**Why do male mice spit soluble enzymes that hydrolyze extracellular nucleotides?** Focus on “Prostatic acid phosphatase is the main acid phosphatase with 5’-ectonucleotidase activity in the male mouse saliva and regulates salivation”

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The 5’-ectonucleotidases found on the surface of most mammalian cells and in blood serum serve as a source of adenosine derived from extracellular nucleotide degradation (11). The 5’-ectonucleotidases are phosphatases whose substrate is extracellular adenosine 5’-monophosphate (AMP) generated from adenosine 5’-tri- and diphosphates (ATP and ADP) released from injured tissues to stimulate cellular responses via P2 purinergic receptors (7). A recent study by Quintero et al. (10) investigated prostatic acid phosphatase (PAP), a 5’-ectonucleotidase that plays a role in the development of adenocarcinoma of the prostate gland. These authors showed that PAP exists as two alternative splice variants, a transmembrane prostatic acid phosphatase (TMPAP) and secreted PAP (sPAP). TMPAP and sPAP are distinguished functionally from other 5’-nucleotidases through inhibition by L-(-)−tartrate,

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Fig. 1. Prostatic acid phosphatase (PAP) signaling in salivary glands and saliva.

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ability to cleave phosphomonoesters besides AMP, and activity over a wide pH range (i.e., 3–8). TMPAP activation inhibits endocytosis/exocytosis through interaction with snapin (10), a soluble N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE)-associated protein (5) that counteract the nociceptive (i.e., pain-producing) effects of ATP (4) occurring through activation of P2X receptor ATP-gated ion channels (2; Fig. 1). However, little information is available concerning physiological roles of sPAP in biological fluids.

In this issue of American Journal of Physiology-Cell Physiology, Araujo et al. (1) attempt to understand the role of TMPAP and sPAP in a secretory organ, the submandibular gland (SMG), which secretes fluid, proteins, and other factors into saliva, thereby bathing the oral cavity with antimicrobial and digestive agents. Using PAP−/− mice, the authors evaluate effects of deletion of this 5′-ectonucleotidase on SMG function. Comparisons between PAP−/− and wild-type SMG indicate that TMPAP is primarily expressed in granular convoluted tubule (GCT) cells of the duct but not acinar cells. Remarkably, deletion of PAP increases α-adrenergic and muscarinic cholinergic receptor-mediated salivary secretion and enhances expression of genes promoting inflammation and proliferation, particularly interferon-dependent proinflammatory genes. The authors suggest that this increase in saliva secretion relates to loss of negative control by TMPAP of exocytosis (Fig. 1). PAP deletion also increases B and T cell infiltration of SMG and levels of miR-146a that have been associated with prevention of tissue damage. Together with observations of proliferating acinar cells after PAP deletion, these results strongly suggest that SMG homeostasis in PAP−/− mice is maintained by an immune response without salivary gland degeneration seen with immune cell infiltration of SMG in the autoimmune disease Sjögren’s syndrome (SS; 3, 8).

Another important finding is that sPAP is only present in male mouse saliva, which correlates with reduced levels of GCT cells in female versus male SMG and is consistent with sexual dimorphism in rodent salivary glands (6). The authors suggest that mouse sPAP plays a male-specific function in which licking of wounds (perhaps caused by fighting) deposits sPAP-containing saliva that induces an anti-nociceptive response in wounded tissue by participating in the generation of adenosine from released nucleotides to activate A1 receptors (Fig. 1). Since SS has a female predominance in rodents and humans (3, 8), it would be interesting to determine whether PAP in males plays a protective role in SS by promoting gland homeostasis and delay in the onset of salivary gland dysfunction and degenerative immune cell infiltration. Another question remaining is whether extracellular nucleotides are released into the oral cavity due to tissue injury of oral epithelium caused by inflammation, exposure to toxins, SS, and radiation-induced damage occurring as a side effect of cancer therapy. Once released, degradation of extracellular nucleotides by ectonucleotide diphosphohydrolases (eNTPDases), ectoATPases, and ectoADPases would generate AMP whereupon 5′-ectonucleotidases including PAP would yield adenosine that could either be taken up by nucleoside transporters in cells and salvaged or activate P1 adenosine receptors (7, 9, 11). Further study is needed to investigate whether sPAP in saliva plays a role in the regulation of purinergic signaling in the oral cavity under physiological and pathological conditions.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

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