P23 & FP – **Development of a novel TNF-driven mouse model of gut & joint inflammation**

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Abstract: The incidence of inflammatory diseases, including IBD and arthritis, have strongly increased in Western society (Bach et al., 2002). These diseases are associated with shifts in the microbiota ecological structure and complexity (dysbiosis), suggesting a contribution to disease development. It has been shown that the intestinal microbiota has profound effects on host's physiology and immunity through the production of specific metabolites (Blacher et al., 2017), but the exact mechanisms explaining the link between microbiota dysbiosis, gut and joint pathology have yet to be found. Relevant mouse models which recapitulate the clinical features of human pathology which are influenced by the intestinal microbiota are pivotal to unravel these mechanisms. Previous studies have shown that mice which express increased TNF levels spontaneously develop intestinal inflammation and arthritis, and this phenotype is strongly impacted by the intestinal gut microbiota composition (Kontoyiannis et al., 1999; Schaubeck et al., Gut 2016). We wish to investigate diet-microbiota-immune networks in a TNF-driven genetic mouse model of gut & joint disease, using CRISPR/CAS9 gene editing technology. By targeting the AU-rich elements in the mouse tnf gene, we generated mice with more stable TNF mRNA. SPF-raised $Tnf^{em\Delta ARE}$ mice have increased TNF expression leading to inflammatory pathology in the intestine and joints. Initial analysis reveals that Tnf emΔARE mice develop spontaneous ileitis and enthesitis as previously described (Kontoyiannis et al., 1999). In addition, bone marrow derived macrophages secrete increased levels of TNF in response to LPS stimulation. We recently established a new germfree and gnotobiotic mouse facility at Ghent University, and $Tnf^{em\Delta ARE}$ mice are currently being rederived germfree for host-microbiota interaction studies in gnotobiotic experiments. We have developed a new TNF/microbiota-driven mouse model of combined gut & joint inflammation, which can serve as preclinical platform to study arthritis and gut inflammation and to test novel therapies, including therapeutic strategies interfering with the microbiota composition.

References

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