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How Epithelial Cells Sustain Autoimmunity in Sjögren's Disease

You're listening to *AudioAbstracts* on ReachMD. I'm Ryan Quigley, and today, I'll be talking about a narrative review published in *Current Opinions in Immunology*.

Sjögren's disease has traditionally been viewed as an autoimmune attack on the salivary and tear glands. But what if the epithelial cells lining those glands aren't simply victims of inflammation? What if they're actively driving the immune response?

That's the central question explored in this review, which brings together decades of immunologic and molecular research.

The evidence supports a concept known as "autoimmune epithelitis." In this model, epithelial cells don't just sustain immune-mediated damage. They actively recruit and stimulate immune cells, helping perpetuate inflammation.

Early evidence came from tissue biopsies showing lymphocytes clustered around epithelial structures in the salivary glands. Similar patterns appeared in the lungs, kidneys, and bile ducts, reinforcing the systemic nature of Sjögren's.

But perhaps more revealing is how these epithelial cells behave.

Studies show that salivary gland epithelial cells abnormally express immune-related molecules, including HLA-DR and co-stimulatory proteins such as CD80 and CD86. These molecules enable epithelial cells to interact directly with T-cells, essentially functioning as nonprofessional antigen-presenting cells.

And importantly, this activity may not depend entirely on surrounding inflammation.

When investigators cultured epithelial cells from patients with Sjögren's, the cells retained their activated immune characteristics outside the glandular environment. Functional studies also demonstrated their ability to stimulate T-cell proliferation.

These findings suggest that epithelial dysfunction may be an intrinsic feature of the disease, rather than simply a consequence of immune-mediated injury.

The review also describes how epithelial cells sustain inflammation by releasing cytokines, chemokines, and B-cell activating factor. These signals recruit and support immune cells, while the release of autoantigens may further amplify autoimmune activity.

Together, these processes create a potential cycle of epithelial dysfunction, immune activation, and tissue injury.

So what triggers this process?

Several mechanisms are under investigation, including viral infections, type one interferon signaling, autophagy, and mitochondrial dysfunction. Coxsackievirus has been implicated, although findings haven't been consistently replicated.

These mechanisms also raise an important therapeutic question: Could restoring epithelial function help interrupt the autoimmune cycle?

Most current therapeutic approaches focus on immune pathways, particularly B-cell activity. But emerging research suggests epithelial cells themselves may represent additional treatment targets.

For example, the review highlights laboratory findings involving tofacitinib, a Janus kinase inhibitor. The drug reversed mitochondrial abnormalities and mitochondrial DNA leakage in salivary gland epithelial cells, suggesting a potential way to reduce innate immune activation. Patient-derived salivary gland organoids may also offer new opportunities to study these mechanisms.

Of course, this is a narrative review, not a clinical trial. Much of the evidence comes from tissue studies and experimental models. Whether epithelial dysfunction initiates autoimmunity remains uncertain, and the clinical benefits of epithelial-targeted therapies still need evaluation.

Still, these findings offer a broader understanding of Sjögren's as a disease driven by interactions between epithelial cells and the immune system. They also point toward a potential therapeutic direction: restoring epithelial function alongside controlling immune activity.

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

Reference:

Moutsopoulos HM. The epithelial cell in Sjögren's syndrome: from passive target to orchestrator of autoimmune reactivity. *Curr Opin Immunol.* 2026;102:102815. doi:10.1016/j.coi.2026.102815