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EDITORIAL

Nobiletin: A Citrus Isolate to Make Sepsis Less Sour

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Septic shock remains a major concern in critically ill patients. Morbidity, as reflected by cardiovascular instability and sequential organ failure, is high and mortality ranges from 20 to 50 % [1]. Treatment options are scarce and mainly cause-oriented and symptomatic. Substantial efforts to control the coordinate but sometimes profuse and potentially lethal sepsis-induced immuno-inflammatory response remained unsuccessful. Indeed, large studies investigating numerous "magic bullets" interfering with sepsis-related immune-inflammatory or coagulation processes failed to show efficacy on relevant outcome parameters [2–4]. Also, the theoretical benefit of blood purification by restoring immune homeostasis through indiscriminate removal of inflammatory mediators could not be confirmed [5].

In this context, the paper of Li *et al.* is highly welcomed. The authors convincingly demonstrate a protective effect of nobiletin, a citrus flavone present in the peels of tangerine, mandarin and oranges, in murine endotoxic shock [6]. Interestingly, apart from inhibiting the "usual pro-inflammatory suspects" tumor necrosis factor-α and interleukin (IL)-6, the study focuses on two key protagonists within the sepsis cascade: high mobility group box-1 (HMGB-1) protein and nuclear factor kappa B (NF-κB) [6].

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Abbreviations: IL, Interleukin; HMGB-1, High mobility group box-1; NF-κB, Nuclear factor kappa B; DAMPs, Damage-associated molecular patterns; RAGE, Receptors for advanced glycation end-products; CRRT, Continuous renal replacement therapy

HMGB-1 is a late mediator of endotoxin lethality [7] and perfectly fits all criteria for an "alarmin" [8]. Alarmins form the endogenous branch of the larger family of damage-associated molecular patterns (DAMPs) that are released by threatened, injured, or necrotic cells [9]. In the nucleus, HMGB-1 stabilizes nucleosome formation and facilitates transcription factor binding. Outside the cell, it functions as a cytokine with weak direct pro-inflammatory activity [10] but considerable ability for indirect triggering of inflammation [11]. HMGB-1, indeed, acts as a potent chemoattractant for neutrophils, monocytes, macrophages, and dendritic cells and engages, among others, Toll-like, IL-1, and receptors for advanced glycation end-products (RAGE) that sustain or enhance the inflammatory process. Moreover, HMGB-1 and endotoxin synergistically reinforce each other at both receptor level and in activating transcriptional responses [11]. Severe sepsis [12] and acute inflammatory lung injury [13] are associated with life-threatening out-of-control HMGB-1 responses. Thus, it makes perfect sense that measures for keeping the HMGB-1 release in check may dramatically influence the course of sepsis. Inhibiting HMGB-1 in murine sepsis protected against development of organ injury and reversed lethality [14]. Nosaka *et al.* recently showed that administration of a monoclonal antibody against HMGB-1 suppressed the immuno-inflammatory response and significantly improved severe lung injury and survival in patients affected with H1N1 influenza A virus [15]. HMGB-1 is also effectively cleared by highly adsorptive dialysis membranes such as the acrylonitrile 69 surface-treated filter [16] which is increasingly used for continuous renal replacement therapy (CRRT) in hemodynamically unstable septic patients [17]. Though obviously an attractive and more easily available alternative for counteracting the noxious effects of HMGB-1, clinical efficacy and benefit of such CRRT approach has not yet been established.

NF-κB transcription plays a pivotal role in innate and adaptive immunity by regulating the expression of cytokines, inducible nitric oxide synthase, enzymes, growth factors, and inhibitors of apoptosis. It also controls the expression of effector enzymes in response to ligation of many receptors involved in immunity including T- and B-cell receptors and members of the toll-like receptor/IL-1 receptor super family [18]. In sepsis, the NF-κB pathway significantly determines magnitude and duration of the inflammatory state [19]. Receptor engagement by HMGB-1 also produces NF-κB activation [20]. Thus, suppressing NF-κB activation certainly is a relevant option to bridle an adrift inflammatory system.

The study of Li *et al*. has some weaknesses. First, treatment with nobiletin was started before initiation of sepsis whereas it is often impossible to correctly delineate the exact onset of clinical sepsis. Second, their model represents hypodynamic sepsis which strongly contrasts with the typically hyperdynamic fluid-resuscitated and often catecholamine-dependent human sepsis. Third, NF-κB activation promotes leukocyte apoptosis. The eventual impact of suppressing this "feedback" control mechanism which may result in a more rapid resolution of inflammation remains to be proven.

In summary, the excellent experimental work of Li *et al*. opens exciting perspectives for a more "core-directed" sepsis treatment but the obtained beneficial results await confirmation in clinical trials.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest. The authors declare that they have no competing interests.

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