· EDITORIAL ·

Immunologic dissonance in the pathogenesis of sepsis

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Sepsis is considered as a symptom complex resulted from an invasion of pathogen(s), provoking a cascade of harmful physiological changes including fulminating inflammatory responses detrimental to structures and functions of tissues and organs. The process may end in septic shock or terminate into multiple organ dysfunction syndrome (MODS) and multiple organ failure, and they are both lethal. As yet both the incidence and mortality of sepsis remain high, and it has become the leading cause of death of non-cardiac diseases in different countries, mainly because its underlying pathogenetic mechanisms are not well elucidated. Thus it continues to be an indocile challenge to human health and economical development worldwide[1].

Extensive studies have been done on sepsis. There is an accumulating clinical evidence and experimental data that there is a perturbation in the innate immune system in the pathogenesis of sepsis. Immunological functions seem to have become dissonant, leading to progressive rampant inflammatory responses on one hand, and immunosuppression on the other hand[2].

A rigorous challenge to the body, regardless a serious trauma or pathogenic invasion, leads to cleavage of complement, releasing an excessive amount of anaphylatoxins, especially C5a through the alternative pathway. This excessive complement cleavage product has been proved to impair bactericidal function of neutrophils. In our burn patients, we have found that in the patients who developed sepsis and MODS, the value of plasma C5a was over 300 fold of that of normal on the first day after the injury, and its plasma level was shown to be greatly elevated in sepsis[3]. At the same time, chemiluminescence of neutrophils was astoundingly low in patients with extensive burn. Since chemiluminescence of neutrophils was positively correlated with bactericidal index of neutrophils, it implied that the bactericidal function of neutrophils was greatly impaired[1]. Therefore these patients are vulnerable to bacterial infection.

When infection is established, the invaded bacteria will certainly release either endotoxin or exotoxin, leading to the release of a cascade of pro-inflammatory mediators through activation of a variety of cells, especially monocytes and lymphocytes. These inflammatory mediators are known to suppress apoptosis of the infiltrated neutrophils. It has been demonstrated by Ertel that serum of trauma patients and sepsis lowered the DNA fragmentation rate of neutrophils, and the effect was dose-dependent[5]. With the majority of neutrophils fail to undergo apoptosis, they would breakdown and degranulate in a short period of time, because the life span of neutrophils is short when they have infiltrated into the tissue. As the result of degranulation, a number of proteases and oxygen reactive products are liberated. Thus, the inflammatory responses will be sustained and more pronounced instead of subsiding.

Human leukocyte antigen locus DR (HLA - DR) is essential in the process of antigen presentation. The main antigen presenting cells are dendritic cells and monocytes. Therefore the determination of HLA - DR can be used as an indicator of the function of these cells. In animal experiment, we can induce a pathophysiological process simulating sepsis in human by injecting zymosan into the peritoneal cavity. It has been shown in this setting that the dendritic cells in the spleen were decreased markedly after the zymosan challenge in mice[6]. It has been demonstrated that the same pathological change occurred in the spleen of a patient died of sepsis and MODS. Interleukin - 12 (IL - 12), which is a biomarker of dendritic cells, was determined in serum and spleen homogenate of mice challenged by zymosan. The results showed that IL - 12 p40 was elevated at the terminal stage of sepsis, signifying also suppression of the function of dendritic cells.

We then quantitatively determined HLA - DR in patients with burn injury. Fifty nine male and 16 female burn patients, ages ranged from 17 to 62, with a mean of 33.16 years, were involved in the study. They were stratified into three groups. Group 1 consisted of 25 patients with burn area covering 30% to 49% total body surface area (TBSA) [mean(40.2±6.5)% TBSA, Ⅱ°(17.6±10)% TBSA], group 2 consisted of 26 patients, with burn area of 50% to 69% [mean(61.8±8.7)%, Ⅱ°(31.0±16.6)%] TBSA, and group 3 consisted of 26 patients, with burn area 70% to 99% [mean(90.2±6.1)%, Ⅱ°(66.3±17.1)%]. A control group of 6 male and 5 female healthy donors, aged 30.81±5.42 years, were also enrolled. HLA - DR of CD14 ocytes was quantitatively determined by the use of flow cytometry with a specific monoclonal antibody. The results showed that there was a marked lowering of the values after burn injury in all the groups up to 28 postburn day, especially in patients with extensive and deep burns[7]. Comparing the results between patients developing sepsis and those without sepsis, the lowering of HLA - DR was more remarkable in the former group. The results also arouse our attention that in patients with burn injury, one link of the immunologic function represented by HLA - DR level persisted to be

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suppressed even when all open wounds have been soundly closed. The phenomenon may imply that the burn patients are infection prone for a prolonged period, so that they should be discharged immediately when wound healing is completed, to avoid nosocomial infections, which are so often in burn wards, and intensive care unit (ICU) alike. They should also be pre-warned that they should be duly protest themselves, when they go back to the community, against contagious diseases such as flu.

Dendritic cells are present in the skin in the form of Langerhan's cells, the number of which has been estimated to be 460 to 1 000 per mm^3 of skin. Therefore, we also wonder the massive destruction of dendritic cells, represented by Langerhan's cells in the skin, contributes to the lowering of HLA - DR in patients with extensive deep burns[8].

In a rabbit experiment with partial ischemia and reperfusion of the intestine, we found that there was increased apoptosis of circulating lymphocytes. In human beings, we have demonstrated eight severely burned patients (50%-90% TBSA, with Ⅱ° 25%-75% TBSA) that there was a persistent lack of blood supply to the intestine during burn shock stage by measuring gastric pHi. In this group of burn patients, undoubtly shock was present. They were fluid resuscitated promptly and adequately, as shown by the amount of fluids given and urinary output. The hemodynamics became normal within 36 hours after beginning of fluid resuscitation. However, gastric pHi was still low (7.3) until 72 hours after the injury, signifying that there was a prolonged hypoperfusion of the gut[9].

With the above finding shown in a rabbit experiment, and very frequent occurrence of lymphopenia at an early period of an extensive burn, we hypothesize that presumably there is also apoptosis of circulating lymphocytes in human patients with extensive burns, pending more clinical studies. As a matter of fact, apoptosis of lymphocytes has been observed in the spleen of human burn patients died of sepsis and MODS. This phenomenon was also seen in the spleen of zymosan challenged rats[10]. The pathogenetic mechanisms of apoptosis of lymphocytes is known to be related to an up-regulation of cysteinyl aspartate-specific protease (caspase) 3, due chiefly to an activation of Fas ligand, pro-inflammatory mediators, and glucocorticoids[11].

As there is an aggravated infection and inflammatory responses due to impaired bactericidal function of neutrophils and excessive breakdown of a large number of non-apoptotic neutrophils, liberating multiple proteases and free oxygen radicals on one hand, and on the other hand there is an impairment of innate immunity function as a result of impaired antigen presenting function of dendritic cells and monocytes, combined with extensive apoptosis of lymphocytes, both in the peripheral blood and spleen, it is our assertion that there is a dissonance in immunologic functions in the pathogenesis and development of sepsis. Therefore, we proposed a novel strategic therapeutic regime to control sepsis. In a multi-center randomized control clinical trial, we gave ulinastatin, a human urinary trypsin inhibitor, aiming at suppressing the production of inflammatory mediators and inhibiting a series of proteases and hydrolase, combined by the administration of α thymosin to raise the level of HLA - DR and inhibit caspase 3. In a group of 275 patients with sepsis, the effect of the treatment was salutary, as shown by lowering of 28-day mortality from 42.54% to 23.40%, and 3-month mortality from 52.24% to 32.62% (unpublished data). Though the mortality rate is still too high, due to heterogeneity of primary diseases of the patients and un-unified treatment protocols of primary diseases in different hospitals, it is hopeful that it could be further reduced when the guideline of treatment of sepsis as formulated by a group of specialists in critical care medicine under the leadership of Dellinger would be implemented later[12]. Nevertheless, this preliminary clinical trial, to certain extent, verifies that the complimentary morbid effects of aggravated inflammatory responses and impaired immunity could be controlled to a degree that the overall mortality could be reasonably reduced by administration of these two drugs on top of traditional treatment of the primary diseases in hospitals involved in this preliminary clinical trial.

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