evidence regarding the effects of IF on food allergy sensitization and effector phase is limited, we begin to understand the immunology behind beneficial health effects of IF. Changes of dietary habits might be a promising tool to restore oral tolerance in the future. It should be noted that the process of re-feeding after the fasting period is considered equally important to promote initiation of alternative metabolic pathways focusing on energy storage and mediating tolerogenicity. Without any doubt, more work needs to be done to elucidate the underlying immune pathways associated with the circadian rhythm and to clarify to which extent the results are caused by intestinal barrier integrity, effects of microbial communities and food content composition.

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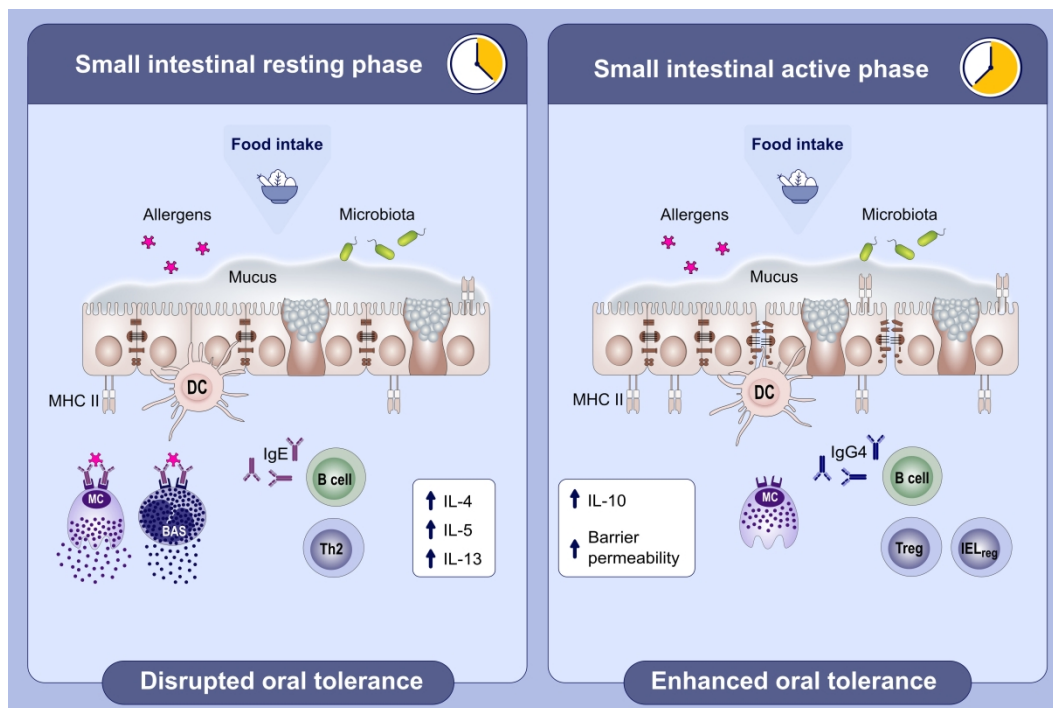
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Figure legends

Figure 1

The immunological activity of the small intestine (SI) fluctuates rhythmically between a more tolerogenic, active phase and a resting phase with enhanced barrier integrity. Food intake restricted to the active phases might counteract pathogenesis and alleviate clinical symptoms of food allergy. MHCII: Major histocompatibility complex class II, DC: dendritic cell, MC: Mast cell,

BAS: Basophil, Th2: Type 2 T helper cell, IgE: Immunoglobulin E, Treg: Regulatory T helper cell, IEL_{reg}: Regulatory intestinal epithelial lymphocyte



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