Activation-induced cell death of peripheral blood
T lymphocytes in patients with primary
Sjögren’s syndrome

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Abstract—Activation-induced cell death (AICD) in T lymphocytes is important for the maintenance of peripheral tolerance. We studied AICD of peripheral blood T cells from patients with primary Sjögren’s syndrome (SS). AICD was induced in mitogen-activated T cells in vitro using mAb to CD3 or Fas (CD95). Cell death and proliferation, Fas and Fas ligand (FasL) expression, and soluble Fas and soluble FasL production were measured. Surface phenotypes and cytokine production of AICD-surviving cells and effects of cytokines on AICD were examined. Anti-CD3 mAb induced cell death in SS and normal T cells in the presence of exogenous interleukin (IL)-2. In the absence of IL-2 anti-CD3 mAb induced cell proliferation in SS and normal T cells. There was no significant difference in Fas/FasL expression and sFas/sFasL production between SS patients and normals. AICD-surviving cells consisted of more CD4+ T cells and less CD8+ T cells in SS compared to normals. AICD-surviving cells produced abundant interferon-γ and little IL-4. There was no significant difference in the effects of cytokines on AICD between SS patients and normals. These findings suggest that IL-2 is a critical factor for AICD. AICD works almost normally in SS T cells when sufficient IL-2 is present prior to T cell receptor re-stimulation.

Key words: Activation-induced cell death; Sjögren’s syndrome; T lymphocytes.

INTRODUCTION

Autoreactive T lymphocytes play a major role in autoimmune disease. Negative selection in the thymus is not a perfect mechanism and some autoreactive T cells exist in the periphery in healthy individuals as well as in patients with autoimmune disease [1–4]. These autoreactive T cells are normally suppressed in healthy
individuals by peripheral tolerance. Peripheral tolerance is maintained by clonal deletion and clonal anergy [5]. If these mechanisms do not work properly in humans, an autoimmune disease could develop. Autoreactive T cells that are resistant to tolerance induction may exist in patients with autoimmune disease [6]. Self-tolerance is easily broken when these autoreactive T cells become expanded in the periphery.

Apoptosis or programmed cell death (PCD) is important to maintain cellular homeostasis in the immune system [7]. PCD is involved in the maintenance of peripheral tolerance by a mechanism called activation-induced cell death (AICD) [8, 9]. Re-stimulation of T cells by the same antigen causes these antigen-specific T cells to die by apoptosis. AICD is thought to be involved in clonal deletion of autoreactive T cells in the periphery and works as a negative feedback mechanism to control unnecessary activity of activated T cells. AICD is controlled by Fas (CD95)/Fas ligand (FasL) [10–12] and tumor necrosis factor (TNF)/TNF receptor system [13]. Abnormal AICD is seen in T cells from lpr mice which have defective Fas expression [14] and in T cells from gld mice which have defective FasL expression [15]. Interleukin (IL)-2 is one of the major regulators of AICD [16, 17]. IL-2-deficient mice develop an autoimmune disease characterized by an uncontrolled proliferation of CD4+ T cells [18]. IL-2 receptor (IL-2R)-deficient mice also develop an autoimmune disease and they show a breakdown in peripheral tolerance due to a possible failure in AICD [19, 20]. Thus, it is important to view human autoimmune disorders in the context as a failure in AICD [21].

Sjögren’s syndrome (SS) is an autoimmune and lymphoproliferative disease in which salivary and lacrimal glands are the major target organs for autoimmune tissue damage [22]. IL-2 production by SS T cells with mitogenic stimulation is suppressed compared to normal T cells [23, 24]. We previously reported that in vitro apoptosis is enhanced in SS peripheral blood (PB) T cells, and that bcl-2 mRNA expression is upregulated in freshly isolated SS PB T cells [25]. Freshly isolated CD4+ SS PB T cells show elevated expression of Fas compared to normal T cells [26]. CD4+ T cells infiltrating the SS salivary gland are Fas+ and Bcl-2+, and these CD4+ T cells seem not to undergo PCD, particularly in dense periductal foci [27]. These findings suggest that abnormal AICD of T cells may exist in the periphery of SS patients.

The present study was undertaken to investigate AICD in PB T lymphocytes from patients with SS. We established in vitro culture systems to analyze T cell AICD. AICD was induced in mitogen-activated T cells by anti-CD3 or by anti-Fas mAb in the presence or absence of exogenous IL-2. Fas and FasL expression, and soluble Fas (sFas) and soluble FasL (sFasL) production were measured. Surface phenotypes of AICD-surviving cells were determined by flow cytometric analysis. Production of IL-4 and interferon (IFN)-γ from AICD-surviving cells was measured by ELISA in order to analyze Th1 or Th2 subtype of the cells. Finally, the effects of Th1 or Th2 cytokines on AICD were examined.