

Commentary

Death of the septic monocyte: is more better?

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See related research by Giamarellos-Bourboulis *et al.*, <http://ccforum.com/content/10/3/R76>

Abstract

Apoptosis is of pivotal importance in the pathogenesis of sepsis. Depending on the cell type involved and the time point of the disease process, apoptosis may be linked to either a good or a bad outcome. Work presented in this issue by Giamarellos-Bourboulis and coworkers suggests that an early increase in the apoptosis of blood monocytes is associated with improved survival in patients with varying degrees of sepsis. Although the mechanism by which monocyte apoptosis influences the outcome of sepsis cannot be determined by this study, these observations represent an important advance in our understanding of this complicated disease process.

Apoptosis is a tightly regulated process by which cells orchestrate their own dismantling and disposal in an orderly and noninflammatory manner. Apoptosis is critical for homeostasis, development and – as highlighted by recent work from Giamarellos-Bourboulis and colleagues [1] (presented in this issue) – for regulation of inflammation and immune cell function. Since its first description in 1972 [2] there has been an explosion of literature on this topic. A Pubmed search for 'apoptosis' yields over 100,000 citations. A question when faced with such a number is coincidentally the same as that raised by Giamarellos-Bourboulis and colleagues; when is enough apoptosis, enough?

Sepsis and septic shock represent an over-exuberant host response to an infectious insult. Neutrophils, monocytes and tissue macrophages play key roles in the initial reaction and release a variety of cytokines to marshal the immune response. Once the threat is contained and/or the adaptive immune response is awakened, the innate immune cells are downregulated and must be disposed of in a timely and noninjurious manner because some of them are proverbial 'ticking time bombs'. Apoptosis represents a key mechanism in this orderly downregulation and disposal.

It has been suggested that dysregulated apoptosis may play a role in increasing the duration and/or severity of the systemic response to sepsis [3]. Clearly, monocytes and macrophages can contribute to inflammation simply by 'hanging around' longer with the opportunity to release their cytotoxic products that damage host cells. Additionally, there is evidence that phagocytosis of apoptotic cells leads to active elaboration of anti-inflammatory signals [4]. Thus, reduced apoptosis may contribute to inflammation in a number of ways, with the end result being that the host immune response contributes more to damaging the host than to protecting it. However, apoptosis is not all good. It is important to note that apoptosis of structural cells such as endothelium or epithelium in systemic inflammatory response syndrome is associated with disrupted organ function [5,6]. Furthermore, lymphocyte apoptosis is associated with a poor outcome in septic shock [7], presumably because these cells are important regulators of the immune response and coordinate the body's response to infection.

Giamarellos-Bourboulis and coworkers [1] add to this literature and present evidence that early monocyte apoptosis confers a survival advantage in sepsis related to ventilator-associated pneumonia. Their study group of patients was divided into those with low (<50%) and high (>50%) rates of monocyte apoptosis when tested on day 1. Forty-nine per cent (28 out of 57) of those with low apoptosis died versus only 15% (5 out of 33) of those with high degrees of monocyte apoptosis. This is a remarkable finding, and theirs is one of the first studies to correlate monocyte apoptosis with survival in sepsis. However, some questions arise from these observations.

First, is monocyte apoptosis in the study simply a marker for another more proximate factor that is causally associated with mortality? The authors note that there is a difference in the

incidence of bacteraemia between the low and high apoptosis groups but they do not discuss any other parameters. Although this group of 90 patients is as homogenous as one can expect in a study of sepsis, there are differences between patients that could contribute to mortality. Thus, demographic factors (age, sex), illness severity (Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment score) and other comorbid conditions (trauma, diabetes, medications, etc.) may be confounding variables if differences exist between the low and high apoptosis groups.

Second, percentage apoptosis changed over the 7 days during which blood was collected, and so those patients assigned to the low group may at times have had more than 50% apoptosis and *vice versa*. What is the significance of this? Timing of apoptosis is sure to be important (theoretically, too much too early may be associated with a poor outcome, as would too little too late). Duration of illness before enrolment in this study may introduce enough variability to make timing difficult to determine.

Third, if monocyte apoptosis is beneficial, then what is the mechanism? One possibility, mentioned by the authors, is a decreased release of proinflammatory cytokines by monocytes undergoing apoptosis. However, of the serum cytokines measured (interleukin-6, interleukin-8 and tumour necrosis factor- α) no correlation with survival was noted. This is a critical issue if we hope to modulate this process to the advantage of patients.

Finally, there are a variety of technical considerations in measuring apoptosis in peripheral blood monocytes that introduce uncertainty into the measurement. Discarded nonadherent cells may have been apoptotic monocytes. The recovery of apoptotic monocytes may not be complete in a Ficoll density gradient because cell density is altered by apoptosis. Also, healthy monocytes may ingest apoptotic cells and through membrane transfer subsequently stain falsely positive for annexin V. Ultimately, it may be the responses of monocytes that have already extravasated from the blood into the tissues that is most relevant to the outcome of sepsis, and this was not measured in the study.

Given these points, it is too soon to say with certainty that increased early monocyte apoptosis confers a survival advantage in the context of sepsis. However, the study by Giamarellos-Bourboulis and coworkers is an important first step in trying to make sense of a complicated and fundamentally important process. At the very least, this assay of monocyte apoptosis may conceivably be used as a prognostic tool, especially if it is combined with other factors in a multivariate model.

Competing interests

The authors declare that they have no competing interests.

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