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Superior But Subordinate: The Adaptive Immune System's Dependency on the Innate Immune System

Introduction

The human immune system is comprised of the innate immune system and the adaptive immune system, and their interaction is what ensures an efficient and comprehensive immune response. The innate system, including components such as Toll-like receptors (TLRs), dendritic cells (DCs), and the inflammatory response, is genetically predetermined, and although its response is quick, it is easily evaded. The adaptive system, which relies on lymphocytes, has a slower response time but can respond to a wide variety of pathogens and protect against reinfection. The adaptive immune system, however, relies on the innate immune system for matters of antigen transportation, antigen presentation, and expression.

Innate and adaptive immunity began as two opposing theories of immunity (Paul, 2011). The two theories were first bridged when in 1989, Charles Janeway argued that activation of the immune system required signals from both the antigen/receptor interaction and the recognition of pathogen-associated molecular patterns or PAMPs (Paul, 2011). His theory was confirmed when the ligands of TLRs were discovered and matched the ligands Janeway expected among PAMPs (Paul, 2011).

The Innate Immune System

The innate immune system is the first line of immunological defense. It operates through pattern recognition to fight off a limited number of antigens (Getz, 2005). It offers a more immediate but less specific and flexible immune response that is easy for pathogens to evade. The innate response involves the use of TLRs to recognize pathogens and DCs to bind to and kill pathogens. This leads to an inflammatory response which is an important link between the innate and adaptive immune systems.

Toll-like receptors (TLRs) are expressed on innate immune system cells such as DCs and macrophages (Paul, 2011). These receptors recognize pathogens by their common structural shapes or patterns (Christmas, 2010). When activated, TLRs directly kill pathogens, secrete cytokines, and activate DCs (Clark and Kupper, 2005). DCs or dendritic cells are present in almost every human organ (Paul, 2011). When a DC's receptor binds to a pathogen, the DC engulfs and degrades the invading cell (Janeway, et al.). An activated DC matures into an antigen-presenting cell which travels into the lymph nodes and comes into contact with antigen-specific adaptive immune system cells called lymphocytes (Janeway et al., 2001).

The Adaptive Immune System

The adaptive immune system, which depends on cells called lymphocytes, provides a more versatile defense and protects against reinfection (Janeway et al., 2001). Lymphocytes are the adaptive immune system's primary response to infection. Each lymphocyte has an antigen

receptor of a different specificity. These cells act both to fight off an infection and protect against reinfection. Because of their receptor diversity, lymphocytes can recognize a wide variety of antigens with high specificity (Janeway et al., 2001). Lymphocyte receptor genes are inherited as gene segments and are joined through the process of DNA recombination to form one receptor gene (Janeway et al., 2001). This DNA recombination allows each naive lymphocyte to have a receptor of a different genetically determined specificity giving rise to the wide variety of lymphocyte receptors. (Janeway et al., 2001).

Only activated lymphocytes proliferate and persist; those that are not activated die or undergo receptor rearrangement (Janeway et al., 2001). Lymphocytes that do come in contact with an antigen clone and differentiate into memory cells (Janeway et al., 2001). A cloned lymphocyte will either differentiate into a central memory cell, which is responsible for long-term immunological memory, or a more aggressive effector memory cell, which is responsible for fighting off a pathogen in infected tissues (Clark, 2005).

Innate Immune System's Regulation of the Adaptive Immunity

The adaptive immune system resides mostly in lymph nodes, and as such, an adaptive immune response depends on an innate immune response to first occur. The adaptive response is also controlled by the innate immune system through the control of DC expression. The system that links the two immune systems must also interface the low specificity of the innate system and the high specificity of the adaptive system. The inflammatory response of the innate immune system is responsible for transporting the antigen to the lymph nodes, DCs present the antigen to the lymphocytes, natural killer (NK) cells control the expression of DCs, and TLRs adapt between the low specificity of the innate and the high specificity of the adaptive immune system.

Inflammation is the innate immune system's primary mechanism for transporting unknown antigens to adaptive immune system cells. It consists of heat, pain, redness, and swelling caused by dilation and increased permeability of blood vessels (Janeway et al., 2001). This change is brought about by cytokines secreted from innate immune system cells such as DCs that have encountered a pathogen (Janeway et al., 2001). The dilation and increased permeability of the blood vessels increases the blood flow and leakage of fluid which allows DCs to drain to the lymph nodes and come into contact with lymphocytes that mount an adaptive immune response (Janeway et al., 2001). Thus the adaptive immune system depends on innate immune cells such as DCs to present antigens to the adaptive immune system's lymphocytes (Hoebe et al., 2004).

Beyond transporting the antigen, DCs can change the nature of the adaptive response. Antigen-presenting DCs also release cytokines that signal how a lymphocyte will differentiate (Paul, 2011). Active DCs that have come into contact with an antigen will send signals to lymphocytes dictating the specificity, nature, and location of the response (Clark, 2005). DCs are also responsible for presenting antigens to lymphocytes in the lymph nodes (Janeway et al., 2001).

The innate immune system can also control the expression of DCs through NK or natural killer cells, thus regulating the adaptive immune response. NK cells have receptors for both self and non-self surface proteins (Hoebe et al., 2004). They can receive signals through these

receptors or be activated by DCs, either directly through proteins on the DC surface or indirectly through cytokines (Hoebe et al., 2004). When activated, NK cells produce interferon-gamma which causes DCs to mature and enhances the lymphocyte response (Hoebe et al., 2004). NK cells can also kill off immature DC, limiting certain lymphocyte responses; therefore, NK cells are responsible for mediating and balancing DC function (Hoebe et al., 2004). Recent research describes another type of DC, the interferon-producing killer DC, that produces large amounts of interferons that allow them to kill target cells, functioning in a similar way to a NK cell (Chan et al., 2006).

Finally, as Janeway predicted, TLRs provide an important link between innate and adaptive immunity specificities. Although not as specified as lymphocytes, TLRs are able to bind to antigens lymphocytes have receptors for by using PAMPs as discussed above (Christmas, 2010). By recognizing simply that a pathogen is foreign, a TLR can succeed in binding to the correct pathogens without requiring the high specificity of lymphoid cells.

Conclusion

The adaptive immune systems, while more flexible and comprehensive, is in many ways subordinate to the innate. Although it is is somewhat limited, the innate immune system is responsible for regulating and facilitating the adaptive immune response. The innate system's regulation plays a key role in distinguishing self versus non-self molecules and in recognizing and transporting invading pathogens to adaptive immune system cells. In this way, although the adaptive immune response is better adapted to most pathogens, it still must depend on the innate immune system to mount an effective immunological response.

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