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Review

Macrophages and antitumor reactions

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Introduction

Since the discovery of tumor-associated antigens there has been reason to suppose that tumor growth might be stopped by immunological means. However, immunotherapeutic approaches have so far been disappointing.

Our group has been working for several years on the role of macrophages in tumor immunology. Some major findings can be summarized as follows. (a) T lymphocytes can become sensitized towards antigens on tumor cells; (b) sensitized T cells can render macrophages specifically cytotoxic towards these tumor cells in both syngeneic [24, 25] and allogeneic systems [13]; (c) macrophages can exert an antitumor effect in vivo [74]; and (d) exudate macrophages and macrophage-like cell lines can stimulate both the local and the systemic antitumor effect of sensitized lymphocytes [76]. Furthermore, no therapeutic effect can be obtained after elimination of macrophages from tumor-bearing mice before the transfer of immune lymphocytes [77].

In these experiments macrophages were eliminated with silica. Intraperitoneal silica treatment did not only result in widespread destruction of macrophages; but those macrophages which could be collected from the mice 2 days after silica treatment showed a decreased ability to survive in vitro, decreased spontaneous cytotoxicity, and a decreased ability to be activated by sensitized lymphocytes [75]. The aspect of macrophage participation in antitumor reactions is an enormous subject. Therefore it is almost impossible to give a detailed analysis of each macrophage activity involved in the antitumor reaction (the role of intratumor macrophages *alone* has recently been the subject of a 15-chapter book [36]).

In this paper a timely re-evaluation is given of current general thinking for tumor immunologists in other fields, together with some suggestions for future research.

Induction of cytotoxic macrophages

Macrophages can express significant levels of tumoricidal activity as a consequence of activation with various stimuli (BCG, LPS, etc.) either in vitro or in vivo (reviewed by Hibbs [42]). In the in vivo situation, injection of muramyldipeptide-containing liposomes [66] or immunization with tumor cells [12, 24] leads macrophages to express antitumor activity. In vitro activation of normal macrophages is possible by factors produced by lymphocytes which have been stimulated either nonspecifically [50] or by specific antigens [13, 56]. Macrophages activated in the latter way in vitro can express antitumor activity in vivo [74]. This suggests that lymphocytes are important for the induction of cytotoxic macrophages in vitro. Induction of the so-called natural cytotoxic macrophages is probably due to certain nonpathogenic bacteria and viruses [56]. These natural cytotoxic macrophages, which can be present in the peritoneal cavity of mice from different breeding colonies, are nonspecifically cytotoxic, and may play a role in the 'immune' surveillance against tumors.

Significance of cytotoxic macrophages

There are several arguments for the contention that cytotoxic macrophages are important as tumor cell killers in vivo: (a) A population of cytotoxic macrophages has been shown to exert an antitumor effect in vivo [74]; (b) the specificity of the rejection of tumor cells in sensitized mice is similar to the specificity of the in vitro cytotoxicity of macrophages isolated from sensitized mice (unpublished results); (c) the positive systemic therapeutic results obtained with transfer of sensitized spleen cells could not be reproduced in macrophage-depleted mice, so that host macrophages seem to be involved in systemic adoptive immunity against tumours [77]; (d) cytotoxic macrophages can kill tumor cells at a low effector cell/target cell ratio of 10 : 1 [24] or even 1 : 1 [16]; and (e) large numbers of macrophages within a tumor are said to be prognostically favorable and low numbers to mean that the tumor metastasizes more easily [19, 49, 65]. However, such a favorable relation between a high macrophage content and tumor growth does not always exist [8, 22, 23, 26, 43].

In this respect the aspect of macrophage function which may be mediated via their Fc receptors should also be mentioned. Evidence has been produced that macrophages might act as important effector cells in antibody-dependent cellular cytotoxicity [37, 38, 44, 60] and in immune-mediated phagocytosis [15].

Regulatory functions of macrophages

Macrophages play an important role in regulating immune response reactions. They not only act as effector cells against tumors [33], but also express both positive and negative regulatory effects on humoral and on cell-mediated immune responses during tumor growth. The stimulatory effect of macrophages is often due to soluble factors (monokines)

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produced by macrophages. One of the best-known factors is interleukin 1 [IL 1, previously called lymphocyte activating factor (LAF)] [14, 28, 53]. The stimulatory effect of macrophages on the immune response can often be replaced by these factors [6]. Macrophages can also enhance the immune response by presenting antigens to the lymphocytes. This presentation of antigen is often a prerequisite for a good immunological response, and is especially important for T-cell responses [21, 63].

Antigen presentation can only be accomplished by macrophages bearing Ia antigens [2, 47, 48, 51, 73]. These antigens are coded in the I region of the major histocompatibility complex (MHC) and are mainly found on B cells and on some of the macrophages [2]. In the peritoneal cavity different percentages (5%–60%) of Ia^+ macrophages are described [27, 51, 52], whereas in lymphoid organs most macrophages are Ia-positive [72]. During inflammatory processes this percentage may be increased [5]. For the development of a secondary response it is necessary that the macrophages presenting the antigen express the same Ia antigens as the macrophages operative in the primary response [67]. During tumor growth direct sensitization of the lymphocytes by the tumor cells might also be important. Recently we have shown that lymphocytes can be sensitized against intact tumor cells without the involvement of macrophages. That is, secondary stimulation of macrophages was not Ia-restricted at the macrophage level, and thus the lymphocytes were obviously triggered directly by the tumor cells [13].

Macrophages can also suppress the immune response [58]. In in vitro cultures, for instance, the lymphocyte: macrophage ratio is important. If too many macrophages are present the response is suppressed instead of stimulated [7, 80]. Macrophages from tumor-bearing mice [40, 78, 79] or monocytes from cancer patients [35] can also be suppressive. Antibody responses or cell-mediated immune responses are suppressed by soluble factors produced by these macrophages. An example of such a factor is prostaglandin [31, 34]. It is known that prostaglandins produced by the stimulated macrophages themselves can also regulate/suppress the expression of macrophage-mediated cytotoxicity [57, 70]. These date suggest that the production of prostaglandins represents a negative feedback mechanism. Other macrophage-secretory products can also have such autoregulatory functions, including protease inhibitors (e.g., α_2-macroglobulin, interferon/s) and other metabolites of arachidonic acid [reviews see 10, 20, 45].

Macrophage products can also influence the antitumor response of other cell types. These macrophage products can cause rat, mouse, and human NK cells to express augmented antitumor activity in vitro [61]. The mechanism of the macrophages in activating these cells and in maintaining their activities in vivo has been ascribed particularly to the production of interferon by macrophages [39]. The requirement of macrophages for activation of K cells mediating antibody-dependent cellular cytotoxicity (ADCC) has also been reported [39].

Finally, macrophages can influence the inflammation and repair processes by secreting products such as neutral proteases (e.g., elastase, plasminogen activator), protease inhibitors (e.g., α_2-macroglobulin, α_1-anti-trypsin), and lysosomal enzymes [9, 54]. Although these products might not be important in direct antitumor activity they have a major function in influencing the penetration of 'immune response' cells into a tumor. In conclusion, the net antitumor effect of activated macrophages is not only determined by their direct cytotoxic effects but also by their activities as regulatory cells. This might explain the lack of correlation described by some authors [8, 22, 26, 43, 71] between the number of macrophages in a tumor and the prognosis of the tumor growth and metastasis.

Significance of macrophage heterogeneity

From the last section it is clear that not all functions can be expressed by one and the same macrophage at the same time. Macrophage heterogeneity can therefore also be expected with respect to function.

Heterogeneity of macrophage populations has been subject of many studies [30, 46, 69, 76]. Maturation, differentiation, and activation states of the macrophages can be important factors causing heterogeneity. In this paper we will not discuss the heterogeneity as such, but only mention a few forms of heterogeneity that are linked with the functioning of macrophages as regulator cells and/or as antitumor effector cells. The presence/absence of Ia antigens on the surface is important in this respect. Cytotoxic macrophages have been described to be large Ia-negative cells, while the macrophages responsible for antigen presentation are Ia-positive. Macrophages responsible for the secretion of LAF (IL-1) can be Ia-positive and Ia-negative [44, 46]. It is known that during several inflammatory reactions the number of Ia^+ cells increases [5], which may also be the case during inflammatory processes within tumors. If so, inflammation in a tumor could be favorable for the induction of an immune response.

It has been suggested that the 'age' of the macrophages determines whether the cell can be activated or not. Ruco and Meltzer [64] stated that only newly formed mononuclear phagocytes could be activated with lymphokines. However, experiments conducted by our own group have clearly shown that resident macrophages can also be rendered cytotoxic by T-cell-derived factors [55].

Macrophage activities during tumor growth

Several immunological processes can be depressed during tumor growth, including macrophage functions [57, 59]. It is also known that accumulation of leukocytes at the inflammation site and the chemotactic response in vitro of macrophages/monocytes obtained from cancer patients [29, 68] can be reduced. These effects can be ascribed partly to substances/factors produced by the tumor cells themselves [31, 62]. However, not every tumor product inhibits or depresses macrophage functions. Recently Dullens and Den Otter [17] described a factor derived from P815 mastocytoma cells which could induce macrophage cytotoxicity in vitro. This cytotoxicity was tumor-non-specific. The in vivo relevance of this product, identified as a low-molecular-weight (molec. wt. 650–700 daltons) peptide [18], still has to be established. A similar product from L5178Y lymphosarcoma cells has been described by Gemsa et al. [32].

Future research

The use of macrophages in immunotherapeutic approaches is often aimed at the induction or transfer of cytotoxic macrophages. However, we should take into account that these activated macrophages may also suppress the development of

an immune response in the recipient. Although a part of the tumor may be destroyed by the cytotoxic macrophages, the development of an immunological response to the tumor may still be depressed in the recipient.

Furthermore, when macrophage activation in vivo (in the cancer patient, e.g., by BCG) is used as a therapeutic approach one should realize that the functioning of the immune system (including the activation of lymphocytes and macrophages) has already been grossly affected. This treatment might result in quite different responses compared with the responses in normal individuals. This means that it may be more important to augment and/or redirect the immune response of the tumor bearer to overcome suppressive phenomena, rather than to transfer cytotoxic effector cells.

On the other hand, transfer of cytotoxic effector cells can be beneficial for the tumor bearer. For instance Van Loveren et al. [79] have shown that incubation of sensitized lymphocytes with nonstimulated macrophage-like cells can result in stimulation of the antitumor efficacy of these lymphocytes when transferred into tumor-bearing mice. The mechanism underlying this stimulation is unknown, but it seems unlikely that the transferred macrophages act as cytotoxic effector cell; probably they merely act as stimulatory cells for the transferred immune lymphocytes.

Another important aspect in future research might be the accessibility of a tumor for antitumor effector cells. Monocytes/macrophages have to reach a tumor via the blood circulation. They leave the circulation via the interendothelial junctions of the capillaries and invade the tumor mass. Under normal conditions these junctions are thought to be closed, but they are opened during inflammatory reactions such as delayed-type hypersensitivity (DTH) reactions [4]. Opening of the interendothelial junctions is regulated by vasoamines released from basophils or mast cells. Tumor vessels are responsive to vasoactive amines, but in a progressively growing tumor there might be an insufficient or ineffective local amine release [3]. Future research will have to show whether vasoamine release induces an increase in the number of macrophages which penetrates a tumor, so facilitating a possible eradication of the tumor cells, Evidence that circulating tumor cells may also be removed by macrophages [11] and that their presence may be essential for the in vivo antitumor activity of monoclonal antibodies in some systems (by means of ADCC reactions [41]) is currently of great interest and deserves further attention.

In conclusion, several data suggest that macrophages can limit the growth and/or dissemination of tumors. If we succeed in understanding how to direct cytotoxic macrophages into the tumor mass and avoid the suppressive effects of macrophages, immunotherapy may grow beyond the status of just an attractive idea.

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