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CONNECTIVE TISSUE DISEASES

Prematurely aged stem cells in pSS

Over the past 25 years, theories around the cause of salivary gland hypofunction, a major clinical manifestation of primary Sjögren syndrome (pSS), have steadily moved away from inflammation towards other possible factors, including salivary gland stem cells. Now, in the first study of its kind, salivary gland stem cells from patients with pSS have been isolated and characterized, revealing a prematurely aged, senescent phenotype.

"Salivary gland stem cells are epithelial populations of adult stem cells," explains corresponding author Sarah Pringle. "They reside in the ducts of the salivary gland and are responsible for maintaining salivary gland homeostasis."

"Prior to this work, nothing at all was known about salivary gland stem cells in pSS," says co-author Frans Kroese. "We investigated the regenerative potential of salivary gland stem cells in pSS to attempt to understand the basis for long-term hyposalivation."

Using a salivary gland stem cell 3D organoid culture system pioneered in the lab of Rob Coppes at University Medical Center Groningen, Pringle and colleagues isolated and cultured stem cells from the parotid glands of healthy individuals, patients with pSS and patients with so-called 'incomplete' pSS, who have hallmarks of the disease but minimal lymphocytic infiltrates in the salivary glands.

Overall, patients with pSS had fewer stem cells in their biopsy-obtained parotid gland tissue samples than did healthy individuals. In vitro, the few stem cells isolated from patients with pSS had a lower capacity to self-renew and proliferate than those from healthy individuals, and also had a diminished ability to form mature organoids, suggestive of reduced regenerative potential. "These results may explain why new, saliva-producing acinar cells are inadequately generated by salivary gland stem cells in pSS, and why saliva production remains low," states Pringle.

Differences in the proliferative capacity of salivary gland stem cells from patients with pSS and from those with incomplete pSS led the researchers to theorize that stem cells might be stimulated to divide early in the disease process and to subsequently become senescent. Telomere length analysis revealed shorter telomeres in stem cells from patients with pSS than in those from healthy individuals, suggesting that stem cells from patients with pSS had replicated extensively.

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Additional studies showed that healthy salivary gland stem cells stimulated in vitro with the pro-inflammatory cytokines TNF, IL-6 and IFNα underwent increased proliferation. "Interestingly, these cytokines also seemed to induce differentiation of salivary gland stem cells into a subset of cells considered to be regeneratively inferior," says Pringle.

"The results of this study suggest that after successful treatment of the glandular tissue to minimize lymphoid infiltration, the salivary gland will still not, or very poorly at best, undergo regeneration," explains Kroese. "Looking to the future, we are aiming to provide a solution for patients with pSS whose salivary gland stem cells are senescent by generating fresh salivary gland stem cells from induced pluripotent cells."

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