Overview of the Immune Response and Regulation

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ABBREVIATIONS: CTLA-4 - cytotoxic T-lymphocyte-associated protein 4, DAMPs - damage associated molecular patterns, FOXP3 - forkhead lineage-specific transcription factor, IFN-γ - interferon-gamma, IL – interleukin, MDSCs - myeloid derived suppressor cells, NK - natural killer, PAMPs - pathogen associated molecular patterns, PRRs - pathogen recognition receptors, Tregs - regulatory T cells, Th - T helper, TNF-α - tumor necrosis factor-alpha.

INDEX TERMS: Adaptive immunity, Autoimmune disease, Cancer, Innate immunity, Immunotherapy

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INTRODUCTION

Both cancer and autoimmune diseases are significant health burdens that pose tremendous financial strains on healthcare services worldwide. Nearly 1.7 million cases of cancer are expected to be diagnosed and 585,000 Americans are expected to die of the disease in the United States in 2014.[1] Furthermore, while the diagnosis of any individual autoimmune disease is relatively rare, as a collective disorder, autoimmune disease is estimated to afflict 1 in every 31 Americans[2] and is among the leading causes of death in young and middle-aged women (ages <65 years) in the United States.[3] Numerous biological and biochemical factors are implicated in both cancer and autoimmune diseases, yet these two seemingly disparate diseases share a common thread: immunopathology.

The immune system can recognize a seemingly infinite repertoire of antigens and has evolved robust protective responses against foreign substances. Inevitably, a system that reacts against such a diverse set of antigens has the propensity to react against itself and is the basis for autoimmunity. Furthermore, the role of protective immunity is complicated since potent pro-inflammatory molecules and immune cells destroy invading organisms and cancer cells while also damaging the surrounding normal cells. As such, a means of restraining the immune system is essential to maintaining a homeostatic immune organization. This immune homeostasis encompasses a means to 1) discriminate self from non-self and regulate insufficient immunity to ensure that pathogens are eliminated and 2) suppress excessive immune responses such that autoimmunity is averted. This Focus series describes the physiological and pathological roles of the immune system in cancer and autoimmune disease of the gastrointestinal tract and how the immune system may be harnessed to treat such diseases using immunotherapy. This article provides a succinct overview of the immune response and it's regulation.

Innate and Adaptive immunity

Innate immunity provides the first line of defense against microbes and immunogenic cells of the body (e.g. cancer cells). It consists of both cellular and biochemical defense mechanisms that are in place and poised to respond to microbes and injured cells by the process of recognition, followed by destruction. Recognition involves soluble proteins and cell-surface pathogen recognition receptors (PRRs) found on phagocytes that bind pathogens carrying unique immunogenic signature molecules called pathogen associated molecular patterns (PAMPs). Likewise, human cells and serum proteins that become altered in the presence of a pathogen or because of some other pathophysiological process (e.g. cancer) carry different immunogenic molecules called danger or damage associated molecular patterns [DAMPs] described in "The Suppression and Promotion of Cancer: The Dichotomy of Tumor Immunology". The cells

responsible for the innate immune response include phagocytes (macrophages and neutrophils), dendritic cells and natural killer (NK) cells. Once the pathogen or immunogenic cell has been recognized, the second part of the innate immune response involves the recruitment of destructive effector cells (i.e. macrophages, neutrophils, natural killer cells) that engulf/attack pathogens and kill virus-infected or immunogenic cells.

While the innate immune response works to remove or slow the immunogenic stimuli, infiltration of cells and fluid leads to inflammation and the recruitment of lymphocytes that commence the adaptive immune response. Adaptive immunity develops against the antigenic nuances of PAMPs or DAMPs (and several other molecules) and provides specificity against those molecules upon subsequent exposure.[4] The main effector cells in adaptive immunity are lymphocytes that primarily function in humoral immunity (antibody production by B lymphocytes) and in cell-mediated immunity (carried out by T lymphocytes). Antibodies recognize antigens on extracellular microbes and their toxins and tag the organisms for elimination. Conversely, intracellular organisms (particularly viruses and bacteria that survive within phagocytes) are inaccessible to antibodies and, like immunogenic cancer cells, are destroyed via cell-mediated immunity. The two branches of the immune system (innate and adaptive) are therefore not truly separate, but are intertwined physically and functionally.

Immune Regulation

The immune system must control the type and extent of response that is elicited through stimulatory and inhibitory signals. Positive co-stimulation contributes to the proper development of T lymphocyte immune responses against pathogens. Conversely, negative regulation through various suppressive cells and molecules is essential to terminate an immune response, to avoid immune-mediated tissue damage, and for peripheral tolerance.[5] T lymphocytes contribute to both positive and negative regulation of the immune system. They have been historically classified as CD4+ and CD8+ lymphocytes with CD4+ cells being further differentiated into Th1 and Th2 "helper" cells. Th1 cells (producing interleukin [IL]-2, interferon-gamma [IFN-γ], and tumor necrosis factor-alpha [TNF-α]) are major effectors for phagocyte-mediated host defense. Th2 cells (producing IL-4, IL-5, IL-6, IL-13, and IL-10) play a significant role in allergic responses, protection against helminthic parasites, and mediate adaptive immune responses.[6] The helper T cell subsets regulate each other by Th1 secretion of IL-2 and IFN-γ to suppress Th2 responses and Th2 secretion of IL-4 and IL-10 to suppress Th1 responses.

Beyond the Th1 and Th2 paradigm are the CD4+ regulatory T cells (Tregs) and Th17 cells that are both crucial for proper immune regulation and autoimmunity. Tregs can prevent activation and the effector functions of auto-reactive T cells that have escaped mechanisms of tolerance (non-reactivity to "self"-antigens or other molecules such as commensal bacteria in the gut). This unique CD4+CD25+ T cell population of "professional" regulatory T cells express the forkhead lineage-specific transcription factor (FOXP3) protein and had been suspected to exist since the early 1970's, but were not characterized until 2001.[7] The cytokines, transforming growth factor- β (TGF-β) and IL-2, are particularly important for the differentiation and expansion of naïve T cells into Tregs while TGF-β and IL-6 are important for the Th17 phenotype.[8] Th17 cells mediate the recruitment of neutrophils and macrophages to tissues infected with certain fungi and extracellular bacteria. Aberrant regulation of both Tregs and Th17 cells may play significant roles in the pathogenesis of multiple inflammatory and autoimmune disorders (discussed in "T Regulatory Cells and Their Role in Autoimmune Disease Involving the Gastrointestinal Tract").

Other cellular and biochemical regulatory mechanisms will be discussed in this Focus series including myeloid derived suppressor cells (MDSCs) and cytotoxic T-lymphocyte-associated protein 4 (CTLA4). In this series we present new findings regarding unique immune cells and biomolecules that are rapidly expanding the potential for clinical applications in a variety of disease settings.

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