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Perspective

# Role of the Immune System in Regulating Cell Death during Development and Homeostasis

**Tokiyoshi Tanegashima***

*Department of Cancer Immunology, Nagoya University, Nagoya, Japan*

## ABOUT THE STUDY

Cell death is an essential process during development and homeostasis to maintain proper tissue architecture and function. Two major forms of cell death, apoptosis, and programmed necrosis, play crucial roles in these processes. The immune system, traditionally known for its role in defending the body against pathogens, also plays a vital role in regulating cell death.

### Developmental cell death

During embryogenesis and tissue formation, cell death is a critical process that eliminates excessive or unwanted cells, allowing for proper tissue remodeling and organogenesis. Apoptosis, a form of programmed cell death, is the predominant mechanism responsible for eliminating unwanted cells. The immune system plays a crucial role in recognizing and engulfing apoptotic cells through a process known as efferocytosis. Immune cells, such as macrophages, neutrophils, and dendritic cells, express specific receptors that bind to apoptotic cell surface markers, facilitating their clearance. Failure to effectively clear apoptotic cells can lead to impaired tissue development and autoimmune disorders. Additionally, immune cells can produce cytokines and growth factors that influence the survival and differentiation of neighboring cells, thereby orchestrating tissue remodeling and organ formation.

### Homeostatic cell death

In adult tissues, maintaining homeostasis requires a balance between cell proliferation and cell death. Excessive cell death can lead to tissue atrophy, while impaired cell death can result in the accumulation of damaged or senescent cells, leading to tissue dysfunction and age-related pathologies. The immune system actively participates in the regulation of cell death to maintain tissue homeostasis. One mechanism by which the immune system controls cell death is through the elimination of senescent cells. Senescence is a state of irreversible growth arrest that occurs in response to various stresses, including DNA damage and telomere shortening. The senescent cells secrete pro-inflammatory factors, known as the Senescence-Associated Secretory Phenotype (SASP), which can promote tissue dysfunction and chronic inflammation. Immune cells, such as natural killer cells and cytotoxic T cells, recognize and eliminate senescent cells through immunosurveillance mechanisms, preventing their accumulation and maintaining tissue homeostasis.

Furthermore, the immune system regulates cell death in response to tissue damage and infection. Inflammation, a hallmark of immune response, coordinates the clearance of damaged cells and promotes tissue repair. Immune cells release pro-inflammatory cytokines, such as Tumor Necrosis Factor-Alpha (TNF-α) and Interleukin-1β (IL-1β), which can induce apoptosis in damaged cells and limit tissue damage. Additionally, immune cells can directly kill infected cells through mechanisms like cytotoxic granule release or by inducing apoptosis *via* death receptor signaling pathways. This immune-mediated elimination of infected cells is crucial for controlling infections and preventing the spread of pathogens.

### Dysregulation of cell death

Disruptions in the balance between cell death and immune regulation can have severe consequences for health. Dysregulated cell death processes contribute to various pathological conditions, including autoimmune diseases, cancer, and neurodegenerative disorders. Autoimmune diseases occur when the immune system mistakenly recognizes self-antigens, leading to chronic inflammation and tissue damage. Impaired clearance of apoptotic cells during development or defective efferocytosis in adulthood can trigger autoimmune responses, as self-antigens are not effectively removed.

Similarly, dysregulated immune-mediated cell death can contribute to the pathogenesis of autoimmune diseases. Cancer is characterized by uncontrolled cell proliferation and resistance to cell death. The immune system plays a critical role in recognizing and eliminating cancerous cells through mechanisms such as immune surveillance and cytotoxicity. However, tumors can evade immune responses by suppressing immune cell activity

**Correspondence to:** Tokiyoshi Tanegashima, Department of Cancer Immunology, Nagoya University, Nagoya, Japan, E-mail: Tanegashimato@noc.go.jp

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or inducing immune tolerance. Restoring immune-mediated cell death mechanisms is a promising approach in cancer immunotherapy to eradicate tumor cells.

## Inflammation and cell death

Inflammation is a critical immune response that is tightly linked to cell death. In response to tissue damage or infection, the immune system initiates an inflammatory response to clear pathogens and promote tissue repair. During inflammation, immune cells release various cytokines and chemokines that can regulate cell death pathways.

For instance, Tumor Necrosis Factor (TNF) and Interleukin-1 (IL-1) can induce apoptosis or necroptosis in target cells. These processes can be protective by eliminating infected or damaged cells. However, excessive or dysregulated inflammation can contribute to tissue damage and chronic diseases.

## Immune regulation of apoptosis

Apoptosis, a controlled form of cell death, plays a critical role in tissue development and homeostasis. The immune system helps regulate the apoptosis through various mechanisms. For example, cytotoxic T cells and NK cells can induce apoptosis in virus-infected or cancerous cells, eliminating them from the tissue. Furthermore, immune cells can produce soluble factors, such as Fas ligand and Tumor necrosis factor-Related Apoptosis-Inducing Ligand (TRAIL), which can induce apoptosis in target cells expressing their respective receptors. Thus, the immune system acts as an important regulator of apoptosis, ensuring the removal of unwanted or damaged cells.

## Immune regulation of programmed necrosis

Programmed necrosis, also known as necroptosis, is a form of regulated cell death that can be induced under specific conditions, such as pathogen invasion or tissue injury. The immune system plays a vital role in regulating necroptosis through various mechanisms. For instance, immune cells can release interferons, which activate the expression of genes involved in necroptosis, promoting the elimination of infected cells. Additionally, immune cells can produce cytokines, such as Interferon-Gamma (IFN-γ), which can sensitize cells to necroptosis. The immune system's regulation of programmed necrosis is crucial for eliminating infected cells while preventing excessive tissue damage.