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Dendritic Cells in Drug-induced Toxicity

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Abstract

Dendritic cells play a key role in immunity and tolerance. They are the most abundant population of leukocytes in a number of different tissues and organs. One of the important functions of dendritic cells is rapid recognition of pathogens or products of tissue injury. Depending on the nature of the inciting stimuli, they may elicit either pro- or anti-inflammatory responses with or without the involvement of the adaptive immune system. Dendritic cells are generally considered beneficial to the host in microbial infections, but can be protective or detrimental in sterile inflammation. This unpredictable nature of dendritic cells is a reflection of the diverse and complex pathogenesis of sterile inflammatory responses. Drugs form a major group of stimuli for tissue injury and, in turn, a sterile inflammatory response. Although many studies have examined the role of dendritic cells in pathogenic infections, their function in drug related organ toxicity is very limited. Here, with a brief introduction of sterile inflammatory response, we review the reported findings about the dendritic cell role in drug induced toxicity.

Keywords: Dendritic cells; Sterile inflammation; Drugs; Cisplatin; Acetaminophen; Kidney; Liver

Studies in humans and animals have firmly established that inflammation plays a key role in the pathogenesis of drug-induced toxicity. Inflammation is commonly defined as a complex biological response against invasive pathogens [1,2]. In response to microbial invasion, it plays a critical role in clearing and/or slowing the infection. Inflammation is initiated through a cascade of signals that leads to the production of cytokines and chemokines by parenchymal cells and tissue resident macrophages and dendritic cells (DCs). The initial inflammatory response is further enhanced by the recruitment of innate immune cells, neutrophils and monocytes. These recruited leukocytes and tissue macrophages and DCs phagocytose infectious agents and produce inflammatory mediators which lead to the activation of lymphocytes and the induction of adaptive immune responses. It is believed that infection has played a vital evolutionary role in shaping the nature of inflammatory responses.

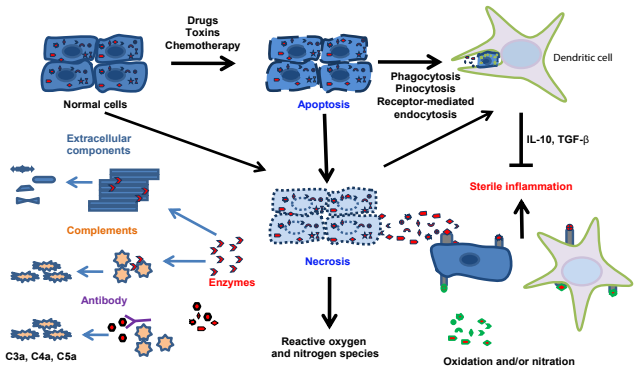

Figure 1: Mechanisms of sterile inflammation. A substantial number of cells undergo apoptosis and/or necrosis in response to drugs, toxins, chemotherapy, hemorrhage, infarction and ischemia. Some of these parenchymal cells and released endogenous ligands are cleared by tissue resident DCs. In the absence of their uptake by DCs, enormous endogenous ligands released from necrotic cells bind to the Pattern Recognition Receptors (PRRs) on surrounding immune cells or normal parenchymal cells, and mediate sterile inflammation. Reactive oxygen and nitrogen species produced during inflammation can cause oxidation or nitration of proteins, carbohydrates and lipids. These altered ligands bind to PRRs and initiate sterile inflammation. Likewise, proteases released from necrotic cells generate new protein epitopes that can initiate inflammatory responses. Enzymes, and ligand bound antibodies can activate complement and mediate sterile inflammation.

Sterile Inflammation

Inflammation can also result from insults other than microorganisms, such as trauma, ischemia, hemorrhage, toxins, drugs, metals or chemicals, and has been termed as germ-free or sterile inflammation (Figure 1). Similar to the inflammatory response to pathogens, sterile inflammation is marked by apoptosis and/or necrosis of an enormous number of cells in different organs and tissues [1]. These dead or dying cells release a large repertoire of endogenous ligands, such as nucleic acids, heat shock proteins, uric acid and intracellular proteins, which can bind to pattern recognition receptors on leukocytes, particularly those on dendritic cells and macrophages, and initiate inflammation, tissue injury and adaptive immune responses [3-8]. In infections, the inflammatory response is usually limited because the microbes are often rapidly cleared by humoral and/or cellular immune mechanisms. Therefore, the collateral tissue damage observed in inflammation is outweighed by the advantage obtained by containing or clearing the potentially life-threatening microbes. Likewise, sterile inflammation, for example in wound healing, may be beneficial. However, very often the inciting stimuli, like that of drugs, may not be potentially harmful to the host yet an overwhelming inflammatory response may still be elicited. As a result, the activation of innate immune inflammatory mechanisms may mediate significantly harmful damage to adjacent healthy tissues. In addition, this may inhibit the ongoing repair and/or remodeling processes in the tissues. If sufficiently robust, these deleterious sterile inflammatory responses can cause acute or chronic diseases.

Concomitant to the induction of inflammatory responses to sterile stimulus, diverse cytoprotective regulatory mechanisms may be activated

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to restrict or terminate inflammation, thereby preventing unnecessary bystander damage of healthy tissues. Resolution and termination of inflammation is accomplished by varied cells and secreted factors, such as DCs, regulatory T cells, IL-10, netrin-1, nitric oxide, adenosine, vascular endothelial growth factor, heme oxygenase-1, TGFβ and others [9-14]. Interestingly, many of the signaling pathways and cells, especially the leukocytes, known to mediate inflammation also are vital in limiting tissue injury and promoting reparative processes. For example, DCs are shown to mediate either pro- or anti-inflammatory functions depending on the nature of the inciting stimulus. Likewise, cytokines produced by Th2 lymphocytes are known to potentiate antibody mediated diseases, but the cytokine interleukin-10 produced by them limits cell-mediated inflammatory responses.

Dendritic Cells in Immunity and Tolerance

Every organ and tissue in humans and animals is armed with immune cells, particularly DCs, to sense and induce inflammatory immune response against harmful stimuli or maintain tolerogenic environment under steady state conditions [15,16]. DCs are antigen presenting cells with an exceptional phagocytosis and pinocytosis potential, and are equipped with special receptors through which they sense tissue injury or pathogens in their immediate microenvironment. These cells are largely derived from bone marrow monocytes which upon entering tissues get differentiated into DCs. Under normal conditions, they possess low abundance of antigen presentation and maturation markers with high phagocytosis and pinocytosis capacity. These immature DCs continuously process apoptotic cells, proteins and other macromolecules in their immediate vicinity and present them to the T cells of the adaptive immune system without the production of inflammatory mediators. This forms the basis for the induction of peripheral tolerance, which is required in addition to the central tolerance acquired during the early days of development of the immune system. In response to pathogens or products of tissue injury, the DCs in tissues undergo maturation and increase their expression of antigen presentation and co-stimulatory molecules and production of cytokines and chemokines, which are required to initiate inflammatory innate or adaptive immune responses [3,4,6,17].

In sterile inflammation, DCs were generally considered as mediators of tissue injury. Because of the lack of animal models that are deficient in DCs, most of the studies reported on DC responses to sterile stimulus were based on in vitro findings using bone marrow-derived DCs. Compared to tissue resident DCs, bone marrow cells differentiated into DCs in the presence of granulocyte-macrophage colony stimulating factor and interleukin-4 for seven days possess an inflammatory phenotype. This difference can be attributed to factors secreted in tissues, because parenchymal cell conditioned medium has been shown to reduce the pro-inflammatory phenotype of bone marrow derived DCs [5]. Therefore, investigation of DC involvement in different pathophysiological conditions requires animal models in which DCs functions can be determined within their physiological context. Thus, the preferred methods involve their ablation in the intact organism. After the advent of clodronate encapsulated liposomes as a means to deplete DCs, many studies were reported regarding the role of DCs in microbial infections or sterile inflammatory responses [18]. However, the clodronate model is not specific because it causes depletion of monocytes and macrophages in addition to DCs [19,20]. Moreover, clodronate, by itself, can inhibit the production of inflammatory mediators [21]. The use of cell-specific antibodies is an alternative method used extensively to deplete different types of leukocytes [22,23]. However, this conventional technique is hindered by the observation that myeloid DCs interspersed in peripheral tissues might be less susceptible to antibody-mediated phagocytosis and cytotoxicity. In 2002, Steffen and colleagues generated a novel Diphtheria Toxin (DT)-based transgenic mouse model system that allows inducible *in vivo* ablation of DCs [24]. These CD11c.DTR/EGFP mice express simian Diphtheria Toxin Receptor (DTR) and Green Fluorescent Protein (GFP) under the control of DC specific CD11c promoter. Injection of DT to these mice, to which mice are typically resistant, causes depletion of DCs. The presence of GFP in DCs in these transgenic mice has helped their visualization in different tissues. Although many other DC ablation mouse models are generated recently, this strain of mice has been extensively used to unravel the functions of DCs in different pathophysiological conditions, especially in microbial infections and non-drug related sterile inflammation [18]. In spite of the availability of a wide range of DC ablation models, studies which have examined their functional significance in drug-induced tissue injury are limited. Review of literature suggests only three studies that have examined, *in vivo*, the importance of DC in drug related toxicity [25,26].

Dendritic cells in cisplatin nephrotoxicity

Kidney is one of the major excretory organs for drugs, metals and toxic metabolites. Therefore, renal toxicity is an usual and occasionally life-threatening adverse effect caused by many therapeutic agents. This adverse effect often restricts usage of some drugs in required patients or causes a new drug having to be taken off from the market. The reason for most drug or toxin-related kidney injuries is unclear; however, there is increasing evidence that inflammation in kidneys caused by drugs contributes for the pathogenesis of renal diseases. Cisplatin is an anti-cancer drug used extensively to treat many forms of solid tumors since its approval by Food and Drug Administration in 1978 [27]. Unfortunately, cisplatin is known to cause acute kidney injury in 25-35% of treated patients. In spite of this major toxicity, cisplatin continues to be widely prescribed to treat tumors of lung, testis, ovary, breast, head, neck and other organs and tissues.

In kidneys, DCs form an extensive network between renal tubules accounting for almost half of all renal leukocytes [28-30]. The first study on DC role in drug toxicity was investigated in a mouse model of cisplatin nephrotoxicity [26]. In this study, we examined the effect of renal DC depletion on cisplatin nephrotoxicity. Ablation of DCs in mice resulted in aggravated renal dysfunction, kidney injury, neutrophil infiltration, and reduced survival rates. DT administration to CD11c. DTR/EGFP transgenic mice causes massive death of DCs, which, by themselves, can serve as danger signal and exacerbate tissue injury. This possibility was addressed using a novel mixed chimeric mouse in which DT caused death of half of renal DCs of CD11.DTR/EGFP mice origin leaving behind the other half of DCs that are negative for DTR. DT treatment to these chimeric mice had no impact on the severity of cisplatin-induced kidney injury, indicating that the worsening renal dysfunction observed in response to DC depletion is due to the absence of DCs, rather than dead or dying DCs. Although the mechanism was not determined this first study demonstrates that DCs present in organs can alleviate drug related tissue injury. These results suggest that renal resident DCs can protect against drug-induced nephrotoxicity and associated inflammation.

In a subsequent study, we examined the role of endogenous IL-10 and DC produced IL-10 in cisplatin nephrotoxicity [13]. Treating mice with cisplatin caused an increase in renal IL-10R1 expression, renal STAT3 phosphorylation, and serum IL-10 levels. Having noticed activation of IL-10 signaling pathway, we examined the effect of endogenous IL-10 deficiency on cisplatin nephrotoxicity. In response

to cisplatin treatment, mice deficient of IL-10 displayed worse renal dysfunction and tissue injury with increased infiltration of neutrophils and expression of adhesion molecules, inflammatory cytokines and chemokines. These findings indicate that endogenous IL-10 attenuates kidney injury in cisplatin nephrotoxicity. Infiltration of IFNg-secreting neutrophils was marked in IL-10 deficient mice; however, IFNg neutralization did not change the extent of renal dysfunction. Interestingly, renal DCs from mice treated with cisplatin showed high expression of IL-10. To examine the functional significance of DC-derived IL-10, mixed bone marrow chimera mice were created containing leukocytes equally derived from CD11c.DTR/EGFP mice and IL-10 deficient mice [23,24]. Treatment of DT to these mice causes depletion of DCs of CD11c.DTR/EGFP origin leaving behind DCs negative for IL-10. In response to cisplatin treatment, chimeric mice lacking IL-10 in DCs displayed greater renal dysfunction than mice positive for IL-10 in DCs. These results demonstrate that endogenous IL-10, and more interestingly, IL-10 produced by DCs reduces cisplatin nephrotoxicity and its associated inflammation.

Dendritic cells in acetaminophen hepatotoxicity

Many drugs continue to fail in animal studies and preclinical trials due to their hepatotoxicity. Because of its close functional relation to gastrointestinal tract and uniqueness in detoxification, the liver is one of most susceptible organs to drugs, chemicals and toxins. Acetaminophen is a commonly used analgesic and antipyretic drug, but causes hepatotoxicity at high doses, and at times even at low therapeutic doses [31,32]. Acetaminophen mediated hepatoxicity is one of the most frequent cause of acute liver injury. Low therapeutic levels of acetaminophen are generally conjugated with glucuronic acid and sulfates, and in case of their saturation, toxic metabolites are glutathionylated in the liver and excreted in urine. Upon depletion of glutathione reserves in liver, toxic acetaminophen metabolites causes acute liver failure characterized by centrilobular hepatic necrosis. Although several mechanisms serve to induce hepatic injury, inflammation remains a common causative factor of hepatotoxicity.

Liver, being one of the larger visceral organs, contains nearly 2-5 fold greater number of DCs than that of other organs, such as heart or kidneys [33]. Subsequent to our study on DCs in cisplatin nephrotoxicity,

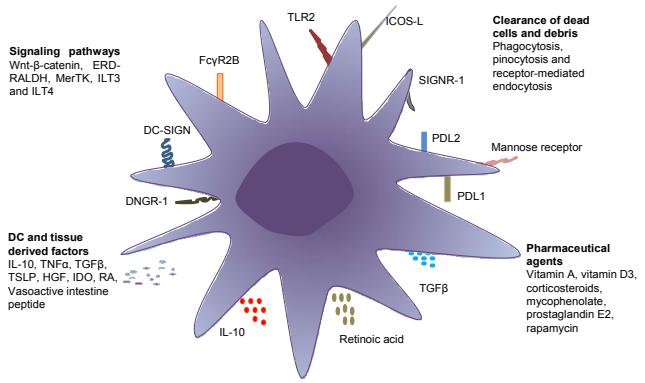

Figure 2: Factors that regulate tolerogenic DCs. A broad range of cytokines, receptors, ligands and signaling pathways mediate protective functions of DCs in different pathophysiological conditions. DC phagocytosis, pinocytosis and receptor-mediated endocytosis promote the clearance of apoptotic cells, necrotic cells and endogenous ligands that can induce sterile inflammation. Various tissue-derived factors and pharmaceutical agents can also program DCs to tolerogenic phenotype and promote secretion of IL-10, IDO and TGFβ that are critical for the induction of regulatory T cells.

Connolly and colleagues reported that liver DCs protect against drug induced toxicity using a mouse model of acetaminophen toxicity [25]. In this study, the authors noticed a change in DC phenotype in response to acetaminophen challenge. In contrast to splenic DCs, the liver DCs increased their expression of antigen presentation and costimulatory molecules, as well as Toll-like receptors and other pro-inflammatory cytokines and chemokines. However, CD11c.DTR/EGFP mice depleted of DCs showed markedly aggravated centrilobular liver necrosis and high mortality to acetaminophen treatment as compared to DC-replete mice. Likewise, administration of FMS-tyrosine kinase3ligand (Flt3L) to induce endogenous DC expansion ameliorated the hepatotoxic effects of acetaminophen. Mice depleted of DCs showed an increase in infiltration of neutrophils and NK cells, and the production of pro-inflammatory cytokines and chemokines, IL-6, TNFα and MCP-1. However, neither the depletion of neutrophils nor NK cells affected the course or severity of liver injury in DC-depleted mice. Likewise, neutralization of IL-6, TNFα or MCP-1 had no impact on acetaminophen heptatoxicity. Taken together, these data clearly indicate that liver resident DCs protect against acetaminophen-induced liver injury.

Dendritic cell protective mechanisms

Dendritic cells induce tolerance or anti-inflammatory responses by various mechanisms (Figure 2). These cells inhibit T cell effector responses by expression of FCγR2B, PDL-1, and PDL-2 [34,35], or inhibit tissue injury and inflammation by secreting factors such as prostaglandin E2, indoleamine 2,3-dioxygenase, IL-10, TGFβ, retinoic acid (RA), IL-27 and others [11,36-38]. Tissue microenvironment and cell-cell cooperation also plays a decisive role in conditioning DCs to an anti-inflammatory phenotype [15]. For example, DCs exhibits tolerogenic functions in the presence of vitamin A, vitamin D3, IDO, hepatocyte growth factor, prostaglandin E2, TGFβ, retinoids, thymic stromal lymphopoietin (TSLP) and vasoactive intestinal peptide [39-45]. Certain ligands can differentiate DCs into tolerogenic phenotype by activating their pattern recognition receptors such as Toll-like receptors (TLRs), RIG-I like receptors (RLRs), C-type lectin receptors (CLRs) and NOD-like receptors (NLRs) [15,46,47]. These receptors are evolutionarily conserved and are primarily involved in recognition of wide range of microbes and activation of innate immune responses. Several signaling networks including Wnt-β-catenin, ERK-RALDH, MerTK, and ILT3 and ILT4 signaling pathways have been attributed for DCs anti-inflammatory functions [48-51]. DCs can also inhibit inflammation independent of above mentioned mechanisms. Tissue resident DCs under steady state conditions are immature and possess high phagocytic and pinocytic activity compared to activated-DCs. These immature DCs can inhibit inflammation by capturing apoptotic and necrotic cells, or by clearing endogenous ligands released from necrotic cells. Thus, these varied secreted factors, receptors, signaling pathways and other mechanisms function in a highly coordinated manner and determine whether DC elicits tolerogenic or inflammatory responses against inciting stimuli.

Concluding Remark

Although review of literature indicates only three studies on DCs in drug toxicity, the findings reviewed here provide clear evidence that DCs resident in tissues ameliorate drug-induced organ toxicity and related inflammation. The major challenge is to determine how the knowledge of DC protective functions in drug toxicity can be exploited for clinical application. In this regard, combined DC and cisplatin therapy in cancer patients may be beneficial for the reason that DCs in addition to inhibiting tumor growth, as evident in clinical trials, may

reduce nephrotoxicity associated with cisplatin without affecting its anti-cancer potential. The next interesting task would be to determine the process by which these tissue resident DCs attenuate drug toxicity. Even though, the advent of transgenic or knock-in mouse models has greatly increased our tools to understand DC functions in different pathophysiological conditions, determining the mechanism by which DCs decrease drug toxicity is challenging. This is mainly because of the involvement of many factors that determines DC response in immunity and tolerance. Elucidation of the mechanism by which tissue resident DCs decrease drug-induced tissue injury may provide openings for more cell-based and pharmacologic interventions. Studies of DCs in other drug toxicities are also warranted.

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