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Research

The Balance Betwwen Inflammatory and Anti-Inflammatory Responses as the Paradigma of the Status of Health

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Abstract

Today, it is known that the interaction between inflammatory and immune responses is mainly regulated by the cytokine network, which may produce both pro-inflammatory, such as IL-1 beta, IL-6, TNF-alpha, and anti-inflammatory cytokines, including IL-10 and TGF-beta, which are all characterized by an inhibitory effect on the anticancer immunity. On the contrary, IL-2 and IL-12, which are the only known anticancer cytokines in humans by promoting the anticancer cytotoxicity, may play both pro-inflammatory and anti-inflammatory effects, depending on the concentrations of the other cytokines, namely IL-6 and TGF-beta itself. At present, it is possible to recognize at least two different origins of the inflammatory response, consisting of macrophage and TH17 lymphocyte systems. Autoimmunity-related inflammation would mainly depend on an enhanced IL-17 secretion due to hyperactivation of TH17 lymphocyte system, whereas advanced cancer-related chronic inflammatory status would be mainly induced by the macrophage system.

Keywords: Biological response; Inflammation, IL-2, IL-6, IL-12, IL-17, TGF-beta

Introduction

The importance of the inflammatory response in influencing the human diseases is known since the beginning of the medical Sciences, being a clinical symptomathological evidence. However, until 30 years ago, the inflammatory response had been considered as a simple local reaction, due to the release of pro-inflammatory agents, such as prostaglandins and leukotrienes, and the clinical status of patients was interpretated in a mechanicistic manner as the simple effect of the inflammatory reaction on the cardiovascular system, including blood pressure and cardiac frequency. In contrast, with the discovery of the cytokinesas immune proteins provided by systemic activities other than the immuno modulatoryones, including metabolic, cardiovascular and neuroendocrine effects, the inflammatory response has appeared to be due to several cytokine interactions, and to depend on the functional status of cytokine network [1]. Then, according to their effects on the inflammatory response, cytokines may be subdivided into two main subgroups, consisting of pro-inflammatory and anti-inflammatory cytokines. However, until few years ago, the inflammatory response was considered to depend substantially on the only granulocyte-macrophage system through the release of inflammatory cytokines, such as IL-1 beta, IL-6, IL-8 and TNF-alpha [2-4], which are responsible for the main inflammation-related symptoms, including fever, asthenia, hypotension and cachexia, with the relevant role of IL-6, produced by macrophages in response to the macrophage release of IL-1 beta [5], because of its stimulatory action on the hepatic production of acute phase proteins, suchas C reactive protein (CRP). Nevertheless, further studies have demonstrated the existence of another immune cell system responsible for the onset of inflammation, consisting of TH17 lymphocytes (CD4+CD17+) through the release of IL-17 [6-8], then successive to the macrophage one from an evolutionary phylogenetic point of view. IL-17 is present in different isoforms, and the most clinically important would be the IL-17A. However, it has to be remarked that IL-17, IL-1 beta and IL-6 are linked by reciprocal stimulatory interactions (2-8), then,

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irrespectively of its origin from macrophage or TH17 lymphocyte systems, the inflammatory reponse tends to involve the whole immune system. Finally, in addition to an inflammatory cell system, it has been demonstrated also the existence of an anti-inflammatory cell system, mainly mediated by regulatory T lymphocytes (T reg) (CD4+CD25+CD17-) [9] through the release of anti-inflammatory cytokines, the most active of them would be represented by TGF-beta [10]. Unfortunately, all anti-inflammatory cytokines, including TGF-beta itself, IL-10 and IL-35, are concomitantly provided by an immunosuppressive activity on the antitumor immunity, due to the inhibition of the secretion of the two main antitumor cytokines in humans, IL-2 [11,12] and IL-12 [13]. According to the knowledgements available up to now, that we have to be constantly able to modify on the basis of new discoveries concerning the activities of new cytokines, at present it is known that the equilibrium between inflammatory and anti-inflammatory responses is mainly depending respectively on the interactions between T reg cell-macrophage immunosuppressive system and the TH1-DC immunostimulatory one.

The Immunosuppressive Macrophage- T Reg Cell System

T reg cells are mainly generated in response to TGF-beta and IL-10 produced by myeloid precursor suppressor cells released from bone marrow and spleen macrophage system (14), and T reg cells realize their anti-inflammatory and immunosuppressive activity on the anticancer immunity through the release of TGF-beta and IL-10 themselves (9,10). T reg cell system may be modulated and modulate both macrophage and TH17 cell systems, then both systems responsible for the origin of the inflammatory status, through complex an reciprocal interactions. In more detail, TGF-beta released from T reg cells inhibits IL-6 secretion from macrophages (10,14), and IL-17 release from TH17 cells (CD4+CD17+CD25-), whereas TGF-beta in association with IL-6 may stimulate TH17 lymphocytes (6, 10). Then, because of its inhibitory effect on the macrophage release of IL-6 and its potential stimulatory activity on IL-17 secretion even though only in the presence of IL-6, the action of TGF-beta would tend to pilot the inflammatory response in a preferential IL-17-dependent way rather than in a macrophage-dependent one by counteracting macrophage-mediated inflammation and potentially promoting the IL-17-mediated inflammatory status, then in a lymphocyte-dependent inflammation. The dual inflammatory and anti-inflammatory effects played by lymphocyte system, with an inflammatory action played by TH17 cells and an anti-inflammatory one by T reg cells are also present into the macrophage system, which would be characterized by the existence of two fundamental subsets of macrophages, the so-called M1 and M2 subsets (2,3), respectively provided M1 subset by pro-inflammatory activity due to the release of IL-6, IL-1 beta and TNF-alpha, and the M2 subset with anti-inflammatory and potential pro-tumoral effects due to the inhibitory effect of TGF-beta on the anticancer immunity, as well as on lymphocyte tumor infiltration, which could destroy cancer cells and allow a more favourable prognosis in cancer (2).

The Immunostimulatory Th1 Lymphocyte-Dendritic Cell System

In addition to the interactions occurring among macrophages, TH17 lymphocytes and T reg lymphocytes involved in the potential auto-regolatory control of the inflammatory response, the other fundamental regulatory immune cell system involved in the control of inflammation, that we have to take into consideration to understand the physiopathology of the cytokine network, is that constituted by TH1 lymphocytes (CD4+CD25-CD17-) and DC system, respectively thorugh the release of IL-2 [11,12,15] and IL-12 [13]. In fact, on the same way that TGF-beta, which is provided by a very strong anti-inflammatory action, may also promote the inflammatory response by stimulating IL-17 release in association with the inflammatory cytokine IL-6 [9,10], both IL-2 and IL-12 may either promote or inhibit the inflammatory response, at least in vitro experimental studies. In more detail, IL-2 may exert both inflammatory effects by stimulating the macrophage system with a following enhanced production of IL-6 (12) and anti-inflammatory activities by stimulating T reg cell system [16] and inhibiting IL-17 release from TH17 cells [17]. On the same way, IL-12 may induce inflammatory effects by inhibiting T reg cells and their TGF-beta production (18), as well as by stimulating TH1 differentiation with a following enhanced release of IL-2 itself [13], but it may concomitantly exert anti-inflammatory effects by inhibiting TH17 cell system and the production of IL-17 [19]. Probably, the dual inflammatory and anti-inflammatory effects of IL-2 and IL-12 would mainly depend on their concentrations, as well as by the functional status of the whole cytokine network. As far as the anticancer immunobiological response is concerned, today it is known that the destruction of cancer cells is mainly realized by NK-LAK cell system after stimulation by IL-2 produced from TH1 lymphocytes (CD4+CD25-CD17-) [11,12,15], and by cytotoxic T lymphocytes (CD8+) after their activation by IL-12 released from dendritic cells (DC) (13), which respectively mediate the antigen-independent and the antigen dependent-cytotoxicity [15].

The Inflammatory And Anti-Inflammatory Cytokine Network

Gnerally, cytokines are subdivided into only two groups, consisting of pro-inflammatory and anti-inflammatory cytokines, but it could be more suitable to recognize three essential subgroups of cytokines, represented by : 1) pro-inflammatory cytokines, the most important or at least the most investigated of them are consisting of IL-1 beta, IL-6, IL-8, IL-13, IL-17, IL-18; 2) anti-inflammatory cytokines: TGF-beta, IL-10, IL-35; 3) ambivalent cytokines provided by both inflammatory and anti-inflammatory effects depending on the

different experimental conditions, essentially represented by IL-2 and IL-12 [11-13]. It is clinically important to put into evidence that both inflammatory cytokines, including IL-6, IL-1 beta and TNF-alpha, and anti-inflammatory cytokines, such as TGF-beta and IL-10, play a major immunosuppressive effects on the anticancer immunity, whereas IL-2 and IL-12, which may exert both inflammatory and anti-inflammatory effects, have been proven to play a clear anticancer action in humans [11,13,20]. In any case, from a clinical physiopathological point of view, in addition to their single in vitro effects, it is still more important to identify their in vivo interactions, which are similar to those occurring between the endocrine glands, with the only difference that the negative feed back systems are the most important in the Endocrinology, whereas within the cytokine network it is possible to identify both negative and positive feed back mechanisms occurring amog the various cytokine secretions. At present, from a clinical physiopathological point of view, it is possible to recognize seven essential cytokine feed-back mechanisms, consisting of two positive feed back circuits, represented by the reciprocal stimulatory relation between IL-2 and IL-12 [20], as well as that occurring between IL-6 and IL-17, by three negative feed-back mechanisms, consisting of the relation between IL- 2 and TGF-beta with stimulatory action of IL-2 on TGF-beta and inhibitory effect of TGF-beta on IL-2 secretion [16], between IL-17 and IL-2 with stimulatory effect of IL-17 on IL-2 and inhibitory activity of IL-2 on IL-17 secretion [17], and between IL-6 and IL-2 with stimulatory effects of IL-2 on IL-6 and inhibitory action of IL-6 on IL-2 secretion and activity [15], and finally by two double negative feed back circuits both involving IL-12 activity, with reciprocal inhibitory effects of IL-12 on TGF-beta and of TGF-beta on IL-12 secretion, as well as with reciprocal inhibitory effects between IL-12 and IL-17 secretions [6,18,19]. Moreover, it has to be remarked that the interactions between IL-17 and TGF-beta secretions are more complex, since IL-17 suppresses T reg cells and TGF-beta secretion [7], whereas the effect of TGF-beta on IL-17 production would depend on the presence of other cytokines, since TGF-alone tends to inhibit IL-17 secretion, while in the presence of IL-6, as well as IL-23, TGF-beta stimulates TH17 cell generation and IL-17 release. The cytokine regulation of the inflammatory response is illustrated in Figure 1.

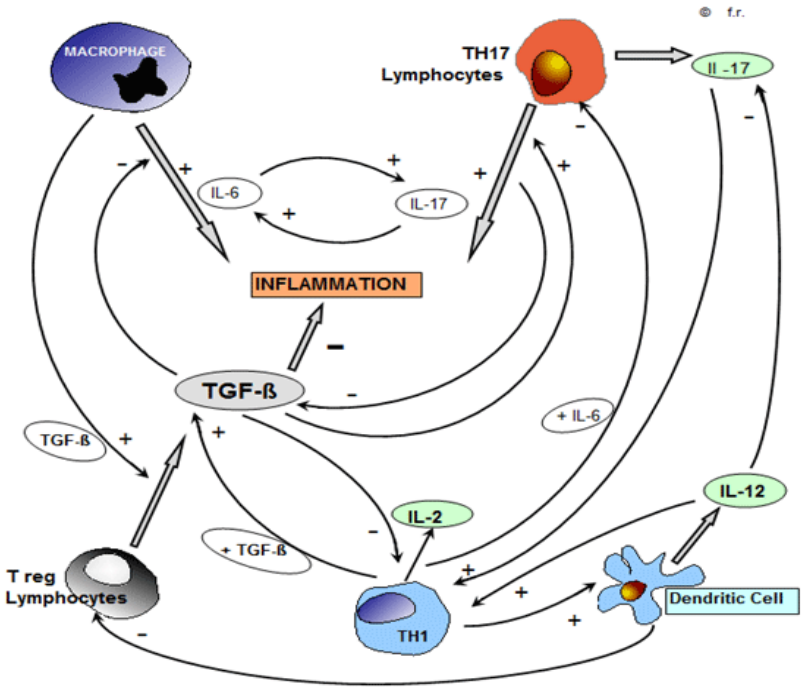

Figure 01: Cytokine regulation of the inflammatory response

The Inflammatory Status of Cancer, Autoimmune and Cardiovascular Diseases

Both advanced tumors and autoimmune diseases, and probably also psychiatric and neurodegenerative diseases, despite their different physiopathology, are characterized by the presence of an exaggerated inflammatory response, which consists of a chronic inflammatory status in the neoplastic diseases, and of an alternating sequences of acute and remission phases of disease in the autoimmune pathologies [2,7]. Moreover, despite the complexity of immune cytokine interactions during the clinical course of the systemic inflammatory diseases, it is possible to suggest that advanced cancer-related

inflammatory status is mainly originated by the macrophage system, whereas that occurring in the autoimmune diseases would mainly depend on IL-17 produced by TH17 lymphocytes, at least at the beginning of the disease [2,7]. The prevalent role of macrophages in mediating cancer-related inflammatory status is salso suggested by the blood levels of IL-6, which tend to be constantly high in the advanced neoplastic disease, whereas controversial data exist about IL-17 behavior in cancer [15]. On the contrary, IL-17 would be essential for the onset of the autoimmune processes [7]. From a therapeutic point of view, TGF-beta cannot be obviously used in cancer patients as an anti-inflammatory agent because of its concomitant protumoral immunosuppressive activity (10). In contrast, TGF-beta could play therapeutic effects in autoimmune diseases, since the evidence of high levels of TGF-beta has been proven to predict a more favourable prognosis in autoimmunity (21). On the other hand, as confirmed by preliminary clinical results (20), IL-12 could be effective in cancer immunotherapy (13), because of its inhibitory action on T reg cell system in association with its stimulatory activity on IL-2 secretion and cytotoxicity of both cytotoxic T cells and macrophages, whereas IL-12 could negatively influence the clinical course of the autoimmune diseases because of its potential further inhibition of T reg cell system and TGF-beta production (13,18). Finally, IL-2 may reserve a great importance in the treatment of both cancer and autoimmunity. IL-2 plays an anticancer role through several mechanisms, including stimulation of the evolution of NK cells into LAK cells, which may destroy fresh human cancer cells (11), and promoting effect on IL-12 production (15), but IL-2 may be paradoxically therapeutically usefull also in the treatment of autoimmune diseases, because of its stimulatory action on T reg cells and TGF-beta secretion. In fact, low-dose IL-2 has appeared to improve the clinical course of the autoimmune diseases [16]. In addition to the well known importance of the inflammatory response in both cancer and autoimmunity, it has recently been demonstrated that the functional status of the cytokine network involved in the regulation of the inflammatory response may also influence the prognosis of cardiovascular pathologies (3,4). In particular, it has been shown that the inflammatory response may negatively influence the prognosis of both myocardial infarction and heartfailure, and this event would be mainly mediated by endothelin-1 (ET-1) [22]. In fact, in addition to its cardiovascular effects, namely consisting of increase in blood pressure, stimulation of cardiac hypertrophy and atherosclerosis processes, ET-1 has appeared to play inflammatory activity by stimulating the secretion of inflammatory cytokines, such as IL-1 beta and IL-6, and to interact with TGF-beta in promoting the fibrotic processes.

Conclusions

To modify the biological response, obviously we have before to known its physiopathology, then the functionless of the cytokine network, with its negative and positive feed-back systems. Unfortunately, despite the great advances in the knowledge of the in vitro immune effects of the different cytokines, very few clinical studies have been carried out to in vivo verify the behavior of the various cytokines in human systemic diseases. However, despite the controversial opinions, at present it is possible to identify at least two major origins of the inflammatory status, consisting of macrophage system through the release of IL-6, and TH17 cell system by releasing IL-17. Both cancer and autoimmunity are characterized by a systemic inflammatory status involving both inflammatory systems, even though the autoimmune diseases would primarily depend on IL-17-dependent inflammation (7), whereas advanced cancer-related chronic inflammatory status would mainly be induced by the macrophage system (2), which allows an enhanced generation of T reg cells [14].

References

1. Foon KA (1989) Biological response modifiers: the new immunotherapy. Cancer Res 49(7): 125-127.

2. Biswas SK, Mantovani A (2010) Macrophage plasticity and interaction with lymphocyte subsets: canceras a paradigm. NatImmunol 11(10): 889-896.

3. Lameijer MA, Tang J, Nahrendorf M, Beelen RH, Mulder WJ (2013) Monocytes and macrophages as nanomedicinal targets for improved diagnosis and treatment of disease.Expert RevMolDiagn 13(6): 567-580.

4. Nahrendorf M, Swirski FK (2016) Abandoning M1/M2 for a network model of macrophage function. Circul Res 119(3): 414-417.

5. Dinarello CA (2006) Interleukin-1 and interleukin-18 as mediators of inflammation and the aging process. Am J ClinNutr 83(2): 447S-455S.

6. Pappu R, Ramirez-Carrozzi V, Sambandam A (2011) The interleukin-17 cytokine family: critical players in host defence and inflammatory diseases. Immunology 134(1): 8-16.

7. Hu Y, Shen F, Crellin NK, Ouyang W (2011) The IL-17 pathway as a major therapeutic target in autoimmune diseases. Ann NY Acad Sci 1217: 60-76.

8. Li D, Guo B, Wu H, Tan L, Chang C, Lu Q (2015) Interleukin-17 in systemic lupus erythematosus: a comprenhensive review. Autoimmunity 48(6): 353-361.

9. Zou W (2006) Regulatory T cells, tumor immunity and immunotherapy. NatRevImmunol 6(4): 295-307.

10. Saunier EF, Akhurst RJ (2006) TGF-beta inhibition for cancer therapy. Curr Cancer Drug Targets 6(7): 565-578.

11. Grimm EA, Mazumder A, Zhang HZ, Rosenberg SA (1982) Lymphokine-activated killer cell phenomenon. J ExpMed 155(6): 1823-1841.

12. Whittington R, Faulds D (1993) Interleukin-2. A review of its pharmacological properties and therapeutic use in patients with cancer.Drugs 46(3): 446-514.

13. Banks RE, Patel PM, Selby PJ (1995) Interleukin-12: a new clinical player in cytokine therapy. Br J Cancer 71(4): 655-659.

14. Gabrilovich DI, Nagaraj S (2009) Myeloid-derived suppressor cells as regulators of the immune system. NatRevImmunol 9(3): 162-174.

15. Lissoni P (2017) Therapy implications on the role of interleukin-2 in cancer. ExpRevClinImmunol 13(5): 491-498.

16. He J, Zhang X, Zhanguo L, et al (2016) Low-dose interleukin-2 treatment selectively modulates CD4+ T cell subsets in patients with systemic lupus erythematosus. NatMed 22(9): 991-993.

17. Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, et al (2007) Interleukin-2 signaling via STAT 5 constrains T helper 17 cell generation. Immunity 26(3): 371-381.

18. King IL, Segal BM (2005) Cutting edge: IL-12 induces CD4CD25-cellactivation in the presence of regulatory T cells. J Imunol 175(2): 641-645.

19. Zundler S, Neurath MF (2015) Interleukin-12: functional activities and implications for disease. CytokineGrowthFactorRev 26(5): 559-568.

20. Lissoni P, Pittalis S, Rovelli F, Vigoré L, Roselli MG, et al (1995) Interleukin-2, melatonin and interleukin-12 as a possible neuroimmune combination in the biotherapy of cancer. J BiolRegulHomeost Agents 9(2): 63-66.

21. Sakaguchi S, Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T (2009) Regulatory T ceòòs: how do theysuppress immune responss? IntImmunol 21(10): 1105-1111.

22. Khan IA (2005) Role of endothelin-1 in acute myocardial infarction. ChestJ 127(5): 1474-1476.