TRAM MB-PhD Project Summary

(The completed form should not exceed 2 pages)

PhD project Title
Developmental programming of salivary gland immune cells in Sjögren's Syndrome

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Background

Sjögren's Syndrome (SS) is an auto-immune disease that primarily manifests in the salivary and lacrimal glands, resulting in severe dryness of the mouth and eyes, but also affects other organ system like the synovial joints, where arthritis-like, painful inflammation is common. The aetiology of SS is complex and incompletely understood, and genetic variants only confer a moderately higher risk (1). Environmental pollutants like ubiquitously present toxins and other factors converging on an inflammatory response have been implicated as additional risk factors. Moreover, it is now widely accepted that adverse environments in early life, including fetal development, can have long-lasting impact on health and disease in later life, a phenomenon known as pathological programming. This may also apply to SS, but this has not been addressed to date.

Immune cells both abundantly reside in healthy salivary glands and mediate the effects of SS. Our preliminary observations (using mouse models complimented with human tissue (2)) indicate that innate immune cells, particularly macrophages, seed the developing glands starting in the fetus, and many of these fetal-derived immune cells persist in adult glands as long lived, tissue resident macrophages, where they only slowly turn over from bone marrow-derived progenitors. This is reminiscent of many non-exocrine organs, and suggests that the resident immune compartment of the salivary gland may be particularly susceptible to environmental perturbations during development (see (3)).

Based on the above considerations, we hypothesise that the immune landscape of the salivary glands undergoes programming upon exposure to early life adversity, and that persisting fetal-derived immune cells contribute to an increased susceptibility to SS in adulthood.

Aims

Our research groups primarily use mouse models complimented with human tissue to genetically label and delete immune cells (e.g. (4)), mimic adverse early life environments and model disease. These will be analysed at different life stages by a combination of confocal imaging, histology, high dimensional flow cytometry and transcriptomics. This approach allows us to determine developmental kinetics of immune cells, establish cause-consequence relationships and address cellular and molecular mechanisms. The student will use such models and analyse mice at different

life stages, using the above techniques that are well established in the respective research groups. Specifically, the aims are to:
1. Characterise the resident immune cells in normal, healthy salivary glands
2. Assess if the salivary gland immune compartment is changed by adverse environments in early life (i.e. maternal immune activation, endocrine-disrupting chemicals)
3. Determine if and how this results in an increased susceptibility to an SS-like syndrome

Training and experience provided

This PhD project will be based at the University of Edinburgh's Institute for Regeneration and Repair (IRR) with access to state-of-the-art facilities. This PhD will be jointly supervised by Dr. Emmerson and Dr. Gentek. Our labs are respectively experts in salivary gland immunology, development and disease (2,5,6); and immune ontogeny and programming (3,4) (e.g. in arthritis). This project is thus collaborative in nature, and benefits from the synergy between the expertise of both labs. In addition to hands-on experience, the student will develop independence in planning and executing experimental work and learn essential scientific skills, ie. writing and analysis, interpretation and presentation of their data. They will join enthusiastic colleagues in dynamic, newly established research groups that already work closely together.

Expected outcomes

This project will advance our understanding of the immune cells present in the healthy salivary gland, as well as their role in the pathogenesis of Sjögren's Syndrome. We expect to identify changes in the adult salivary gland immune landscape in response to adverse early life environments that have been linked to an increased likelihood of developing chronic inflammatory and auto-immune disease. Exploiting the power of mouse in vivo models, we will also experimentally determine if and how such changes affect the susceptibility to SS. Thus, whilst fundamental in nature, this project also has translational relevance: Signatures of "programmed" immune cells that we identify can be screened for their relevance to humans. Ultimately, this project could therefore help stratify individuals at risk of developing SS. Moreover, any cellular or molecular mechanisms identified may in the future be exploited as novel targets for preventive or early therapeutic intervention.

References

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