This issue of the *Journal of Innate Immunity* is devoted to exploring 'Apoptosis, cell death and innate immunity' and aims to spotlight a few selected issues that might provide future opportunities to modulate inflammation. Infections elicit diverse host responses that include activation of the innate immune system, inflammation and programmed cell death, which is a pivotal process that tailors host–pathogen interactions. The mechanisms of pathogen-induced cell death often involve modulation of the apoptotic response, as has been demonstrated in neutrophils [1].

Apoptosis, the best-described form of programmed cell death, is mediated by the caspases, which are cysteinyl aspartate-specific proteinases. Initiator (2, 8, 9 and 10) and effector (3, 6 and 7) [2] caspase family members are involved in various cell death events: mitochondrial outer membrane permeabilization, cytochrome c and Smac/DIABLO (second mitochondrion-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low p) release into the cytosol, DNA fragmentation, chromatin condensation, loss of membrane asymmetry, apoptotic body formation and generation of 'eat-me signals' that stimulate apoptotic cell phagocytosis by macrophages or surrounding cells. Because the cytoplasmic contents of apoptotic cells are not spilled into the extracellular medium, apoptosis does not trigger an inflammatory response and, hence, is considered immunologically silent [3].

Cell survival during infection or tissue injury is regulated by integrating different pathways via immune receptors (e.g. members of the TNF superfamily such as TNFR1, CD95 or Toll-like receptors [4]), or the intracellular sensors, nucleotide-binding and oligomerization domain (NOD)-like receptors [5, 6], all of which can instigate inflammatory responses and modulate the cell's survival/death balance. NOD-like receptors can assemble into large multiprotein complexes, termed inflammasomes, which can activate caspase-1, a proteolytic enzyme that cleaves and activates the secreted cytokines interleukin-1β and interleukin-18, thereby initiating an inflammatory response [7]. The review by Yazdi et al. [8] provides a comprehensive overview of the inflammasome, caspase-1 activation and how this protein complex is regulated. Diverse endogenous, microbial or chemical stimuli activate that oligomeric protein platform, thereby initiating inflammatory cell recruitment and engagement. Inflammasomes are essential regulators of inflammation and their dysregulation has clinical implications. Notably, activated caspase-1 can also trigger pyroptosis, a form of cell death with necrosis, whose most prominent morphological feature is the loss of plasma membrane integrity, with liberation of the cytoplasm's highly inflammatory contents into the extracellular medium, thereby emphasizing the distinct form and function of this programmed cell death [9]. It has become apparent that cells also combat infection by activating autophagy, an alternative route to the digestive lysosomes [10].

Neutrophils and monocytes/macrophages, professional phagocytic cells, are key anti-infectious actors in host defense but are also inflammatory cells able to medi-
ate tissue damage [11]. Although most ingested microorganisms are killed readily inside neutrophils, several obligate or facultative intracellular pathogens survive even in this hostile environment. Extension of the life span of neutrophils is a general escape mechanism of pathogens residing in neutrophils. Since microbes entering macrophages via the uptake of infected apoptotic neutrophils may survive and multiply in macrophages, apoptotic neutrophils can serve as ‘Trojan horses’ for certain pathogens [12].

Neutrophil apoptosis and elimination must be tightly regulated to avoid uncontrolled inflammation. Herein, Fox et al. [13] review recent advances in our understanding of the molecular mechanisms governing neutrophil apoptotic pathways and their therapeutic manipulation in excessive innate immune responses. Cystic fibrosis (CF) is such an example: it is characterized by chronic bacterial colonization with intense and uncontrolled neutrophil-dominated airway inflammation. The observations by Moriceau et al. [14] demonstrate late neutrophil apoptosis in CF children and their parents, who do not have chronic bacterial airway infections, thus suggesting that CF neutrophils are constitutively dysregulated. These data identified neutrophils as relevant cells to target to dampen CF-associated airway inflammation [14]. Neutrophil extravasation at inflammation sites precedes a second wave of emigrating monocytes [15], whose life span must be tightly controlled by appropriate signals (reviewed by Parihar et al. [16]). Recent advances in monocyte biology support the existence of several monocyte subsets with distinct functions and recruitment behaviors, and generated hypotheses that their survival might be differentially modulated, an exciting but still undeciphered aspect of innate immunity regulation. Indeed, because they can phagocytose apoptotic cells, monocytes play a crucial role in inflammation resolution. Hence, unraveling the molecular basis of apoptotic cell recognition is of critical importance in innate immunity, and numerous receptor–ligand pairs have been implicated in apoptotic cell engulfment [17]. The low-density lipoprotein receptor-related protein-1 (LRP/CD91) mediates macrophage–apoptotic cell interactions but its role was recently challenged. Kozmar et al. [18] provide new data showing that the operative molecular pathway involved in apoptosis induction might affect the ensuing macrophage recognition of apoptotic cells and the resulting inflammatory response, thus indicating that monocyte recognition of apoptotic cells is more complex than previously thought.

The highly conserved heat-shock proteins (HSP) can be considered stress proteins, because they accumulate in cells exposed to heat or other various stressful stimuli, and are considered potent regulators of cell death. Notably, Joly et al. [19] focus on the dual mediating roles of HSP: modulating cell apoptosis intracellularly and regulating the innate immune response extracellularly. Their review emphasizes the potential therapeutic contribution of controlling intracellular and extracellular HSP functions to modulate cell survival in cancer, which might also be pertinent for modulating immune-cell survival during inflammation.

This selection of topics dealing with apoptosis and innate immunity highlights the tight connections between immune-cell activation and cell death. This overview also exposes the wide range of ways in which innate immunity could be modulated as a therapeutic approach to numerous pathologies.

Véronique Witko-Sarsat, Paris

References


Editorial


