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Autodigestion in Physiological Shock, Organ Dysfunction and Death

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Abstract: A longstanding question in research on organ failure after physiological shock (such as trauma, burns, sepsis, surgery and medical emergencies) is the underlying mechanism for a progressive loss of cell and tissue functions. Our systematic analysis of this problem has served to identify digestive enzymes as key players [1, 2]. After synthesis and discharge from the pancreas, the digestive enzymes are usually contained inside the lumen of the small intestine where they break down food every day. Escape of the digestive enzymes out of the lumen of the intestine is kept to a minimum by the mucosal barrier in the intestine, an epithelial cell sheet covered by an outer mucin layer with low permeability for digestive enzymes.

Our evidence suggests, however, that containment of digestive enzymes may be compromised when the mucosal epithelial permeability rises. For example, during low blood pressure perfusion of an intestine or exposure to bacterial products (e.g. endotoxins), the epithelium opens to molecules the size of digestive enzymes. These degrading enzymes escape into the systemic circulation via venules and lymphatics draining the intestine and by transport across the wall of the small intestine into the peritoneum. In the wall of the intestine they severely degrade the intestine itself ("autodigestion") [3]. In the circulation, digestive enzymes trigger secondary events that degrade cell functions. For example, digestive proteases (e.g. trypsin, elastase) activate other degrading enzymes such as matrix metalloproteinases, and in combination degrade plasma proteins and membrane receptors. Activated proteases in plasma may cause insulin resistance (i.e. type II diabetes) by cleaving the extracellular domain of the insulin receptor, compromise blood pressure regulation by clipping adrenergic receptors in arteries and arterioles, increase endothelial permeability and cause tissue swelling by clipping inter-endothelial junction proteins, promote capillary rarefaction and apoptosis by cleaving growth factor receptors on endothelial cells, or contribute to immune suppression by cleaving membrane adhesion receptors (selectins, integrins) on leukocytes and endothelium. The evidence suggests that the essential digestion process in life can be accompanied by autodigestion and death. We will discuss how to bioengineer new approaches to reduce autodigestion.

Keywords: Organ failure; digestive enzymes; intestine; epithelium; mucosal barrier; membrane receptor cleavage

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