Immune Response and Apoptosis – Introduction

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Programmed cell death or apoptosis is one of the major contributors to the development of a normal immune system, the developmentally correct architecture of tissues and organs and the proper maintenance of organ homeostasis. However, dysfunctional induction of apoptosis appears to be critical for the aberrant survival of pathological cells in many chronic immune-mediated disorders, inflammation and cancer.

This Special Issue of the Journal of Clinical and Cellular Immunology devoted to “Immune Response and Apoptosis” reviews the recent advances in our understanding of how the balance between cell survival and apoptosis is regulated and maintained in the normal state including the role apoptosis plays in regulating T-lymphocyte development, how apoptosis acts as a fundamental cellular process responsible for suppressing the activity of antigen-presenting dendritic cells (DCs) a key step in controlling innate tolerance, and how apoptosis acts as the critical modulator of innate and adaptive immunity.

Several pathologies are also reviewed. These disorders are characterized either by an abnormally low frequency of apoptosis with a skewed number of pathological cells surviving and outnumbering those deleted by apoptosis or by the aberrant deletion and loss viability of normal cells. Thus, aberrant apoptosis is intimately associated with both the pathogenesis and progression of chronic inflammatory diseases such as intestinal bowel disease (IBD), rheumatoid arthritis (RA) and necrotizing enterocolitis (NEC). Finally, from a therapeutic perspective, panoptocic drugs are proposed as drugs which modulate cancer cell proliferation and immune cell activation via their capacity to induce apoptosis. This focus demonstrates the chemotherapeutic potential of natural products in influencing research in this area.

Apoptosis Regulates Normal Immune Cell Development

Carolina Francelin and Liana Verinaud (Institute of Biology, State University of Campinas, São Paulo, BRAZIL) review the evidence that apoptosis regulates T-lymphocyte (i.e. T-cells) development through positive and negative selection [1-3]. Of note, the results of several studies [4-6] have shown that T-cell receptor (TCR)-independent, ligand-induced TCR-signaling and the relative expression of pro- and anti-apoptotic proteins during intrathymic development lead either to rescue from cell death through positive T-cell selection and/or cell death via negative T-cell selection.

DCs are considered the most efficient antigen-presenting cells in both lymphoid and non-lymphoid tissues [7]. Min Chen and Jin Wang (Baylor College of Medicine, Houston, Texas, USA) review the accumulated evidence showing that dysregulated DC apoptosis results in abnormal DC survival which is associated with the development of systemic autoimmune diseases [8,9]. Thus, maintenance of the correct number and activity of DCs is required for maintaining immune system homeostasis, including the capacity to orchestrate appropriate inflammatory responses and the regulation of immune tolerance.

A detailed review of apoptosis as the ultimate immunomodulatory cellular event is presented by Anuradha K. Murali and Shikhar Mehrotra (Medical University of South Carolina, Charleston, South Carolina, USA). These investigators point out that impairment of apoptotic pathways or the lack of strict regulation of apoptosis results in autoimmune and inflammatory disorders, viral and bacterial infections as well as cancer. Importantly, recent evidence implicating specific microRNAs in regulating a special form of T-cell death called rapid-activation-induced cell death [10] is discussed.

Role of Impaired Apoptosis in IBD, RA and NEC

IBD is a term used to describe two mutually independent yet chronic inflammatory conditions of the intestine namely, ulcerative colitis and Crohn’s disease. Importantly, key mediators of apoptosis and autophagy are implicated in the genetic susceptibility, pathogenesis and perpetuation of IBD [11-13]. Michael Schnoor (Max-Planck-Institute of Molecular Biomedicine, Münster, GERMANY) and Nancy A. Louis (Emory University School of Medicine, Atlanta, Georgia, USA) review how pro-inflammatory cytokines skew the balance between pro- and anti-apoptotic responses of the intestinal epithelium that primarily result from activation of key pathways involving type I [14] and type II interferon proteins [15], nuclear factor-xB (NF-xB) [16], and Wnt-mediated signaling [17,18], as well as the role that oxygen tension [19] and nutritional factors [20] play in regulating these pathways.

In RA, elevated levels of the pro-inflammatory cytokines including tumor necrosis factor-a (TNF-a), interleukin-(IL)-1β, IL-6, IL-17 and interferon-γ, among others, results in a skewing of the balance between the survival of cells in synovial tissue and apoptosis, favoring the former. Charles J. Malemud (Case Western Reserve University School of Medicine, Cleveland, Ohio, USA) reviews the cellular mechanisms in RA that favor synovioctye, immune and inflammatory cell activation, proliferation and survival with resultant synovial tissue hyperplasia and chronic inflammation characterized by resistance to apoptosis. This resistance to apoptosis has been connected to a deregulated activation of the Stress-Activated Protein Kinase/Mitogen-Activated Protein

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Chemotherapy with Ganoderic Acid Induces Apoptosis

The anti-tumor properties of the 
Ganoderma lucidum
mushroom are reviewed by Faisal F.Y. Radwan, J. Manuel Perez and Azizul Haque (Medical University of South Carolina, Charleston, South Carolina, USA). The ganoderic acids are methanol-soluble triterpenoids [34] derived from Ganoderma lucidum with potent cancer chemotherapy/therapeutic activity [35]. Although significant compelling evidence reveals that ganoderic acids induce apoptosis in cancer cells [36-38] with a lower toxicity towards normal cells, more recently published data showed that ganoderic acids can also alter the immune system and its anti-tumor activity [39,40]. The long-term goal of employing nanoparticle polymer-coated [41] ganoderic acid for the targeted delivery of these Ganoderma lucidum-derived compounds to malignant tissues in vivo is also discussed.

Taken together, these reviews underscore the critical nature of the tight regulation of apoptosis in development, inflammation, and cancer. It is clear that apoptotic pathways provide promising targets for the prevention or attenuation of disease in multiple tissues. However, the complex balance of pro- and anti-apoptotic proteins regulating cellular function and tissue homeostasis must be considered during the rationale design of cell and tissue-specific tools to manipulate these processes.

Disclosure Statement

The authors disclose no conflict of interest.

References


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