CHAPTER 12

GRANULOCYTE DEATH REGULATION BY NATURALLY OCCURRING AUTOANTIBODIES

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Abstract: Programmed cell death (PCD) plays a central role in the regulation of granulocytes that are key effector cells of the innate immune system. Granulocytes are produced in high amounts in the bone marrow. A safe elimination of granulocytes by cell death (apoptosis) is essential to maintain the numbers of these cells balanced. In many acute and chronic inflammatory diseases, delayed apoptosis is one mechanism that contributes to accumulation of neutrophil and eosinophil granulocytes at the site of inflammation. On the other hand, a safe elimination of granulocytes by cell death is required to avoid unwanted tissue damage for instance by secretion of toxic products from these cells. Recent evidence shows that humans produce an array of naturally occurring autoantibodies (NAbs) with the capacity to regulate granulocyte death, including agonistic and antagonistic NAbs that bind to the receptors Fas, Siglec-8, and Siglec-9. Together with other factors, these various NAbs exhibit different properties in terms of the form of cell death they induce, the molecular signaling pathways they engage, as well as the efficacy or potency by which they induce cell death. Moreover, several regulatory mechanisms seem to exist that control their biological activity. Novel insights support the concept of granulocyte death regulation by NAbs, which might have important implications for our understanding of the pathogenesis and treatment of inflammatory diseases, including many autoimmune and allergic disorders.

INTRODUCTION

Regulation of immune cells by programmed cell death is a key process in the maintenance of immune homeostasis, the control of immune responses, and the

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resolution phase of inflammation. As effector cells of the innate immune system, neutrophil and eosinophil granulocytes are involved in a broad range of acute and chronic inflammatory diseases. Unspecific secretion of toxic products and phagocytosis are key functions of these cells and a tight regulation of their lifespan is required to avoid uncontrolled tissue damage. Granulocytes are short-living cells that die in the absence of inflammation, within a few days in a process called spontaneous apoptosis. At the site of inflammation, granulocyte apoptosis is delayed by the presence of survival factors including cytokines, a process that supports the often massive accumulation of granulocytes. Certain granulocyte survival factors have the capacity to block caspase-dependent, pro-apoptotic death pathways, as shown for the cytokines granulocyte/macrophage colony-stimulating factor (GM-CSF) or interleukin-5 (IL-5). On the other hand, granulocytes express death receptors of the tumor necrosis factor (TNF)/nerve growth factor (NGF) family, including Fas, with the capacity to accelerate the apoptosis of neutrophils and eosinophils.

Recent evidence shows that members of the novel receptor family of sialic acid binding immunoglobulin (Ig)-like lectins (Siglecs) are also empowered to transmit death signals into granulocytes. Siglec-8 is expressed on eosinophils, whereas neutrophils express the structurally related family member Siglec-9. Interestingly, Siglec-8- and Siglec-9-mediated granulocyte death is dramatically enhanced in the presence of cytokines. By recruitment of alternative caspase-independent death pathways, Siglecs have the capacity to transmit death signals despite an anti-apoptotic microenvironment, such as at the site of inflammation. Therefore, Siglecs are also viewed as “safeguards” to protect from overwhelming immune responses by granulocytes.

Evidence is accumulating that human intravenous immunoglobulin (IVIG) preparations, derived from the pooled plasma of thousands of healthy blood donors, contain functional NAbs to Fas, Siglec-8 and Siglec-9 receptors, that trigger granulocyte death at clinically relevant concentrations. IVIG is increasingly being used as a high-dose therapy for the treatment of inflammatory diseases for licensed indications and off-label applications. The mode of its anti-inflammatory action is complex and experimental evidence suggests that, among other factors, death regulation of immune cells by NAbs is involved. These mechanisms may act in a mutually nonexclusive fashion depending on the pathogenesis of the disease, and may include both F(ab)- and Fc-related processes. IVIG-induced programmed cell death of granulocytes appears to be F(ab)- and not Fc-mediated, as revealed by experiments using F(ab)2 fragments of IVIG, Fcγ receptor blocking experiments and other controls.

In 1998 Viard et al. identified blocking antibodies directed against Fas within IVIG with the capacity to inhibit Fas-mediated keratinocyte apoptosis in toxic epidermal necrolysis (TEN), also known as Lyell’s syndrome. Soon thereafter it became clear that IVIG not only contains blocking, but also agonistic anti-Fas antibodies with the capacity to induce caspase-dependent apoptosis in human neutrophils, monocytes and lymphocytes. Both, the protection of tissue cells by blocking anti-Fas antibodies, and the elimination of immune cells by agonistic pro-apoptotic antibodies might contribute to the anti-inflammatory effect of high-dose IVIG treatment. The concurrent presence of agonistic and antagonistic anti-Fas antibodies in IVIG has been confirmed and it has been shown that the resulting effect on granulocyte death is concentration-dependent. The balance between Fas-stimulating and Fas-blocking antibodies has recently been shown to vary among different IVIG preparations.