The Autologous Mixed Lymphocyte Reaction

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I. INTRODUCTION

At the turn of the century, Ehrlich (1957) proposed that the immunity to autologous antigen is highly abnormal and would result in a disease process. At midcentury, Burnet (1959) proposed his immunologic theory of clonal selection, which included deletion of autoreactive clones during ontogeny. According to this theory, autoantibodies and other autoimmune reactions are the result of the appearance of forbidden clones secondary to somatic mutation. However, in the last 15 years, there has been increasing evidence that immune reactions are driven by recognition of both self and nonself antigens. A number of major histocompatibility complex (MHC)-restricted immune reactions demonstrated the requirement of identity at the MHC loci for interactions between lymphocytes and macrophages. Thus, lymphocyte receptors for autologous MHC determinants play a crucial role in the recognition and effector phase of immune response.

The earliest evidence of the autologous mixed lymphocyte reaction (AMLR) was reported by Fridman and Kourilsky (1969). These investigators showed that peripheral blood lymphocytes could be stimulated in one-way mixed lymphocyte cultures by autologous leukemic lymphocytes. However, it was not clear whether the stimulating antigen was a “self” antigen or a tumor-associated antigen. Steel and Hardy (1970) and Junge et al. (1970) observed increased DNA synthesis by peripheral blood leukocytes on stimulation with autologous lymphoid cell lines established during acute infectious mononucleosis. Green and Sell (1970), Knight et al. (1971), and Birnbaum et al. (1972) reported...
lymphocyte proliferation on stimulation with noninfected autologous lymphoblastoid cells from healthy donors. Opelz et al. (1975), using fractionated T and non-T cells from normal donors, observed an increased proliferative response of T cells upon stimulation with autologous non-T cells.

Recently, there has been concern among investigators about the true existence of the AMLR. Huber et al. (1982) reported data to suggest that the proliferative responses of T cells in the AMLR are not caused by self antigens but rather by xenoantigens [sheep red blood cells (SRBC) or fetal calf serum] used in the culture medium or during the separation procedure for T and non-T cells. However, under experimental conditions in which no xenoantigens were used, it was clearly shown that both the syngeneic mixed lymphocyte reaction (SMLR) in mice and the AMLR in man were largely caused by stimulation by self antigens (Moody et al., 1983; Laffon et al., 1983; Thorbecke et al., 1983). The true existence of the AMLR is further supported by the establishment of T-cell clones and T-cell hybrids in man and experimental animals that recognize self antigen and not the xenoantigens (Richardson and Stobo, 1983; Glimcher and Shevach, 1982).

Although the true significance of the AMLR is presently unclear, it is considered an immune response in which immunoregulatory and effector T-cell functions are generated and perhaps are essential for maintaining normal immunostasis. Furthermore, the author believes that the AMLR provides perhaps the best model to study various interactions in cellular and cytokine cascades that might take place in vivo. The AMLR and SMLR have recently been reviewed (Weksler et al., 1981; Battisto and Ponzio, 1981; Gupta, 1983). In this chapter, a detailed review of the AMLR, with regard to cell types responding to and stimulating it, production and influence of cytokines, generation of immunoregulatory and cytotoxic effector functions, and the surface molecules involved in the self-recognition, is presented. The cellular and molecular bases of abnormal AMLR in rheumatic disorders are discussed in detail. Recently, it has become apparent that the AMLR is not only between T and non-T cells but also between T and T cells.

II. T–NON-T INTERACTIONS IN THE AMLR

A. Cell Types Responding in T–Non-T AMLR

There is a general agreement among investigators that in the AMLR, the major responding population is T lymphocytes; however, the nature of the major stimulating population remains somewhat controversial (discussed below). Opelz et al. (1975), using a purified population of T and non-T cells, found that T lymphocytes were the responding cells in the AMLR and that increasing or decreasing the number of stimulator non-T cells could increase or decrease the AMLR response. Kuntz et al. (1976), using macrophages, B cells, or third-population lymphoid cells as stimulators against autologous responder T cells, demonstrated that T cells proliferate in the AMLR. Smith and Knowlton (1981), using a percoll gradient to isolate T-cell subsets, observed that the low-density T cells were most responsive to autologous non-T cells and to the lectin concanavalin A (Con A). In contrast, both high- and low-density T cells responded in the allogeneic MLR.

Stobo and Loehnen (1978) fractionated purified T cells into five fractions using a