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Moving from a Cytotoxic to a Cytokinic Approach in the Blood Purification Labyrinth: Have We Finally Found Ariadne's Thread?

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For almost three decades, researchers have invested in strategies that involved removal of excess inflammatory mediators from the circulation (that is, the "cytotoxic" approach). Blood purification techniques using an extracorporeal device can indeed nonspecifically remove a wide array of inflammatory mediators from the circulation. In animal models, this multimediator targeting or pleiotropic approach was shown to downregulate systemic inflammation and to restore immune homeostasis. In this issue, Namas *et al.* seriously challenge this cytotoxic hypothesis and propose to replace it by a cytokinic approach. In a rodent model of sepsis, these authors elegantly demonstrate that hemoadsorption using a large surface-area polymer could reduce and, more importantly, relocalize and reprogram sepsis-induced acute inflammation, while simultaneously lowering infectious burden and liver damage. Although challenging, this new theory can be considered complementary to the existing cytotoxic hypotheses by coupling reduced endothelial damage at the interstitial level (cytotoxic approach) with the concept of reprogramming leucocytes and mediators toward infected tissue, thus emptying the bloodstream of important promoters of remote organ damages (cytokinic approach).

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INTRODUCTION

Considerable progress in blood purification techniques over the years has not yet ended the ongoing discussion regarding the exact place and most convenient mode of blood purification in patients with septic shock (1,2). Septic shock indeed remains a leading cause of mortality in intensive care patients (3), and sepsis research focuses on developing methods to improve outcome of this devastating disease. Unfortunately, attempts to decrease mortality in septic shock by using pharmacological (4) and blood purification (5,6) approaches have been disappointing. Therefore, every effort to improve the understanding of rationale of blood purification can be seen as a key process to succeed in therapy—an elegant description is in the report by Namas *et al.*, published in this issue (7).

Despite growing insight into key physiological aspects and valuable incentives on technical issues, therapeutic targeting and more adequate dose determination (8), the rationale of blood purification as part of treatment in severe sepsis and septic shock is still questioned. Sepsis is a complex and multifaceted inflammatory condition (9) initiated and rekindled by stimulated host immune effector cells. The intensity of the inflammation is determined by a myriad of biologically active substances such as cytokines, chemokines and reactive oxygen/nitrogen species. This process functions properly when mediators remain restricted to specific tissues, inducing a well-controlled inflammatory response to local injury or infection. However, any "overflow" of mediators in the bloodstream may generate a relentless and harmful systemic inflammation. Sustained elevation and/or uncontrolled production of pro- and antiinflammatory cytokines may finally turn into a toxic self-propagating cascade reaction that causes remote organ damage, multiorgan failure and, in some patients, ultimately death (9).

THE "OLD" CYTOTOXIC APPROACH

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tors from the circulation (that is, the "cytotoxic" approach). Blood purification techniques that an extracorporeal device can indeed nonspecifically remove a wide array of inflammatory mediators from the circulation (10,11). In animal models, this multimediator targeting or pleiotropic approach was shown to downregulate systemic inflammation and to restore immune homeostasis (12). In this issue, Namas *et al.* (7) seriously challenge this cytotoxic hypothesis and propose to replace it with a "cytokinic" approach. They used the word *cytokinic*, meaning that cytokines are attracting inflammatory cells and in fact are messengers between cells. Every technique that can relocalize cytokines will also in itself relocalize inflammation toward the infected tissue and emptying secondary to the blood compartment. In a rodent model of sepsis, these authors elegantly demonstrated that hemoadsorption using a large surface-area polymer could reduce and, more importantly, relocalize and reprogram sepsis-induced acute inflammation while simultaneously lowering infectious burden and liver damage.

The "New" Cytokinic Approach

This novel revolutionary theory needs to be positioned within the current perspective of blood purification use in sepsis and the different theories underlying the cytotoxic approach. As stated previously, it was advocated (13,14) that reducing the cytokine load in the blood compartment could lower mortality in the septic patient. However, such gross oversimplification seems inappropriate because of the complex pharmacodynamic and pharmacokinetic behavior of the intricate cytokine network. Indeed, according to the "peak concentration" theory described by Ronco *et al.* (15,16), efforts must be directed to removal of mediators and cytokines from the blood compartment during the proinflammatory phase of sepsis. It was postulated that by significantly diminishing the amount of free cytokines, remote organ and associated damage could be limited and mortality attenuated. Accordingly, blood purification techniques that facilitate a rapid and substantial removal of mediators are privileged in this setting. This theory, however, fails to account for eventual variations in interstitial and tissue concentrations of mediators and cytokines that may be clinically relevant. Therefore, a model was developed coupling mediator removal from the blood compartment to changes in interstitial and tissue mediator levels. This "threshold immunomodulation" hypothesis, initially elaborated by Honore and Matson (17,18), fosters a much more dynamic viewpoint. After removal from the blood compartment, (pro)mediators are progressively extracted from interstitium and tissues until a threshold level is reached, at which particular inflammatory pathways and cascades are brought to a complete standstill, stopping any further harm to the organism. However, correct determination of this threshold is difficult in clinical practice because the applied blood purification technique (for example, high-volume hemofiltration) might cause significant changes in mediators at the interstitial and tissue level that are not mirrored by alterations in the blood compartment. Observational studies on continuous hemofiltration in septic shock have indeed demonstrated improved hemodynamics and survival that was not accompanied by a significant fall in inflammatory mediator blood levels (19,20). It can thus be assumed that the biological effect of blood purification does not depend on a dramatic fall in plasma cytokine levels, but rather relies on neutralizing harmful mediator effects at the tissue level. Still, it remains to be determined how blood purification promotes and manages mediator and cytokine flow from tissue and interstitium to the blood compartment. The "mediator delivery" hypothesis, suggested by Di Carlo and Alexander (21), emphasizes the use of high replacement volumes (that is, 3–5 L/h) during blood purification. Several reports have demonstrated a 20- to 40-fold increase in lymphatic flow (22,23), displacing a substantial amount of mediators and cytokines to the blood compartment from where they are subsequently eliminated. Thus, the use of high volumes of replacement fluid might be of great importance for extracting mediators, but also for enhancing lymphatic transport between the interstitium/tissue and blood compartments. Taken together, all aforementioned cytotoxic hypotheses indicated that elimination of cytokines at tissue level rather than at plasma level was mandatory for a beneficial biological and clinical effect of blood purification. The ill-explained relationship between compartments encouraged Honore and Joannes-Boyau to develop a fourth cytotoxic hypothesis based on active transportation between two asymmetric compartments (24,25). This theoretical model assumed that effective removal of tissue-damaging mediators and transporting them to the central circulation must have a positive effect. It is highly unlikely that such transport is merely passive. Indeed, the central blood compartment (CEBC), which is the limiting factor for passive transport, has a much lower surface area ($\pm$ 30 m^2) than the capillary blood compartment (CABC; $\pm$ 300 m^2) (24). Passive removal of 40% of the mediators from the CEBC thus will represent only 4% removal from the CABC (24), suggesting an active transportation assist (25). In their newly proposed cytokinic theory, Namas and colleagues (7) further expand this viewpoint by demonstrating that transport between two compartments (that is, redirection) may occur over a great distance and not only between adjacent compartments. Also, the newly established homeostasis after mediator removal may reorganize inflammation in itself. In fact, most leucocytes remain concentrated with mediators around infected tissue and do not pass into the blood, limiting their potential to cause remote organ damage (7). This is in contrast with cytotoxic theories that focus on reduced mediator concentrations in the interstitium around endothelial cells, whereas circulating mediator levels remain high and thus potentially harmful (24,25).

The randomized design and highly sophisticated protocol of the study by Namas and colleagues (7) convincingly allows us to unravel the trafficking of mediators and leucocytes throughout the animal body. However, as confirmed by the authors, the study has several limitations. Mortality, which is the most important clinical endpoint, could not be assessed. More importantly, significant key mediators of the septic process (for example, high-mobility group box-1 [HMGB-1] protein) were not evaluated. Actually, other types of sorbents and adsorptive membranes that are currently used can effectively remove HMGB-1 among others mediators (26) and may thus even more dramatically influence outcome of septic animals and humans (27,28). Further mechanistic studies in humans are needed to confirm these preliminary data.

CONCLUSIONS: THE CYTOKINIC APPROACH IS COMPLEMENTARY TO THE CYTOTOXIC APPROACH

In conclusion, the novel and fascinating cytokinic theory elaborated on by Namas and colleagues (7) will undoubtedly fuel the debate on blood purification use in sepsis. Although challenging, this new theory can be considered complementary to the existing cytotoxic hypotheses by coupling reduced endothelial damage at the interstitial level (cytotoxic approach) with the concept of reprogramming leucocytes and mediators toward infected tissue, thus emptying the bloodstream of important promoters of remote organ damage (cytokinic approach). Recent large randomized studies on intensive kidney support in patients with severe sepsis (5,6) showed that higher doses of (or high-volume) blood purification did not improve outcome. Consequently, some experts make a distinction between blood purification for acute kidney injury and blood purification for septic shock with or without acute kidney injury (29). In the absence of an active primary therapy against sepsis (4), this fascinating cytokinic theory can pave the way for new investigations on the role of blood purification in septic shock with or without acute kidney injury. In this context, optimal device development and better estimation of timing, dose and targets are mandatory before embarking on large randomized studies to assess morbidity and mortality issues.

DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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