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Hypotheses, Concepts, Theories

ANTI-INFLAMMATORY RESPONSE: NEUROENDOCRINE-IMMUNE INTERACTIONS

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Abstract

The role of inflammatory and anti-inflammatory responses in the course and outcome of crush syndrome, acute pancreatitis, and sepsis were analyzed.

Clinical and experimental findings demonstrate that the level of inflammatory cytokines cannot be considered as a criterion for the degree of crush syndrome severity. Modeling of the crush syndrome in rats showed that despite the similar increase of inflammatory cytokines (IL-1β, TNF-α) in groups of different crush time, the level of increased anti-inflammatory cytokine IL-10 differed and correlated with the crush time. Moreover, it was also revealed that there is a significant relation (according to χ^2 criterion) between the lethality and absence of IL-10 levels decrease during the observed period.

In patients with acute pancreatitis the IL-10 level was elevated and considered a criterion of severity degree. In addition, the dynamics of IL-10 level alteration is a marker for the course and outcome of a pathological process.

The research presents an analysis on features of IL-10, the leading anti-inflammatory cytokine, which allows explaining why and in what conditions the high level of anti-inflammatory cytokine IL-10 may correlate with the severity degree, define the course and outcome of the illnesses, at which systemic inflammatory response is developed.

The neuroendocrine-immune interactions play an important role in development of the anti-inflammatory response. It has been shown that the crush syndrome and acute pancreatitis destruct neuroendocrine-immune interactions. Furthermore, at acute pancreatitis there is a certain significant relation between the IL-10 level and derangement of neuroendocrine-immune interactions.

Keywords: system anti-inflammatory response, pro- and anti-inflammatory cytokines, neuroendocrine-immune interrelations.

At extensive traumas, burns, numerous surgical interventions, and bacterial infections the inflammatory cytokines (IL-1β, IL -1α, IL-6, IL-8) are ejected into the blood circulation resulting in development of the systemic inflammatory response syndrome (SIRS) [*Bone R. et al., 1997*]. The SIRS defines protection of an organism from injuring impacts. Cytokines regulate the process of migration of various cells to the inflammation site, the functional activity thereof, and the process of rehabilitation of injured tissues [*Ketlinski S. et al., 1992; Dinarello C., 1998*].

It is not always that SIRS is of an adequate nature, and the excessive lasting production of inflammatory cytokines may cause a range of implications, whereas the inflammatory cytokines make an effect rather injurious than protective. Such effects of inflammatory cytokines may result in circulation disorders, including collapse, disseminated intravascular blood clotting with subsequent deficiency of coagulability, outburst of the blood liquid part into tissues, haemorragic necroses, microcirculation disorder and development of polyorganic deficiency [*Dinarello C., 1998; Karima R. et al., 1999*]. Thus, the inflammatory cytokines might make a negative effect instead of protective one.

To limit the inadequately excessive production of SIRS in an organism the system of compensatory anti-inflammatory response comes into effect [*Bone R. et al., 1997*]. The compensatory anti-

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inflammatory response syndrome (CARS) development is conditioned by the production of anti-inflammatory cytokines (IL-10, transforming growth factor, IL-4) and other inhibitors of anti-inflammatory cytokines. An adequate CARS suppresses the systemic inflammatory syndrome and recovers the homeostasis. The inadequately low activity of anti-inflammatory cytokines results in excessive production of inflammatory cytokines. The deficiency of anti-inflammatory cytokines may also be caused by hyperactive Toll-like receptors that recognize components of viruses and bacteria and evoke synthesis of inflammatory cytokines [*Hein H., Lien E., 2003*]. The inadequate CARS, excessive or lasting, suppresses the immune system and develops polyorganic dysfunction with lethal outcome at later stages.

The role of SIRS and CARS in their interaction during and upon outcome of diseases, at which the systemic inflammatory response develops, is of great interest. Such diseases include sepsis, acute pancreatitis, and crush syndrome.

The concept of systemic inflammatory response was not yet developed at the time of the Armenian earthquake in 1988. However, many of the aspects of IL-1 biological role and its participation in the development of the inflammatory reaction were known [*Dinarello C.*, *1984*; *1986; Tracey K. et al., 1986*]. It is considered to be established that IL-1 is secreted at tissue injury. It could be assumed that major traumas are responded with full-blown inflammation, where IL-1 is of particular importance. Given the above-mentioned, the study on IL-1 levels in patients with crush syndrome and identification of the relation between its levels and the clinical picture was of high priority. For measurements on IL-1 level the co-stimulating test of proliferative activity assessment of thymocytes in mice C3H was applied. It was revealed that the supernatant of mononuclear cells of patients with crush syndrome activated with lipopolysaccharide (LPS) added in thymocytes culture stimulated much more apparent intensification of thymocytes proliferation in mice (ejected in sub-optimum doze of Con A) than the supernatant of mononuclear cells of volunteers (laboratory standard). Consequently, at crush syndrome the ability of mononuclear cells to synthesize pro-inflammatory cytokine IL-1 increases. The revealed findings showed that IL-1 dependent full-blown inflammatory response develops at such pathology. It was also identified that the co-stimulating activity of the supernatant of mononuclear cells in patients of various severity groups was similar. As the level of such an increase was similar in all groups, this indicator cannot be applied for defining the severity level of an injury.

The latter seems somewhat paradoxical, as the systemic inflammatory response develops at crush syndrome.

By the time of large-scale studies on pathogenesis and specificity of the clinical course of crush syndrome in patients injured as a result of Spitak earthquake in Armenia (1988) by some technical reasons we failed to carry out immune enzyme analyses for IL-1 determination in this specific contingent. One could only suppose that shifts of IL-1 content correlated with the degree of disease state severity. However, experiments performed by us on modeling the crush syndrome in small experimental animals allowed to draw a conclusion, according to which the level of pro-inflammation cytokines and, in particular, IL-1, in blood plasma could not be considered as diagnostic and prognostic criteria of crush syndrome severity degree [*Pandikyan N., 2005; Gambarov S. et al., 2006*].

Thus, under conditions of crush syndrome modeling in rats we studied peculiarities of cytokine-dependent inflammatory and anti-inflammatory responses in dynamics of the pathological process: on day 3 and 7 after decompression. Hind limbs of rats were exposed to compression during 2, 3, and 4 hours. The shifts of IL-1 and TNF-α blood plasma content in experimental animals were studied as markers of the inflammatory response, while as markers of anti-inflammatory response the shifts of IL-10 content were studied. The research thus performed succeeded in establishing that 2, 3 and 4 hours post decompression the level of studied pro-inflammatory cytokines in blood plasma increased. Moreover, almost similar indices were recorded in all periods of the study. In 3 days in all study groups, i.e. in animals exposed to 2-, 3- and 4-hour compression high indices of pro-inflammatory cytokines IL-1 and TNF were also revealed. In the same period of the pathological process, there occurred a significant increase of IL-10 blood plasma levels; this latter obviously signified to the fact that cytokine-dependent anti-inflammatory response was also engaged in order to limit the inflammatory response. After the 7-day duration of the pathological process in all study groups, i.e. in animals exposed to 2-, 3- and 4-hour compression there was observed a clear tendency towards normalization of pro-inflammatory cytokines IL-1 and TNF-α blood plasma levels.

In 7 days IL-10 levels markedly decreased in animals exposed to 2- and 3-hour compression (as compared with levels observed on day 3, but never achieving control values. Taking into consideration differently directed character of IL-10 blood plasma content shifts in experimental animals exposed to 4-hour compression, this study group was conditionally divided into 2 sub-groups. In the first sub-group relatively high indices of IL-10 were registered, while in the second sub-group a decrease of IL-10 levels was observed (as compared with the 3rd day of observation). The following circumstance should be emphasized: in animals of the first sub-group there was established direct strong correlation dependence (according to χ^2 criterion) between the high level of IL-10 and the lethality.

The results obtained precisely in the studied sub-group do not fit the known scheme of inflammatory reaction inhibition by anti-inflammatory cytokines. Thus, it was possible to suppose that elevation of IL-10, which is considered a leading mediator of anti-inflammatory system, should result in inhibition of inflammatory response manifestations and, therefore, have a positive part in case of crush syndrome.

Indeed, the experiments revealed that CARS had a positive role for development of the systemic inflammatory response. In the model of LPS induced sepsis the levels of lethality and pro-inflammatory cytokines increased in mice with IL-10 deficiency. Besides, injection of IL-10 to the experimental model protects from shock development and reduces the consecutive lethality level [*Howard M. et al., 1994; Rongione A. et al., 2000*]. IL-10 reduces lethality at experimental pancreatitis [*Cook J. et al., 2001*]. However, clinical observations, as well as our experiments, revealed the results paradoxical at first sight. IL-10 in patients with acute pancreatitis, at which the systemic inflammatory response also develops [*Berney T. et al., 1999; Mayer J. et al., 2000*], is at high level [*Pezzili R. et al. 1997; Mayer J. et al., 2000*], it appears a criterion of severity level of the pathologic process [*Berney T. et al., 1999; Chen C. et al*., *1999; Gambarov S. et al., 2002*]. Moreover, it was demonstrated that the dynamics of the IL-10 level alteration is a marker for the course and outcome of the pathologic process. It was identified by the χ^2 criterion that there is a certain relation between the absence of alteration of IL-10 level (towards reduction) in a week-time and development of polyorganic deficiency and lethal outcome [*Gambarov S. et al., 2002*].

Similar results were found in the study on another disorder, namely sepsis, at which systemic inflammatory response also develops [*Tracey K. et al., 1986; Okusawa S. et al., 1988; Blackwell T., Christman J., 1996; Karima R. et al., 1999; Van der Poll T., Van Deventer S., 1999; Arnalich K. et al., 2000; Arslan E. et al., 2000*]. It was revealed that IL-10 level correlates with the level of severity of the disorder, development of polyorganic deficiency and lethal outcome [*Tracey K. et al., 1986; Okusawa S. et al., 1988; Kasai T. et al., 1997; Van Dissel J. et al., 1998; Nasraway S., 1999; Van der Poll T., Van Deventer S., 1999; Gogus C. et al., 2000; Yak F. et al., 2000*]. Then what is the reason for the correlation between the high level of IL-10, the leading anti-inflammatory cytokine, which theoretically should result in suppression of SIRS symptoms, with the severity of condition and lethal outcome at systemic inflammatory disorders. This contradiction is explained from the perspective of inadequacy of anti-inflammatory response (its excessiveness and/or duration) and specificities of its main mediator, IL-10, which has an important role in regulation of immune response of the organism. IL-10 was described in 1989 as a T-helper factor of the II type (Th_2), inhibiting proliferation of T-helpers of the I type (Th_1), production thereof, as well as NK cells IF-gamma and IL-2 [*Fiorentino D. et al., 1989; 1991*].

Later it was identified that Th are also able to produce IL-10, whereas the latter in this case is able to inhibit expression of IL-4 and IL-5 Th_2 [*Yessel H. et al., 1992; Del Prete G. et al., 1993*].

Major IL-10 producers in human organism are monocytes and B-lymphocytes, and among T-cells the higher levels are of CD45 RO, T-cells of memory phenotypes Th_1, Th_2, Th_0 [*Moore K. et al., 1993*].

IL-10 suppresses the function of macrophages through suppression of the expression of HLA II molecules, CD80/CD86 ISAM 1 co-stimulators [*De Waal Malefyt R. et al., 1991; Willems F. et al., 1994*]. IL-10 inhibits secretion through monocytal-macrophage sequence of inflammatory cytokines IL-1, IL-6, IL-8, IL-12, TNF-α, granulocyte macrophage colony-stimulating factor (GM-CSF) [*Moore K. et al., 1993*; *Sfeir T. et al., 2001*]. At the same time, it intensifies the production of IL-1RA. Based on these data it was assumed that IL-10 suppresses inflammatory process in an organism. Indeed, in the system *in vivo* IL-10 has an anti-inflammatory function [*Kuhn R. et al., 1993; Powrie F. et al., 1994; Weiner H., Van Rees E., 1999*].

As identified, IL-10 along with the transforming growth factor is the mediator of a special sequence of T-cells regulating the function of other cells [*Groux H. et al., 1996; Hayday A., Viney J., 2000*]. IL-10 induces antigen specific energy in CD4 T-cells of human organism and contributes *in vitro* to differentiation of regulatory sub-population of T-cells suppressing the response of other T-cells. Consequently, the full-blown immunosuppressive potential of IL-10 becomes obvious.

Probably, at excessively high level of IL-10 or duration of effect, i.e. inadequacy of anti-inflammatory response, the suppression of immune system develops.

If at sepsis the suppression of immune system caused by inadequacy of CARS may result in apposition of an opportunistic infection, then at crush syndrome and acute pancreatitis the disorder of adaptive reserves of an organism takes priority, in regulation of which the immune system has an important role to play.

Perhaps, the above specificities of CARS cause the failure of anti-inflammatory cytokines application strategy (anti-cytokine strategy) at treatment of sepsis, at which SIRS develops. Application of anti-cytokine strategy was considered to be proven by clinical and experimental data. The experiment has shown that shock development in animals can be prevented by injection of anti-bodies to TNF or soluble receptors thereof [*Fisher C. et al., 1996*]. However, clinical tests with application of anti-bodies to TNF, soluble receptors thereof, IL-1 receptor-antagonists and other blockers of inflammatory mediators completely failed [*Nasraway S., 1999*]. The application of anti-inflammatory strategy for treatment of systemic inflammatory disorders was implemented without consideration of the fact that CARS system was switched on in the organism (to which rapid development is typical) that might have caused the failure of such an approach to treatment. It is also worthwhile to mention that in the experimental systems CARS modeling (with injection of IL-10) was implemented before the induction of systemic inflammation, i.e. anti-inflammatory mechanisms were employed not for limitation and inhibition of inflammatory reactions, as it is *in situ*, but in order to suppress development of inflammation. Consequently, in these experimental systems anti-inflammatory system was positioned ahead of the inflammation, which is not the case in reality.

Data described allow for assumption that the process and outcome of disorders, at which SIRS develops, are defined by the development of systemic inflammatory and anti-inflammatory responses in the context of their interrelation.

One of the mechanisms of anti-inflammatory response induction is the neuroendocrine effect of inflammatory cytokines. The inflammatory cytokines are known to activate hypothalamo-pituitary-adrenal axis at all levels [*Spangelo B., Gorospe W., 1995; Besedovsky H., Del Rey A., 1996; Buckingham Y. et al., 1997*], thus resulting in significant increase of corticosteroids serum levels. The increased level of corticosteroids generates anti-inflammatory response not only due to the direct suppression of inflammatory response, but also due to the increased synthesis of IL-10 by T-cells of the leading anti-inflammatory cytokine [*Elenkov I. et al., 1996; Ramierz F. et al., 1996*].

Glucocorticoids stimulate the IL-10 level directly, as well as through blocking the ways of suppression of IL-10 synthesis through IL-12 and γ-interferon [*Ramierz F. et al., 1996; Biotta M. et al., 1997*]. Catecholamines, which suppress the production of inflammatory cytokines (IL-1, TNF-α) by cells of various character directly [*Koff W. et al., 1986; Elenkov I. et al., 1996*], as well as through increased production of IL-10 [*Hetier E. et al., 1991; Van der Poll T., Lowry S., 1997*] have similar effect. Catecholamines suppress the synthesis of IL-12 by antigen-presenting cells through two adrenergic receptors [*Hasko G. et al., 1998*].

Thus, neuroendocrine-immune interactions are among the most important elements of anti-inflammatory response.

At the time of start-up of the presented experiment, no concept of systemic inflammatory and anti-inflammatory responses was developed, and hence the neuroendocrine-immune interactions at crush syndrome were considered only from the standpoint of adaptive mechanisms of an organism. The misbalance of these systems and disorder of interaction processes thereof result in disruption of adaptive reserves of an organism.

Particularly, we studied the sensitivity of proliferative response of lymphocytes to dexamethasone. It is known that dexamethasone significantly suppresses the proliferative response.

In patients with crush syndrome of groups I and II (mild and medium severity of disease course, appropriately) a reduction of proliferative response sensitivity of lymphocytes to dexamethasone was observed. Such reduction of sensitivity in patients of group II was less expressed than in patients of group I.

A different picture was observed in patients with severe crush syndrome (group III). In this group, despite the low proliferative response of lymphocytes to mitogenetic stimulation, the sensitivity to dexamethasone was significantly higher than in patients of groups I and II. The index of proliferative response inhibition of lymphocytes to dexamethasone in these patients was actually the same as in healthy volunteers.

Most likely, the reduction of proliferative response sensitivity of lymphocytes to dexamethasone at its low level is demonstration of adaptive processes occurring in patients with crush syndrome of groups I and II. The fact that despite the extremely low level of lymphocytes proliferative response in patients of group III the level of its suppression by dexamethasone is significantly high signifies to disruption of adaptive processes of the organism as a result of disorder of neuroendocrine-immune interactions at severe crush syndrome.

Further, the neuroendocrine-immune interactions in a human organism were studied from the perspective of CARS at acute pancreatitis. In patients with acute pancreatitis, the level of IL-10 is considered an indicator for defining the severity level of the pathologic process [*Chen C. et al., 1999; Arslan E. et al., 2000; Gambarov S. et al., 2002*]. Moreover, by χ^2 criterion, there is a proven relation between the absence of alteration of IL-10 level (reduction) in a week-time and development of polyorganic deficiency and lethal outcome.

Disorders of neuroendocrine-immune interactions at severe acute pancreatitis were mainly observed in patients with the level of the leading anti-inflammatory cytokine IL-10 remaining high during the first 7-10 days after diagnosing. Applying the χ^2 criterion it was identified that there is a proven relation between the dynamics of the level of alteration of IL-10 (absence of reduction on the 7-10th day) and absence of reduction of proliferative response sensibility of lymphocytes to dexamethasone [*Gambarov S. et al., 2002*].

Summarizing the above-mentioned, one could conclude that the achievements of clinical or, more precisely, medical immunology allow revising the main postulate of medicine that heavy process and negative prognosis of a disease are conditioned by insufficient response of an organism to the disease. The inadequately strong response is equally important in unfavorable process and outcome of the disease.

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