The Salivary Gland Epithelial Cell in Sjögren's Syndrome: What Are the Steps Involved in Wounding or Killing Their Secretory Function?

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Editorial

The Salivary Gland Epithelial Cell in Sjögren’s Syndrome: What Are the Steps Involved in Wounding or Killing Their Secretory Function?

In their article in this issue of *The Journal*, Ping, *et al* used *in vitro* cultures of epithelial cells from salivary gland tissues of patients with Sjögren’s syndrome (SS), and from control patients lacking inflammatory infiltrates.

The basic process of salivary gland cell death (apoptosis) was similar both in SS salivary epithelial cells and in normal salivary epithelial cells. Thus, the key difference in the salivary gland dysfunction of the patient with SS *in vivo* appears to be the presence of focal T cell infiltrate in the SS gland that serves as a source of CD40 ligand (CD40L).

Although their article is a nice exercise in molecular biology, with the expected molecular gymnastics (electrophoretic mobility shifts, Western blots, and TUNEL assays), the ultimate questions that arise are: What do these results mean for the patient with SS with dry mouth? How do these results influence the future for therapeutic selection of options?

The current study by Ping, *et al* is an extension of their report from 2005 on the role of CD40 and Fas in SS salivary gland cells. Subtle points in the present study include the observation that inhibition of p38 and nuclear factor-κB (NF-κB) activation does not fully prevent CD95-mediated apoptosis (see their Figure 4). So there must be other pathways that CD40 is activating.

Particularly in the regulation of p38 and NF-κB, many different factors influence their canonical and noncanonical activation. Thus, additional factors *in situ* determine the epithelial cell’s decision toward apoptosis or not.

Overall, the situation is a good bit more complicated *in vivo* than measured during *in vitro* cultures. Nevertheless, these studies provide a framework for preclinical evaluation of novel therapeutic agents to improve epithelial cell function. In particular, the regulation of p38 and NF-κB may subsequently influence many different pathways (including both their canonical and noncanonical activation) to allow a return of normal functional status of salivary gland epithelial cells even in a proinflammatory microenvironment.

There has been extensive literature on the differences between salivary gland epithelial cells of healthy controls and of patients with SS. These include the upregulation of HLA-DR due to interferon-γ, Fas and Fas ligand (FasL) induction by CD4 T cells, as well as changes in other intracellular markers such as aquaporin and costimulatory cell-surface markers. The paradox of these studies is that the initial steps of apoptosis (Fas and FasL) are expressed in SS biopsies, but the actual progression to apoptosis (i.e., DNA fragmentation) *in situ* is a rare event in the SS biopsy.

In order to understand the state of the SS salivary gland epithelial cell in purgatory (i.e., the gland becomes dysfunctional but not actually destroyed with fragmented DNA), we need to learn more about the enzymatic activation cascade that leads to molecular “demise” or “dysfunction” of the salivary gland.

Since the initial flurry of activity about Fas and FasL expression in SS glands a decade ago, studies in this area have largely dropped from research interest in SS. However, research into pharmacologic inhibitors of p38 mitogen-activated protein kinases (p38MAPK) and NF-κB has made extensive progress during this interval as agents for treatment of rheumatoid arthritis.

In short, the good news is that the SS gland is not destroyed (only about 50% loss of the acini or ducts in SS patients with severe dryness). We might be able to mitigate the dysfunction of the epithelial cells if we better understand the underlying mechanisms. This is in contrast to type I diabetes, endstage liver disease, or renal failure, where significant symptoms appear only after irreversible destruction of over 90% of the parenchymal cells.

It is time to see if we can use the knowledge of familiar molecules such as p38MAPK and NF-κB (and the abundant supply of their inhibitors) to resuscitate the salivary gland epithelial cells of patients with SS. Thus, it is worth a new look at these familiar (and incredibly multifaceted) mole-
In summary, Ping, et al note that CD40L upregulates the expression of p38MAPK and Fas, resulting in the induction of apoptosis. This process occurs equally in salivary gland cells derived from both healthy controls and patients with SS. Normal salivary epithelial cells could be “tricked” into expressing proapoptotic factors when incubated with interferon-γ and anti-CD40 monoclonal antibody to mimic the conditions of the SS epithelial cell.

The prior state of “inflammation” in the SS gland does not appear to be a necessary factor for “early death” of epithelial cells. Now that well defined factors such as p38MAPK and NF-κB have been implicated, a new array of therapeutic options might be considered.

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