Biological and Clinical Relevance of Human Macrophage Migration Inhibitory Factor (MIF)

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Summary. The first isolation and characterization of a lymphokine, the human MIF (MSF), and the availability of a specific MIF (MSF)-antibody provide an opportunity to establish a new parameter for detection of cellular immune mechanisms in various clinical situations. The precise estimation of quantitative amounts of MIF by sensitive immunochemical techniques could gain new insights into the pathogenesis of a number of clinical disorders. In addition, the exact detection of quantitative amounts of MIF in body fluids could have prognostic value.

Key words: Lymphokines – Macrophage migration inhibitory factor (MIF) – Biochemical parameters – Biological function – Clinical relevance
Mononuclear phagocytes (macrophages and monocytes) are involved in host resistance against infectious diseases and cancer. These cells are known as effector cells in cell-mediated immunity and thus participate in mechanisms of recognition and neutralization of antigens. The reactions of cell-mediated immunity can be divided into two broad categories: (a) the lymphocyte-dependent, antigen-induced cellular cytotoxicity and (b) the macrophage-dependent, antigen-induced proliferation of sensitized lymphocytes. The latter kind of reaction is accompanied by the release of mediator substances (lymphokines) which are produced by immunocompetent cells in vivo and in vitro following contact with specific antigens. This reaction provides a link between the cell-mediated immune response and the inflammatory system.

Although various lymphokines have been shown to affect the biological activity of the mononuclear phagocyte system, their exact role is far from being understood.

One of the best studied lymphokines is the macrophage migration inhibitory factor (MIF). In 1932, Rich and Lewis [41] demonstrated the phenomenon of migration inhibition of macrophages from tissue explants of tuberculin-positive guinea pigs in the presence of PPD. About 30 years later Bloom and Bennett [6] and David [11] showed the correlation between migration inhibition of macrophages in vitro and the delayed hypersensitivity reaction in vivo. Based on this finding the MIF-test is being used in various clinical situations (see below).

**How is MIF Produced?**

MIF is released in vivo by sensitized immunocompetent cells following contact with specific antigen, however, its production in vitro does not appear to be antigen specific, since MIF can be produced by lymphocyte cultures after incubation with mitogens (e.g., Concanavalin A) [34].

In addition, MIF-activity can be obtained from supernatants of malignant cell lines (e.g., HeLa- and mastocytoma cells) [22, 8]. It is therefore unknown, whether this MIF-like activity is identical with MIF or is caused by entities which can mimic the MIF effect. In this regard it is interesting to note, that antigen-antibody complexes can mimic MIF action [25]. It is possible hereby that the macrophage preparations, which were used for testing MIF-activity, were contaminated with immunocompetent cells and thus produced MIF in presence of the antigen-antibody complexes.

Various other substances have the ability to mimic the effect of migration inhibition of macrophages (e.g., 3',5' cyclic AMP) [35], but it is questionable whether MIF is identical with these MIF-like activities or not.

The induction of MIF is sensitive against actinomycin D, mitomycin, and puromycin [12], indicating the dependence of MIF-production on transcriptional mechanisms.

Under in vitro conditions both B- and T-lymphocytes appear to be capable of producing MIF (Fig. 1). According to Newman et al. [33] MIF-production by helper T-lymphocytes (Ly I+, 2-) is thereby controlled by killer- and suppressor-T-cells (Ly I-, 2+). Besides Ly I+, 2- and I-, 2+ B-lymphocytes have been shown to produce MIF. Using supernatants of Ly I-, 2+ cells Cohen [9] was able to-