Chapter 10
Clearance of Dying Cells and Systemic Lupus Erythematosus

Dror Mevorach

Abstract: Death-Associated Molecular Patterns (DAMPs) maintain peripheral tolerance and immune suppression following binding and phagocytosis of apoptotic cells. In systemic lupus erythematosus (SLE), a multisystem autoimmune disease of unknown etiology, alteration in cell death patterns, apoptotic cell recognition and DAMP signalling generate the characteristic pathogenic autoantibodies to a diverse group of autoantigens.

The normal innate immune response to cell death and the abnormalities identified in SLE are presented, along with possible relations to mechanisms of autoantibody generation in SLE, the phenomenon of drug-induced lupus, and the paradoxical role of complement in the clearance of dying cells and in disease progression.

Keywords: Apoptosis • Necrosis • Clearance • Autoimmunity • Dendritic cells • SLE

10.1 Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease of unknown etiology characterized by the presence of high titers of autoantibodies to a diverse group of autoantigens. Autoantibodies are present in 88% of patients an average of 3.3 years before diagnosis (Arbuckle et al. 2003). Of the characteristic panel of autoantibodies, antinuclear, anti-Ro, anti-La, and antiphospholipid antibodies appear first, followed by anti-dsDNA, anti-Sm and anti-RNP. These autoantibodies have features of an antigen-driven, T cell-dependent immune response (Diamond et al. 1992; Radic and Weigert 1994). Once these antibodies are present,
the course of SLE is characterized by disease flares and autoimmune dysregulation. Treatment is based on immunosuppressive drugs, such as corticosteroids, azathioprine, mycophenolate mofetil, and cyclophosphamide. Prognosis depends on the organs involved, the outcome of treatment, and the extent of adverse effects inflicted by the immunosuppressive drugs.

Programmed cell death (PCD), an essential developmental and homeostatic mechanism (Krysko et al., Chap. 1; Diez-Fraile et al., Chap. 2, this Vol.), is the preferred physiological death process for cells and also an important regulator of the immune response. Appropriate clearance of apoptotic material completes the PCD process, and is essential for regulating inflammation and maintaining self-tolerance (Ucker, Chap. 6; Lacy-Hulbert, Chap. 7; Gregory and Pound, Chap. 9; Divito and Morelli, Chap. 11, this Vol.).

In this chapter we will discuss altered mechanisms for clearance of dying material, which represent a central pathogenic process in the development and acceleration of SLE.

10.2 Cell Death in the Human Body

It estimated that every day more than one billion cells/kg of the human body undergo apoptosis (Fig. 10.1). Granulocytes, with a half lifetime of 6–7 hours, provide about 50 billion apoptotic cells each day in an average adult (Dancey et al. 1976). Apoptotic cells, which carry cellular components that could be antigens, present ‘find me’ and ‘eat-me’ signals and are engulfed by phagocytes such as macrophages and immature dendritic cells (iDCs; Peter et al., Chap. 3; Napirei and Mannherz, Chap. 4; Lacy-Hulbert, Chap. 7; Divito and Morelli, Chap. 11, this Vol.). Endosomes containing the engulfed dead cells fuse with lysosomes, where the dead cell components are degraded into amino acids and nucleotides. The degradation of chromosomal DNA occurs in two steps (Napirei and Mannherz, Chap. 4, this Vol.). First, the chromosomal DNA of apoptotic cells is cell-autonomously cleaved into nucleosomal units (Wyllie 1980) by caspase-activated DNase (CAD; Enari et al. 1998; Sakahira et al. 1998). Then, following engulfment by macrophages, the DNA of the dead cells is further degraded into nucleotides by DNase II, an acid DNase located in the lysosomes of macrophages (Kawane et al. 2003).

The terms apoptosis and PCD were once used interchangeably. However, PCD today can be further subdivided into at least three death pathways: apoptosis, necrosis (Krysko et al., Chap. 1; Diez-Fraile et al., Chap. 2, this Vol.; Chiarugi 2005; Kroemer and Martin 2005; Zong and Thompson 2006), and autophagy (Levine and Deretic 2007; Maiuri et al. 2007). Cell necrosis is morphologically different from apoptosis and is characterized by cellular swelling, chromatin digestion, organelle vacuolation, and plasma membrane disruption (Darzynkiewicz et al. 1997). Primary necrosis was for a long time considered as an ‘accidental cell death,’ in contrast to ‘programmed cell death’. However, there is now extensive evidence that necrosis can be due to either accidental or programmed cell death (Chiarugi 2005; Kroemer