BESTE POSTER NAJAARSDAGEN 2017

Exhaustion of salivary gland stem cells causes hyposalivation in primary Sjögren's syndrome

S. Pringle

Sarah Pringle received her Ph.D. in 2010 from King's College University, London. She studied the generation of articular cartilage from human embryonic stem cells, for the replacement of damaged cartilage in rheumatoid arthritis. She moved to Groningen in 2010 to begin a post-doctoral position in the laboratory of Prof. Rob Coppes (Department of Cell Biology, UMCG), studying the application of salivary gland stem cells in the therapy of radiation-induced hyposalivation. Thereafter she transferred her skills and knowledge to study the involvement of salivary gland stem cells in primary Sjögren's syndrome. The project is a collaboration between Rheumatology and Clinical Immunology/Expertise Center Sjögren (Prof. Bootsma, Kroese, Spijkervet, Vissink) and Cell Biology.

Dr. Sarah Pringle.

WHAT IS THE MOST IMPORTANT MESSAGE OF THE POSTER?

Hyposalivation, reduction of saliva production, characterizes primary Sjögren's syndrome patients. The cause of this hyposalivation was until fairly recently presumed to arise from the effect of mass infiltration of lymphocytes into the gland. Salivary gland stem cells (SGSCs) are cells which reside in the epithelial compartment of the salivary gland, and which proliferate and differentiate into saliva-producing acinar cells, to maintain the homeostasis of the gland. Logically therefore, there must be something wrong with the salivary gland stem cells of patients with pSS, if saliva is no longer produced. We recently developed protocols for the isolation and characterization of SGSCs from human salivary gland biopsy material, and show using these techniques that SGSC functionality (yield, proliferation and differentiation ability; Figure 1) from pSS salivary gland biopsies is reduced. When healthy SGSCs were incubated with proinflammatory cytokines involved in autoimmune disorders such as pSS, namely IFNα, TNFα and IL-6, increased proliferation was observed. Intriguingly, when analyzed using STELA, a technique optimized by collaborators in Cardiff Medical School to determine telomere length, SGSCs from pSS biopsies had significantly shorter telomeres than healthy SGSCs. Pringle suggested that exposure of SGSCs to proinflammatory cytokines induces proliferation and eventual senescence (exhaustion) of the cells, culminating in the inability to proliferate and differentiate into acinar cells and maintain saliva production. She hypothesizes that exhausted SGSCs may therefore underpin hyposalivation in pSS, not lymphocytic infiltration. Pringle will continue experiments to determine exactly which (combination of) cytokines are responsible for SGSC proliferation, and which subset of SGSCs are most susceptible to cytokine-induced proliferation.

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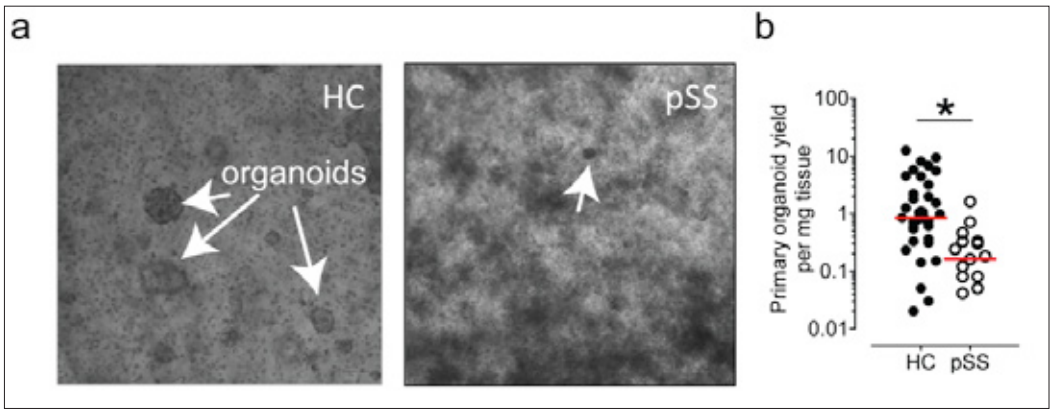

Figure 1. Yield of salivary gland stem cells is significantly lower from pSS biopsies than healthy controls. Salivary gland stem cells are cultured as organoids in a three-dimensional matrix. a) Representative phase contrast microscopy of salivary gland stem cells isolated from healthy controls (HC) and primary Sjogren's syndrome (pSS) biopsies. Arrows depict organoids. b) Quantification of salivary gland stem cells yield per mg of biopsy. Each point is a separate biopsy donor.

WHAT DID SHE THINK OF THE NVR NAJAARSDAGEN?

This was Pringle's second time attending the NVR Najaarsdagen. Several people remembered her project from the year before, and were eager to hear an update. These interactions are in her opinion the most valuable aspects of the NVR Najaarsdagen!

WHAT COULD BE FOLLOW UPS TO THIS RESEARCH?

pSS patients with senescent SGSCs will not benefit, in terms of saliva production, from blockade of immune signaling cascades or immune cells, for example by using JAK-STAT inhibitors. Pringle and colleagues predict that employment of embryonic stem cell technology, to generate new populations of SGSCs from patient skin fibroblasts (iPS technology) will provide a fresh supply of cells to replace those exhausted by cytokines, and provide a durable therapy for hyposalivation in pSS.

WHAT DOES SHE WANT TO DO IN THE NEXT 5 YEARS?

In the coming 5 years, Pringle is excited to further explore the role of the epithelium in Sjögren's syndrome, beginning with project she presented at the NVR Najaarsdagen, and expanding into examining the nature of lymphocyte interactions with the SG epithelium, the involvement of specific chemokine receptors on epithelial cells in pSS pathology development, development of an epithelium-based mouse model of pSS and investigating the generation of SGSCs from embryonic-like iPS cells.

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