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Perspective

The Concerns to Use Anti-inflammatory Medicines to Inhibit the Actions of Macrophages

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Abstract

The members of the immune cells that play the key roles as the antigen presenting cells (APCs) are macrophages, dendritic cells (DCs) and B lymphocytes. Macrophages and DCs play the critical actions as the APCs to activate naïve T cells to be the effective T cells. With the entire process of their antigen presentation to promote the adaptive immunity to fight against infectious agents, macrophage and DCs also cause unpleasant stage of inflammation. To eradicate inflammation, some medicines especially new discovered herbal drugs have been reported to play a mechanism to inhibit an inflammatory process of macrophages which is blamed to be the main cause of inflammatory-related pathogenesis in many diseases. This article presents the concerns to use anti-inflammatory drugs to inhibit the functions of macrophages. The illusion for the good outcome in a short term of these medicines can cause the subsequent problem by decreasing the immune response of the individuals. The general views of this concern will be discussed.

Introduction

Abbreviation

APC: antigen presenting cells
DCs: dendritic cells
MHC: major histocompatibility complex
IL: interleukin
MDR: multi-drug resistance
Th: Helper T cell
TCR: T cell receptor

Overviews Of Antigen Presenting Cells

Antigen-presenting cells (APCs) play a role to elicit and regulate adaptive immune responses. There are three populations of APCs; macrophages, dendritic cells (DCs) and B lymphocytes. Macrophages and DCs play an intermediate role to link an innate immunity to adaptive immunity. Both macrophages and DCs play a primary role to induce an adaptive immune response by activation T lymphocytes. They play the APCs' role by recognizing the invaded antigens and then process the antigenic oligopeptide, so-called epitopes, to form the complex molecules with the major histocompatibility complex (MHC). These complex molecules then activate the specific helper T cell or cytotoxic T cell clones [1,2]. At present, there is not sufficient information to indicate the difference between macrophage and DCs in term of their role as the APCs. In general, both cells activate naïve T cell clones in secondary lymphoid organs such as lymph nodes, spleen and mucosal lymphoid tissues in mucosal organs. Eventually, APCs alters naïve T cells to be the effective T cells [3,2].

On the other hand, B lymphocytes act as the APCs in the later stage. B cell receptor (BCR) of B lymphocyte must recognize and interact with an antigenic epitope before upregulating to express MHC-II molecules and B7 costimulatory molecules to be able to play the APC's role. The activated B cell then processes an antigenic epitope thru MHC-II molecules to form the MHC class II-antigen-peptide complex to activate a specific helper T cell (Th) thru its T cell receptor (TCR) [4,2]. In addition, Th cell also requires a recognition of co-stimulation between B7 molecule of B lymphocyte and CD28 expressed on the surface of Th cells membrane. Eventually, the specific Th cell clone can proliferate and play its role by upregulating the expression of CD40L which then combine with CD40, a kind of B cell membrane receptor, to produce the second stimulus signal, making B cells to be plasmocytes that mediate humoral immune response by secreting various classes of immunoglobulin [5,2]. On the other hand, another kind of antigen with the repetitive components such as lipopolysaccharide (LPS), which does not contain any parts of T cell epitope, cannot support the interaction between B and T cell. Accordingly, the B cell cannot play the APCs' role. Thus, the B cell will lack the second stimulus signal from the specific Th cell. Eventually, the B cell cannot differentiate to be plasmacytes to synthesize other classes of immunoglobulin except IgM [6].

Definition And Functions Of Macrophages And Dcs

Macrophages are originally known as the phagocytic mononuclear cells. They also play a role to present an antigen to T cells, more or less the same as DCs [7-9]. Macrophage and monocyte are accounted for the same white blood cell but located in the different location of a body. Monocyte was discovered earlier in blood circulation while macrophage was later found in tissues. Although both names were given differently in the early day, they have been proved to generate from the same progenitor and considered as the same kind of cell. Accordingly, monocyte is actually a macrophage [10]. In contrast, the discrimination of macrophages and DCs is truly confusing. As originated from the common myeloid progenitor, both cells have the characteristics of adaptability and plasticity which might be due to their high sensitive to different tissue environments. This led to the query that macrophages and DCs which overlap most of their functions might actually be the same kind of cell, as well [11]. With the uncertain information concerning macrophages and DCs, this article will describe the characteristics of macrophages and DCs in a general information only for the purpose of our discussion concerning the anti-inflammatory drugs.

Herein, macrophages can be simply classified into two types. The first is an inflammatory M1 which can be identified by the high expression of IL-12 and low in IL-10. The second macrophage is the wound healing M2 which is low of IL-12 but high of IL1-10 [7,9]. M1 macrophages synthesize pro-inflammatory cytokines such as alpha-tumor necrosis factor, IL-6, and IL-12 which are the keys to cause inflammation in infectious diseases. M2 macrophages play the main role to eliminate dead cells and do not cause inflammation which response to tissue injury and some pathogenic infections especially fungal infection and parasitic infestation. However, there are reports that M2 promote infectivity of some pathogens [12,13]. There was an additional report that M2 also indirectly suppress local immune responses by accumulating suppressor T cells or regulating T cells (Treg) to the region [14].

DCs has a morphology of pseudopodia-like protrusions or dendritic as named. There is only a small amount of DCs population, perhaps approximately 0.2-0.3% of the total white blood cells in a human body. Even with a low percentage, DCs distribute in all of the body but, like most of the other white blood cells, they do not distribute in immune privilege organs such as the central nervous system. They accumulate more in skins than the rest of the body [15,16]. After generation from the progenitor cell in bone marrow, the immature DCs express only a limit amounts of MHC molecules so they do not act effectively to present antigen to activate Th cells. However, the immature DCs have a high capacity to capture an antigen by phagocytosis. This subsequently induces the differentiation process of the immature DCs to be the mature DCs which can express high levels of MHC molecules. At this stage, the mature DCs can play the full role of APCs by moving from the peripheral tissue into the secondary lymphoid organs to activate the Th cells. As mentioned, the DCs might be a member of mononuclear phagocyte system (MPS) as is macrophage [17,18]. The nomenclatures of different cell types in the MPS family has been a subject of attention to understand the overall actions of the antigen presenting cells but the definite taxonomy is still in question. At present, there is no evidence to include DCs as an actual member of MPS [19,20]. DCs have also been identified to be heterogeneous. The so-called sub-populations are monocyte-derived DCs, conventional DCs (cDCs), and plasmacytoid DCs [21,18] while other sub-population have been cryptic [22,23].

The Medicines To Inhibit Inflammation Process Of M1 Macrophage

Recently, there is the discovery of drugs including herbal medicines with an action to eradicate inflammation. The mechanisms of these medicines involve the pathway to inhibit the pro-inflammatory actions of M1 macrophages including promoting the action of M2 [24-26]. Although this could be a good approach to help the suffering patients from the inflammatory-related diseases, including the inflammatory associated infectious diseases, it could be a dilemma. The mechanism of the medicines to irritate the balance actions of M1 and M2 should be more considerate. Does the inflammation by M1 is an initiation process for the success to present an antigen by the macrophages? If so, lacking an inflammation procedure including the related cytokines might defect the efficacy of adaptive immunity which needs APCs' activation. In addition, raising the activity of M2 has been reported to increase pathogenic susceptibility and promote the role of regulatory T cells to cause more severe symptoms [27,28]. If so, this could cause greater problems, especially the long-term use of the drug. In addition, there were the reports that M1 might be the key to inhibit carcinogenesis. Lowering the M1 level by overusing anti-inflammatory drug could promote carcinogenesis to the patients [29,30].

At present, we encounter the problems of multiple drug resistant (MDR) bacterial infection. Putting an inappropriate way to treat the disease at a wrong spot could accumulate the bigger problem since inhibition M1 role does not mean that the culprit of the infectious agents is truly gone. This will be like putting garbage under the carpet. The MDR bacterial can become the unresolvable problem for the reason. It will be premature to put the M1 anti-inflammatory drug to the markets before the mechanisms and nomenclatures of macrophages and DCs are truly understand [31].

Competing Interests

This article was written without any conflict of interest

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