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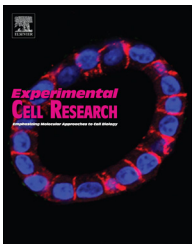

Review Article

Pathophysiology and spectrum of diseases caused by defects in lymphocyte cytotoxicity

Marie Meeths[a,b], *Samuel C.C. Chiang*[c], *Alexandra Löfstedt*[a,b], *Martha-Lena Müller*[c], *Bianca Tesi*[a,b], *Jan-Inge Henter*[a], *Yenan T. Bryceson*[c,d,*]

[a]*Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institutet, Karolinska University Hospital Solna, Stockholm, Sweden*

[b]*Clinical Genetics Unit, Department of Molecular Medicine and Surgery, and Center for Molecular Medicine, Karolinska Institutet, Karolinska University Hospital Solna, Stockholm, Sweden*

[c]*Center for Infectious Medicine, Department of Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden*

[d]*Broegelmann Research Laboratory, Institute of Clinical Sciences, University of Bergen, Bergen, Norway*

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ABSTRACT

In experimental settings, lymphocyte cytotoxicity has been recognized as a central mechanism for immune defense against infected and neoplastic cells. More recently, molecular determinants of lymphocyte cytotoxicity have been identified through studies of rare, inherited hyperinflammatory and lymphoproliferative syndromes that include hemophagocytic lymphohistiocytosis (HLH). These studies have unraveled a set of genes pivotal for the biogenesis and directed release of perforin-containing lysosomes that mediate target cell killing, in addition to other pathways including Fas that also contribute to induction of cell death. Furthermore, studies of such human primary immunodeficiencies have highlighted non-redundant roles of perforin for maintenance of immune homeostasis. Besides providing mechanistic insights to lymphocyte cytotoxicity, studies of individuals with rare hyperinflammatory diseases are highlighting the relevance of lymphocyte cytotoxicity to more common human diseases. It is increasingly recognized that mutations abrogating lymphocyte cytotoxicity not only cause HLH, but also are associated with susceptibility of cancer and autoimmune syndromes. In addition, patients may initially be present with neurological symptoms or severe infectious disease masquerading as variable immunodeficiency syndrome. Here, we highlight new knowledge regarding the molecular mechanisms regulating lymphocyte cytotoxicity and review how mutations in genes associated with HLH cause disease. We also discuss the wider implications of impairments in lymphocyte cytotoxicity for human disease predisposition.

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*Corresponding author at: Center for Infectious Medicine, Department of Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, S-14186 Stockholm, Sweden.
E-mail address: yenan.bryceson@ki.se (Y.T. Bryceson).

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Contents

Introduction

In evolutionary terms, the immune system has evolved to protect organisms from an array of microbes, including intracellular pathogens. In experimental settings, two main subsets of cytotoxic lymphocytes have been defined as capable of killing infected and malignant cells, namely cytotoxic T lymphocytes (CTL) and natural killer (NK) cells. Whereas CTL recognize target cells using somatically rearranged, clonally distributed T cell receptors that bind specific major histocompatibility complex (MHC) class I/peptide complexes on target cells, NK cells recognize target cells using numerous germline-encoded activation receptors, with such recognition being potentiated by the loss of MHC class I expression on target cells. Thus, NK cells guard proper surface expression of MHC class I molecules, a hallmark of all nucleated cells. In turn, T cells base their immunosurveillance of intracellular homeostasis on MHC class I peptide presentation. 20 years ago, through targeted deletions of genes in mice, it was determined that CTL and NK cells can use two different mechanisms for killing of target cells, one based on the secretion of perforin and the other depending on cell-surface expression of Fas ligand for induction of Fas-mediated apoptosis in target cells [1,2]. These discoveries provided a basis for understanding the relevance of lymphocyte cytotoxicity in human disease.

Here, focusing on perforin-mediated cytotoxicity, we review insights gained with respect to the significance of lymphocyte cytotoxicity in human diseases, and discuss current models for cytotoxic granule released by CTL and NK cells that to a large part have been elucidated from the study of rare human diseases.

Molecular mechanisms of lymphocyte cytotoxicity deciphered through studies of rare hyperinflammatory syndromes

Genetics of hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory disorder characterized by unremitting fever, hepatosplenomegaly, hyperferritinemia, cytopenia, and sometimes hemophagocytosis. Familial forms of the disease are typically early-onset and often triggered by infections, *e.g.* herpes viruses, that lead to acute, fulminant inflammation. High levels of pro-inflammatory cytokines, including interferon (IFN)-γ, tumor necrosis factor (TNF), interleukin (IL)-6, IL-12, and IL-18, as well as the anti-inflammatory cytokine IL-10, have been reported in HLH [3]. Histologically, HLH is characterized by activated macrophages and expansions of CTL ($CD3^+CD8^+$ T cells) that infiltrate tissues. According to current clinical criteria, at least five of the eight defined criteria need to be fulfilled for the diagnosis of HLH [4].

Through seminal studies of patients with familial forms of HLH by Kumar and colleagues, biallelic loss-of-function mutations in the gene encoding perforin, *PRF1*, were found to be a cause of primary HLH [5]. Thus, this study provided a link between perforin-mediated cytotoxicity and disease, demonstrating that not only is such activity required for clearing abnormal cells, but also for controlling the magnitude of immune responses. Of note, defects in Fas ligand-mediated killing of lymphocytes, typically caused by somatic, dominant-negative mutations in the Fas receptor are also associated with lymphoproliferative disease [6], termed autoimmune lymphoproliferative syndrome (ALPS). However, in contrast to HLH, ALPS is typically characterized by chronic, non-infectious lymphoadenopathy or splenomegaly, in addition to an elevated frequency of $CD3^+TCR\alpha\beta^+CD4^-CD8^-$ double-negative T cells in peripheral blood [7].

In subsequent studies of other families with familial HLH (FHL), biallelic loss-of-function mutations in *UNC13D*, *STX11*, and *STXBP2* were also associated with disease [8–11]. These genes encode the Munc13-4, syntaxin-11, and Munc18-2 proteins, respectively, which are widely expressed in the immune system as well as other tissues. Cellular studies have established that HLH-associated mutations in these genes abrogate exocytosis of perforin-containing cytotoxic granules, providing an explanation for why such mutations may give rise to syndromes that clinically closely resemble perforin-deficiency [8,10–12]. Mutations in these genes appear to equally impair cytotoxic granule exocytosis by CTL and NK cells [13], and represent a good example of how studies of rare diseases can provide novel molecular insights to important physiological processes. In addition, Griscelli syndrome type 2 (GS2) and Chediak-Higashi syndrome (CHS), caused by mutations in *RAB27A* and *LYST*, respectively, display partial albinism and are also associated with development of HLH [14,15]. Both GS2 and CHS patients display impaired lymphocyte cytotoxicity due to defective cytotoxic granule exocytosis [14,16].

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