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Review

Regulation and pathophysiological role of epithelial turnover in the gut☆

Q3 Claudia Günther, Barbara Buchen, Markus F. Neurath, Christoph Becker*

Department of Medicine 1, University of Erlangen-Nuremberg, Erlangen, Germany

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ABSTRACT

Cell death in the intestinal epithelium has to be tightly controlled. Excessive or misplaced epithelial cell death can result in barrier dysfunction and, as a consequence thereof, uncontrolled translocation of components of the microbial flora from the lumen into the bowel wall. Susceptibility to gastrointestinal infections or chronic inflammation of the gut, as observed in patients with inflammatory bowel disease, can be the result of such dysregulation. Conversely, defects in cell death initiation might lead to an irregular accumulation of epithelial cells and cause intestinal cancer development. Until recently, activation of caspases in the intestinal epithelium was considered as a potential contributor to barrier dysfunction and as a pathogenic factor in the development of intestinal inflammation. Thus blocking of caspases appeared to be a potential therapeutic option for patients with inflammatory bowel disease. Recent studies on necroptosis however demonstrated that also inhibition of caspases can cause barrier dysfunction and intestinal inflammation. Caspase-8 on top of its functions in the extrinsic apoptosis pathway also controls necroptosis and turns out to be an essential molecule in regulating tissue homeostasis in the gut. Epithelial caspase-8 therefore emerges as a checkpoint not only of cell survival and cell death, but also as a regulator of the mode of cell death. According to this model, both excessive activity as well as a lack of activity of caspase-8 results in epithelial cell death and intestinal inflammation and caspase-8 needs to be tightly controlled to warrant tissue homeostasis in the gut.

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Contents

1. Introduction 00
Q4 2. Characteristics of cell death in the intestinal epithelium 00
3. Necroptosis: a new mode of cell death with implications for gut homeostasis 00
4. The signalling pathways towards necroptosis 00
4.1. Tnf-R complex 2a (cell survival) 00
4.2. Tnf-R complex 2b (apoptosis) 00
4.3. Tnf-R complex 2c (necroptosis) 00
5. Triggering factors for apoptosis and necroptosis in the intestinal epithelium 00
5.1. Death receptor mediated epithelial cell death 00
5.2. PAMP mediated cell death 00
5.3. TLR4 00
5.4. TLR3 00
5.5. Cell death induced by interferons 00
References 00

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* Corresponding author at: Department of Medicine 1, University of Erlangen-Nuremberg, Hartmannstrasse 14, 91054 Erlangen, Germany. Tel.: +49 9131 8535886; fax: +49 9131 8535959.
E-mail address: christoph.becker@uk-erlangen.de (C. Becker).

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1. Introduction

The gut harbours the largest part of our individual immune system. The reason for this high number of immune cells is seen in the fact that the gut is permanently exposed to a plethora of antigens and potential pathogens which are present in the food or the microbial flora [1]. To maintain intestinal homeostasis and prevent an excessive activation of immune cells within the gut wall, it is necessary that the microbiota is strictly separated from the underlying immune system. It has been reported that excessive infiltration of bacteria or bacterial products leads to a deregulated intestinal immune response resulting in the development of gastrointestinal disorders, including inflammatory bowel diseases (IBD) or infectious colitis [2].

The first line of defence of the intestinal mucosa is represented by a single cell layer of intestinal epithelial cells (IECs). These epithelial cells are of paramount importance in host defence by providing on the one hand a physical barrier and on the other hand highly specialized innate immune functions [3]. The physical barrier is established by the close and firm contact of neighbouring intestinal epithelial cells, which relies on the formation of tight junctions. Innate immune functions are carried out mainly by goblet cells and paneth cells, highly specialized epithelial cells with secretory functions [3]. Goblet cells release mucins, which give rise to a viscous mucous layer on the gut wall, hampering the access of bacteria to the epithelial surface [4]. Paneth cells in contrast release granules containing antimicrobial peptides [5]. These antimicrobial peptides are thought not only to kill bacteria; their diversity and regulated expression patterns are believed to actively shape the microbial communities present within the gut lumen. Antimicrobial peptides and mucins together form a thick bactericidal mucous layer which hampers access and survival of bacteria adjacent to the epithelium [5].

Besides its important functions in generating a barrier against the external environment, the intestinal epithelium is also the most vigorously self-renewing tissue of adult individuals [3]. Intestinal epithelial cells are generated by proliferating stem cells at the bottom of the Crypts of Lieberkühn [6]. During their short lifetime of 4–5 days, intestinal epithelial cells move up towards the intestinal surface [3]. During this process undifferentiated cells differentiate to functionally active absorptive enterocytes or to other epithelial cell types. Once the cells reach the luminal surface, they die and are released from the epithelial cell layer. Disturbances within this highly regulated system can cause serious diseases. Excessive or misplaced cell death has been shown to cause barrier disruption and chronic inflammation. Conversely, deficient cell death can lead to dysplasia and cancer [7]. It is therefore obvious, that cell death has to be tightly controlled in order to maintain tissue homeostasis in the gut.

Historically, cell death was differentiated into apoptosis, a programmed form of cell death initiated by intracellular or extracellular triggers, and necrosis, an unregulated form of injury-like cell lysis [8]. Studies of the past years have made it very clear, that this simplistic discrimination might be an oversimplification of cell death regulation. The discovery of alternative forms of cell death including autophagy and necroptosis has dissolved the strict classification into necrosis and apoptosis. In this review we will revise the differences between apoptotic and necrotic cell death in the intestinal epithelium and will then explore the mechanisms and triggering factors which induce and regulate apoptosis and programmed necrosis.

2. Characteristics of cell death in the intestinal epithelium

Cell death with its different characteristics is an elementary process for tissue development and homeostasis to eliminate superfluous, damaged or aged cells. This is of major importance for the GI-tract, since the intestinal epithelium undergoes continuous and rapid self-renewal. The majority of intestinal epithelial cells have a very short life span and are renewed every 4–5 days [3,6]. The small intestinal epithelium can be divided into villi, which contain terminal differentiated cells and the crypts of *Lieberkühn* which contain a small number of stem cells [6]. Intestinal stem cells at the crypt bottom proliferate and therefore are critical to renew the intestinal epithelial cell layer. Few stem cells at the crypt bottom give rise to a larger number of so called transient amplifying cells, undifferentiated cells that still have mitotic potential [6]. Newly generated cells within the crypts migrate upward towards the villous tip. During this migration period, the cells differentiate to specialized epithelial cells, including absorptive enterocytes, goblet cells or enteroendocrine cells [3]. The continuous proliferation at the crypt bottom is thought to be the driver of this upward cellular movement. Once the cells reach the tip of the villous, they are shed into the gut lumen in a process, which is associated with epithelial cell death [9].

The continuous self-renewal therefore critically depends on proliferation of stem cells within the crypts and cell loss at the villous tip. Epithelial cell renewal and cell death needs to be tightly regulated as irregularities might cause pathologies, like inflammation and cancer [10–13]. As such, excessive cell death of IECs on the one hand is thought to cause barrier defects, invasion of bacteria and subsequent inflammation [10]. On the other hand, defective cell death activation has been associated with the development of colorectal cancer [14].

Historically, cell death has been divided into a regulated or programmed form and an unregulated more injury-like form. The most common form of programmed cell death has been described in the early 1970s as apoptosis [8]. Apoptosis can be initiated by a wide variety of stimuli including DNA damage, nutrient deficiency, endoplasmic reticulum (ER) stress, growth factor withdrawal, heat shock, developmental cues and ligation of death-receptors on the cell surface [15]. Depending on the origin of the death inducing stimuli, apoptosis is mediated through either the intrinsic or extrinsic pathway. Both apoptotic pathways depend on enzymatic cascades of caspases [16]. Morphological characteristics of apoptosis include membrane blebbing, apoptotic body formation, cell shrinkage, chromatin condensation and DNA fragmentation [16,17]. Apoptotic cells can be recognized by neighbouring immune cells, like macrophages, leading to the phagocytosis of dying cells, a mechanism that might protect the host from cell death associated inflammatory processes [Taylor, 2008, #241, 18]. Under steady state conditions cell death is rarely observed in the intestinal epithelium [11]. However, it has been described that it can occur at one hot spot along the crypt-villus axis, represented by the villus tip, where aged epithelial cells are replaced by neighbouring cells [18,19]. This process has been referred to as “homeostatic cell shedding” [20]. Although cells activate caspases during the process of shedding shortly before they are expelled into the gut lumen, accumulating evidence indicates that homeostatic cell shedding occurs at least functionally independent of apoptotic cell death initiation [9,21,22]. The fact that apoptosis might not be required for epithelial turnover in the gut, at least under steady state conditions, is supported by studies demonstrating that mice deficient for central molecules of the apoptosis pathway show only little structural changes [19,23]. For example mice deficient for caspase-3 were described to show no major morphological differences in the development of the gastrointestinal tract, suggesting that the effector caspase-3 might be dispensable for tissue homeostasis in the gut [24–26]. This was further supported by murine knockout studies of other cell death related genes like Bcl-2 (B-cell CLL/lymphoma 2) and Bax (BCL2-associated X protein) [27]. It has been demonstrated that homozygous Bcl2-null mice show equal levels of spontaneous

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