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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Epithelial Cell Activation in Sjögren's: A New Target in Chronic Inflammation

Ryan Quigley:
You're listening to *Living Rheum* on ReachMD, and this is an *AudioAbstract*. I'm Ryan Quigley, and today, I'd like to highlight some new insights into the underlying mechanisms of primary Sjögren's disease—particularly, how certain transcription factors may regulate key inflammatory signals at the genetic level.

Sjögren's disease continues to challenge clinicians because of its broad spectrum of symptoms and its uncertain pathogenesis. While we know it involves chronic autoimmune activation and glandular dysfunction, the initiating events—and why they persist in some patients—remain only partially understood. Greater awareness of those upstream regulatory mechanisms could be the key to developing more effective therapies.

A study published in June 2025 in the *International Journal of Molecular Sciences* took a closer look at exactly that question, using salivary gland epithelial cells exposed to interferon gamma in vitro to simulate the chronic immune stimulation seen in Sjögren's. Researchers focused on how this immune exposure changed the expression of key genes involved in inflammation, including *IL33*, *STAT1*, and *ETS1*.

What the study found helps fill in some missing pieces. The findings showed that prolonged interferon gamma stimulation led to significantly increased expression of *STAT1*, which functions as both a signaling transducer and a transcriptional activator. Elevated *STAT1* is a known marker in many autoimmune conditions, and in Sjögren's, it appears to amplify the inflammatory cascade within epithelial tissue—essentially reinforcing the immune system's attack on the salivary glands.

Equally interesting is the role of *ETS1*, another transcription factor that was found to be upregulated under chronic stimulation. While *ETS1* is traditionally associated with T cell development, this study found that it also plays a role in epithelial cells by regulating *IL33*, a cytokine increasingly implicated in autoimmunity. IL-33 is part of the alarmin family—molecules that alert the immune system when tissue is damaged—and its increased expression suggests that epithelial cells in Sjögren's are not passive targets but may actively shape the local immune environment.

These findings carry important implications for how we conceptualize the disease process. Rather than viewing salivary gland damage as simply the result of lymphocytic infiltration, this model supports a more interactive framework where epithelial cells, under prolonged interferon signaling, become immunologically active and sustain chronic inflammation through gene-level changes.

Of course, it's important to remember that these findings come from an in vitro model using immortalized salivary gland epithelial cells, not primary tissue from patients. While this approach helps isolate specific pathways, it can't fully replicate the complex immune microenvironment seen in vivo. There's also the question of whether these transcriptional changes occur in the same way across all patients, given the known heterogeneity of Sjögren's. So while the data are compelling, further validation in primary tissue and animal models will be essential.

But that being said, these findings could have significant impacts on care, pointing to potential future therapeutic targets. Modulating *STAT1* signaling, for example, could help interrupt the amplification loop of chronic inflammation. Targeting IL-33 pathways could also offer new avenues for patients whose disease is refractory to B-cell depletion or hydroxychloroquine.

These findings could also suggest that Sjögren's may need to be managed earlier and more aggressively, even in patients who appear to have limited systemic involvement. If the disease process begins with dysregulated epithelial responses, then waiting for overt glandular destruction or systemic flares may represent a missed opportunity for early intervention.

And finally, at a practical level, these results reinforce the idea that not all patients with primary Sjögren's follow the same molecular trajectory. Understanding which transcriptional programs are active in a given patient could eventually allow us to stratify care, choosing therapies that match not just symptoms but the dominant signaling pathways at work.

This knowledge contributes to a larger shift in our understanding of autoimmune disease from a purely immune cell–driven process to one where tissue-resident cells also play a critical role in disease maintenance and progression. For Sjögren's, this may represent a turning point in how we think about diagnosis, monitoring, and eventually, targeted therapy.

This has been an *AudioAbstract* for *Living Rheum,* and I'm Ryan Quigley. To access this and other episodes in our series, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

Reference:

Kepple DD, Thornburg TE, Beckman MF, Bahrani Mougeot F, Mougeot JC. Elucidating Regulatory Mechanisms of Genes Involved in Pathobiology of Sjögren's Disease: Immunostimulation Using a Cell Culture Model. *Int J Mol Sci*. 2025;26(12):5881. Published 2025 Jun 19. doi:10.3390/ijms26125881