The Role of Lymphokines in Delayed-Type Hypersensitivity Reactions

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Introduction

The state of delayed-type hypersensitivity (DTH) is characterized by the reaction elicited by intradermal injection of the sensitizing antigen. Such reactions were clearly distinguished from other forms of skin reactions by Zinsser [257], and were shown by Landsteiner and Chase [115] and Chase [29] to be due to what is now termed cell-mediated immunity (CMI). DTH is important because it accompanies many manifestations of CMI and because the skin reactions have provided a model for the elucidation of effector mechanisms in CMI.

DTH can be elicited by a variety of antigens including microbial antigens, viral antigens, parasite antigens, soluble proteins, synthetic peptides, contact sensitizing agents, xenogeneic erythrocytes, and transplantation antigens [224]. Mantoux [129] first described a quantitative measure of the sensitivity of donors challenged intradermally with Old tuberculin. The reaction reaches maximal intensity after 24–48 h when it appears as an indurated, erythematous swelling. The manifestations of

Supported by grants from the National Health and Medical Research Council of Australia and the New South Wales State Cancer Council

Abbreviations used in this paper. DTH delayed-type hypersensitivity; CBH cutaneous basophil hypersensitivity; CMI cell-mediated immunity; LPS bacterial lipopolysaccharide; LIF leukocyte inhibition factor; NIF-T neutrophil migration inhibition factor; MPCA monocyte/macrophage procoagulant activity; MIF macrophage migration inhibition factor; MPIF macrophage procoagulant inducing factor; MAF macrophage activating factor; MaggF macrophage aggregation factor; MCF chemotactic factor for macrophages; NCF chemotactic factor for neutrophils; LCF chemotactic factor for lymphocytes; BCF chemotactic factor for basophils; MF mitogenic factor; IL1 interleukin; IL2 interleukin 2; LNPF lymph node permeability factor; SRF skin reactive factor; Ig immunoglobulin; PA plasminogen activator; PG prostaglandin; Con A concanavalin A; PHA phytohemagglutinin; PMN polymorphonuclear leukocytes; PEC peritoneal exudate cells; TG thioglycollate; mol. wt. molecular weight; SI stimulation index; PPD purified protein derivative of Tuberculin
the lesions may vary with the species under investigation; the manner and degree of sensitization of the individual; with the chemical nature, concentration, and route of administration of the sensitizing agent, and with the nature of the antigen challenge [review 224]. Typically, however, the reactions are delayed in onset and persistent. Histologic studies show that neutrophils predominate in the early phase of the DTH response [225] whereas perivascular infiltrates of bone marrow-derived blood-borne macrophage [38, 122, 231, 232] and lymphocytes [225] comprise the later phase. Basophils are present to varying degrees in DTH lesions, but form a much larger proportion of the cells of cutaneous basophil hypersensitivity (CBH) and of chemical contact sensitivity reactions [48, 49, 177, 178]. Eosinophils are not prominent cells in DTH except at sites of repeated skin tests [6] or when parasites are the invading antigens. In addition to the cellular infiltrate, fibrin deposition in the extravascular spaces is a regular feature and is thought to contribute to the induration observed in skin test reactions [2, 47, 63].

T lymphocytes have a central role in DTH reactions [reviews: 78, 131, 209; 224]. Transfer of DTH to heterologous erythrocytes and soluble protein in the mouse is mediated by the Lyt-1 +2−, Ia− subset of circulating T cells [96, 226]. T-T cell interactions can mediate the effector phase of DTH [214], and the response of Lyt-1 +2−, Ia− cells may be augmented by a population of Thy1+, Lyt-1 +2−, Ia+ cells, the phenotype characteristic of proliferating T cells [132]. DTH against allogeneic cells and viral antigens can be mediated by an Lyt-1−2−3+ subset [118, 199, 200]. The recent reports of antigen-specific clones of mouse cell lines indicate that DTH may be mediated by both Lyt-2− and Lyt-2+ cells [19, 105, 215, 219, 246], and that these T cells display considerable flexibility in their function [19, 44, 133].

Fewer than 1% of the infiltrating cells in DTH reactions are specifically reactive to the eliciting antigen [reviews: 78, 224]. The cutaneous response to tuberculin is characterized by enrichment of the T helper subset (OKT4) of lymphocytes in tissue infiltrates with subsequent evidence of T-lymphocyte activation [161]. The first event required for the manifestation of DTH responses is activation of antigen-specific T cells which requires two signals: antigens presented in association with the appropriate Class II major histocompatibility antigens on the macrophage or dendritic cell surface [104, 193, 195, 217], and a nonantigen-specific mediator, with the properties of interleukin I (IL1), produced by macrophages [43, 101]. These events may result in expression of interleukin II (IL2) receptor sites and IL2 production by T cells with receptors for antigen and Ia, which would result in antigen-specific proliferation [1, 43]. Among the metabolic consequences of stimulation is the production of lymphokines. The final manifestation of a DTH response is, however, controlled by Ir-genes of the responding animal [review 224; 197, 213, 214], by the activity of regulatory suppressor cells or mediators (see below) which may be responsible for variations due to age, diet [review, 224] illness, drug treatment, and even state of mind [21].

Following the demonstration of inhibition by antigen of the migration of lymphoid cells from sensitized animals [75, 175], David [41] and Bloom and Bennett [23] showed that a soluble product of antigen-stimulated cells from sensitized animals could inhibit the migration of peritoneal exudate cells (PEC) from normal animals. The term "lymphokine" was applied to similarly produced