

**AMP and microamps: neutrophil-derived chloride secretagogue identified.**

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Research Article

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Neutrophils represent important constituents of the inflammatory response to infectious agents in the intestine. However, in intestinal inflammation, where there is a marked increase in the number of neutrophils in the mucosa, there is also associated intestinal dysfunction. Several studies have sought to examine the role of neutrophils in mediating pathophysiological responses of the intestine in Crohn's disease and ulcerative colitis. In these conditions, neutrophils migrate through the intestinal mucosa into the intestinal lumen, under the influence of both endogenous and luminal chemoattractants which are present in increased amounts in inflamed tissue. Neutrophils are thought to contribute to the tissue damage of inflammatory bowel disease and other colitides by virtue of their ability to synthesize and release a panoply of cytotoxic mediators.

An important symptom of intestinal inflammation is secretory diarrhea, which may be a primitive defense mechanism that serves to "flush" the lumen and thereby dilute and expel toxins, microorganisms, and damaged cells. An increasing body of evidence suggests that immune effector cells, and in particular mast cells and neutrophils, may directly contribute to this diarrhea by releasing substances that stimulate the principal transport process underlying intestinal fluid secretion, epithelial chloride transport (1). Madara's group has made significant contributions to this field, particularly in regard to the ways in which neutrophils may contribute to the process. They have established an *in vitro* model of the crypt abscess, an accumulation of neutrophils above the apical surface of intestinal epithelial cells that is a common feature of ulcerative colitis. In this model, neutrophils or their products are incubated with monolayers of T84 cells, a human cell line which displays the chloride secretory function of the native intestinal crypt epithelium (2). They have shown previously that neutrophils release an epithelial chloride secretagogue (NDS) that is preferentially active on the apical surface of T84 cells (3). In this issue of *The Journal* (4), they definitively identify this secretory activity as 5'-AMP.

Previous findings with NDS had revealed that its secretory activity on T84 cells appeared similar to that induced by adenosine, as studied by our laboratory (5, 6). Thus NDS was apically active and appeared to use signal transduction pathways that differed from the classical mechanisms known to activate epithelial chloride secretion, namely cAMP, cGMP, or calcium (3). In fact, recent studies have implicated arachidonic acid or a metabolite in the secretory action of adenosine (7). It is of interest, therefore, that the activity of NDS, now identified as 5'-AMP, appears to be dependent on the apical expression of a glycosyl phosphoinositide-linked ecto-5' nucleotidase with properties similar to the cluster of differentiation antigen CD73, and thereafter on the presence of adenosine receptors. Adenosine rather than 5'-AMP appears to be the ultimate medi-

ator in the chain of signaling from neutrophils to the epithelium. The ability of 5'-AMP, but not adenosine, to increase chloride secretion across T84 cells was attenuated by an ecto-5' nucleotidase inhibitor. In contrast, the activity of both 5'-AMP and adenosine could be inhibited by an adenosine receptor antagonist.

The requirement for hydrolysis on the apical surface of epithelial cells to activate a paracrine factor such as 5'-AMP multiplies the possibilities for regulation both at the site of release and at the site of hydrolysis. Because adenosine receptors are widespread, the need for both the receptor and the ectoenzyme in close proximity permits very specific targeting of the signal. In the intestine, a prosecretory effect of neutrophils is thus directed at the apical domain of crypt epithelial cells. Furthermore, NDS would only be expected to have significant activity in the setting of ongoing inflammation, once neutrophils have been concentrated within the lumen. Future screening for the precise location of CD73 in other tissues may indicate sites where 5'-AMP is also likely to be an important regulator. CD73 has in fact been identified in the liver, on mononuclear blood cells and in mammary myoepithelium.

These studies have wide-ranging implications. Adenosine receptors are present on multiple cell types; among others, airway and renal epithelial cells and epidermal keratinocytes, autonomic, sensory, and central neurons, mast cells and even neutrophils themselves. Where CD73 is also present, activated neutrophils have the potential for autocrine regulation or regulation of the function of these diverse cell types. In the airway, for example, neutrophil accumulation occurring during asthma or the adult respiratory distress syndrome might thus alter the amount and composition of lung lining fluid. In turn, this would contribute both to symptomatology and to the further secondary regulation of other cells in the airway lumen. The additional and more general significance of this study lies in its delineation of a paracrine defense mechanism mediated by a low molecular weight "promediator," 5'-AMP. The activity of this promediator, which may involve novel signal transduction pathways (3, 7), is targeted not only by specific receptors, but also by the expression of a membrane-bound enzyme needed to hydrolyze the promediator to its active form. Further examples of such binary regulation of mediator action are likely to be forthcoming.

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