IMMUNOMODULATORY ACTION OF EICOSANOIDS
AND OTHER SMALL MOLECULAR WEIGHT PRODUCTS OF MACROPHAGES

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Summary. - There is an increasing body of evidence that T cell-mediated immune response is regulated by a variety of small molecular weight products of macrophages. One of the best known immunoregulatory products in this context is prostaglandin E₂ (PGE₂) which is known to regulate both T cell and macrophage functions. Recently, ornithine, cysteine, and lactate have also been recognized as immunoregulatory mediators. In analogy to the hormone-like cytokines and lymphokines, all these substances are produced by immunologically relevant cells (macrophages) at a variable and regulated rate; and they have been shown to regulate the functional activities of other cells (T cells and macrophages). This brief review describes the key observations that underscore the important regulatory role of these metabolites in physiological and pathological conditions.

KEY WORDS: immunomodulation, eicosanoids, macrophages.

Introduction

Macrophages play an important role as stimulator cells and accessory cells in T cell-mediated immune response. The exchange of regulatory signals between macrophages and T cells is facilitated by the fact that both cell types can form intimate contact. The regulatory interactions can be divided into at least 3 categories including: a) the interaction of cell surface molecules with their corresponding receptors; b) the release of hormone like proteins (i.e. IL-1 and TNF) and their interaction with corresponding surface receptors and c) the release of small molecular weight substances by the macrophages. This review deals with the immunoregulatory role of several small molecular weight substances. Three of these substances, i.e. ornithine, cysteine and lactate have been recognized only recently as immunoregulatory mediators [1-3].

Regulatory effects of prostaglandins

Regulatory effects of prostaglandins on immune responses are known since 1971 [4, 5]. It is now well established that prostaglandin E₂ is produced by macrophages and that it acts on various immunologically relevant cells. In vitro, prostaglandins have been shown to inhibit several types of T cell responses [6]. The most profound effect is the inhibition of the production of the T cell growth factor interleukin 2 (IL-2); and there is a possibility that other inhibitory effects may be (at least partly) the consequence of the insufficient availability of this T cell growth factor. Prostaglandins are also known to regulate macrophage functions and to inhibit especially the expression of Ia
antigens and the development of tumoricidal activity. Both effects are antagonized by the T cell-derived lymphokine IFN-γ. The capacity of macrophages to convert arginine into ornithine and to release ornithine into the extracellular space, in contrast, is synergistically augmented by PGE₂ [7]. The capacity to release ornithine, in turn, plays also an important role in the regulation of immune responses as described later. There is evidence that prostaglandin E₂ augments certain T cell-mediated immune responses in vivo [8-11]. PGE₂ acts on its target cells by using a cell surface receptor, which is linked to adenylate and increases the intracellular concentration of cAMP.

Regulation of T cell functions by variations of the extracellular concentration of cysteine

Studies on several mitogenically stimulated T cell populations and T cell clones revealed that the proliferative activity and intracellular glutathione concentration of these cells is strongly dependent on the extracellular concentration of cysteine even in the presence of several-fold higher concentrations of cystine or methionine. Moreover, the effect of cysteine was not obtained by the addition of a corresponding amount of cystine or methionine [12]. This observation is in line with earlier reports that most cell types in higher organisms have a weak cystathionase activity and can, therefore, not use methionine for the biosynthesis of cysteine [13]; and it is also in line with earlier reports that lymphoid cells have, in average, a strong membrane transport activity for cysteine, but weak or no transport activity for cystine [14].

The regulatory effect of cysteine for T cell functions is based not only on the limited transport activity for cysteine, but also on the fact that blood plasma contains relatively high concentrations of cysteine (100-200 µM), but only relatively low concentrations of cysteine (10-20 µM). Macrophages, in contrast to lymphocytes, have a strong transport activity for cysteine [15]. Moreover, only a small proportion of the cysteine that is taken up by the macrophages is consumed by their own metabolic processes, while a major proportion of this amino acid is released again into the extracellular space in its reduced form cysteine [16]. This capacity to release cysteine is strongly increased in activated macrophages after stimulation with lipopolysaccharide or tumor necrosis factor (B. Benninghoff et al., manuscript in preparation). It is also increased by a moderate elevation of the extracellular concentration of ornithine.

The immunoregulatory effect of ornithine

Since LPS or TNF treatment of macrophages stimulates the arginase activity of macrophages and enhances thereby the endogenous production of ornithine [2], it is concluded that ornithine plays a role as an intermediate regulatory mediator in this signal pathway. In agreement with this regulatory effect of ornithine on the capacity of macrophages to release cysteine into the extracellular space, and in line with the complementary observation that T cell func-

The immunoregulatory role of lactate

L-lactate is another immunoregulatory product of macrophages [3]. It is produced from glucose by the glycolytic metabolism. In vitro, L-lactate has been shown to support the production of the T cell growth factor interleukin 2 in mitogenically stimulated accessory cell depleted T cell populations. Since it is capable of replacing accessory cells in this system, it is well possible that the release of lactate by glycolytically active macrophages is particularly important for their function as accessory cells. Lactate was also shown to augment the IL-2 production and activation of cytotoxic T cells in unfractionated lymphocyte preparations and exerts strong immunopotentiating effects in vivo [3].

Evidence for a glutamate-linked immunodeficiency syndrome (GIDS)

Glutamate, finally, is a substance which inhibits the uptake of cystine and the subsequent release of cysteine by macrophages. As a consequence, elevated extracellular concentration of glutamate inhibits T cell responses in vitro. It was shown, furthermore, to cause certain pathological conditions with elevated plasma glutamate concentrations are correlated with reduced lymphocyte functions. This applies to tumor patients [17] and patients with the acquired immunodeficiency syndrome (AIDS) [18-20]. AIDS patients were found to have up to 7-fold the normal level of plasma glutamate [19] and showed, moreover, a strong intra-individual and inter-individual variation (H.-P. Eck, unpublished observation).

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