The influence of infectious factors on dendritic cell apoptosis

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Abstract

Pathogens can have a negative influence on dendritic cells (DCs), causing their apoptosis, which prevents active presentation of foreign antigens. It results in a state of immunosuppression which makes the body susceptible to secondary infections. Infected immature DCs have lower expression of co-stimulatory and adhesion molecules, reduced ability to secrete cytokines and an inhibited maturation process and are incapable of effective antigen presentation and activation of T-lymphocytes. In some cases, the ability of DCs to undergo rapid apoptosis is important for the body defense, which is probably because of DCs' ability to cross-present and cooperate with other cells. Apoptotic bodies released from the infected DCs are phagocytosed by other DCs, which then stimulate the effector cells and present antigens more efficiently than infected cells. The aim of this article is to review how the DCs respond to viral and bacterial factors and which biochemical mechanisms are responsible for their apoptosis.

Key words: dendritic cells, apoptosis, viruses, bacteria.

Introduction

Dendritic cells (DCs) are the only professional antigen-presenting cells (APC) which are both a component of the innate response and an essential element to induce adaptive immunity [1]. They are an important component of the body's line of defense, because they are the first to make contact with foreign antigens and then stimulate other cells of the immune system to combat the invaders [1–3]. Dendritic cells are a heterogeneous population which can be divided into several subtypes which differ according to immunophenotype and function [1].

Conventional DCs (formerly termed myeloid) are characterized by very long cytoplasmic processes which are found on the surface of the cell body and which mainly specialize in absorbing, processing and presenting captured antigens [2]. They play an important role in stimulating lymphocytes, especially naive T lymphocytes [3], which are necessary for immune memory formation and the selective recognition of foreign antigens. Conventional DCs are derived from lymphoid and myeloid progenitors [4, 5]. Plasmacytoid DCs are the body's main producers of type I interferon, which is related to the anti-viral response [2]. Unlike the conventional type, plasmacytoid DCs demonstrate a reduced ability to present antigens [1, 3]. The other three subpopulations of DCs found in

human skin are epidermal Langerhans cells, which are characterized by a longer lifespan (weeks) than other DC types (3–10 days) [1, 6], dermal myeloid DCs and dermal plasmacytoid DCs [7].

Dendritic cells derive from multipotent CD34+ bone marrow hematopoietic stem cells and, depending on their environment, they may differentiate into distinct subpopulations. However, pathways leading to the generation of DCs have not been fully elucidated [8]. In a steady-state condition, most DCs are generated from progenitors (especially from the myeloid rather than the lymphoid lineage) [9–11]. Previous studies indicate that during the inflammation process, they may also develop from monocytes and create a subset of inflammatory DCs [8, 12]. However, recent findings indicate that DCs can be derived from monocytes also during steady-state conditions [13, 14]. Monocytes are most likely not the direct precursor of DCs, but presumably they differentiate into specialized DC subsets under particular conditions [8]. The process of DC maturation is very important to initiate an appropriate response to an infectious agent, because only mature DCs are able to activate other immune cells. Immature DCs are characterized by high phagocytic ability and the presence of multiple receptors that recognize pathogen-associated molecular patterns (PAMPs) [1]. As a result of contact with foreign antigens, DCs mature and migrate to the lymphoid organs, where they present captured antigens and undergo apoptosis [15, 16]. Programmed cell death is an important element of the lifespan of DCs, because it regulates the spread of the immune response to invading pathogens by limiting the access of antigens for T cells [17]. Defects in the genes that regulate this process may result in autoimmunity [17, 18], whereas if that process is of a significant intensity, it may contribute to a state of immunosuppression, making the body prone to infections [17, 19]. There are many mechanisms that initiate this process, but most of them proceed on two main pathways: extrinsic and intrinsic (mitochondrial pathway) [17, 20].

Extrinsic pathway of dendritic cell apoptosis

The extrinsic pathway of apoptosis is mainly based on the interaction of membrane receptors located on the cell surface, called "death receptors", with corresponding ligands which trigger mechanisms leading to programmed cell death (PCD) (Figure 1). Samples of such proteins are receptors of the tumor necrosis factor superfamily (TNF) such as TNFR1/DR1, TNFR2, Fas/CD95/DR2/Apo1, DR3/Apo3, TRAILR1/DR4/Apo2 or TRAILR2/DR5 and their ligands: TNF-α, FasL/CD95L/Apo1L, Apo3L and TRAIL/Apo2L, respectively [20–22]. Each death receptor is composed of three parts: the extracellular and transmembrane parts, as well as the cytoplasmic part, which contains the death domain (DD). Connection of the appropriate ligand to the death receptor leads to changes in the DD and binds various proteins, e.g. adapter protein FADD, as well as inactive zymogens of initiator caspases: procaspase-8 or -10 [20]. This process leads to the creation of an active complex, death-inducing signaling complex (DISC), which is capable of performing proteolysis of the mentioned zymogens into their active form. Activation of these enzymes induces an executive caspase cascade, directing the cell to the programmed cell death pathway [23–25].

The extrinsic pathway may also be linked with the mitochondrial pathway via Bid protein, which may be proteolyzed (as a result of caspase-8 action) to a shorter form, tBid. The shortened form of this peptide moves to the mitochondrial surface and influences release of cytochrome c from these organelles. It irreversibly triggers initiation of the intrinsic apoptosis pathway [20, 24, 26].

Intrinsic (mitochondrial) pathway of dendritic cell apoptosis

The intrinsic apoptotic pathway is dependent on mitochondria and can be activated as a consequence of direct DNA damage, oxidative stress, disturbances in the hydrogen electron transport system or a lack of growth factors [20, 24]. As a result of these stimuli, cytochrome c (Apaf 2), an important component of the mitochondrial electron chain, is released into the cytoplasm by megachannels located at the junction of two mitochondrial membranes. The released cytochrome c connects with pro-apoptotic apoptosis protease-activating factor 1 (Apaf 1) and inactive procaspase-9 in a complex called the apoptosome, which is capable of activating caspase-9 (Figure 1) [27]. This active cysteine protease affects the activity of other executive caspases such as caspase-3, -6 and -7, whose activity results in characteristic morphological changes in apoptotic cells [24].

The intrinsic pathway of apoptosis is also regulated by proteins belonging to the family of Bcl-2 proteins. Some of them, such as Bax and Bak, are pro-apoptotic proteins, whereas Bcl-2 and Bcl-XL have apoptosis-inhibitory effects [28, 29]. The purpose of the anti-apoptotic protein is to reduce the semipermeable properties of the mitochondrial membrane by inhibiting the pro-apoptotic proteins that induce its depolarization. Immature DCs have a high level of Bcl-2 protein expression; however, this decreases significantly during cell maturation, which is related to the natural process of DC apoptosis after antigen presentation. This process regulates the lifespan of DCs and prevents intensive and prolonged stimulation of T and B cells [17, 30].

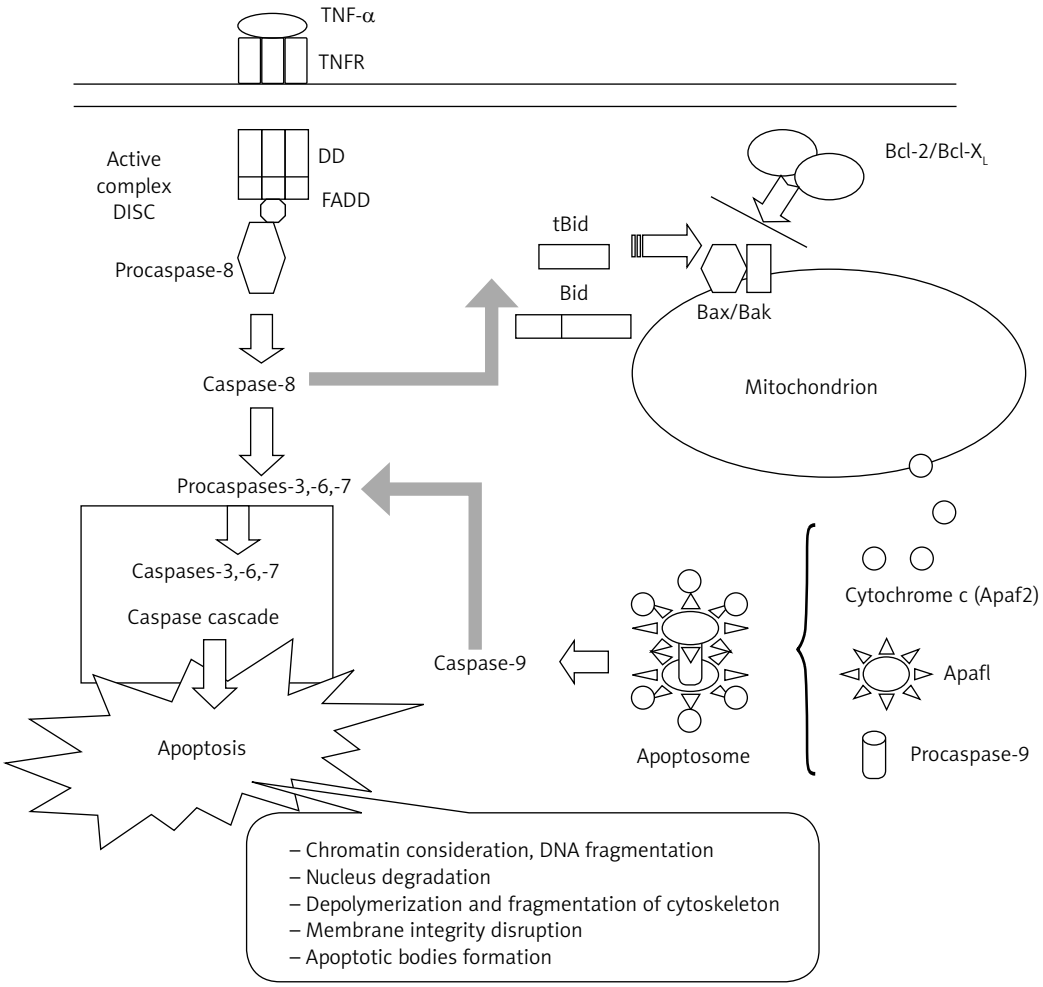

Figure 1. The apoptosis of DCs may be launched by two pathways: extrinsic (which requires activation of the "death receptor" and creation of the DISC complex) or intrinsic (caused by the release of mitochondrial cytochrome c, as a result of the apoptotic stimuli)

Viral factors versus dendritic cells apoptosis

Viral infections enhance DC apoptosis in many cases, thereby weakening the body's major line of defense. Measles infections are often associated with secondary infections, which are a result of the impaired ability of the immune response. Immunosuppression induced by the measles virus can also in many cases lead to death [31, 32]. This virus infects both mature and immature DCs, resulting in their apoptosis, which is dependent on Fas receptors and possibly TRAIL receptors [19, 33]. During the infection, intensive virus replication has been observed and, at the same time, apoptosis of both DCs and T cells has been seen to increase dramatically. The measles-infected cells may undergo the Fas-dependent pathway of apoptosis or be activated by T cells and become cytotoxic DCs, which are able to inhibit lymphocyte proliferation [19] and even to direct them to the path of TRAIL-dependent programmed cell death [33]. Such cytotoxic measles-infected DCs also undergo apoptosis induced by FasL. Thus, apoptosis facilitates the release of new virions, which replicate inside the DCs and infect other host cells [19].

Another virus that inhibits DC maturation and induces their apoptosis is the Epstein-Barr virus (EBV). The strategy of the EBV is to eliminate DCs, in order to prevent the response of the host, to induce a state of immunosuppression and maintain chronic infection. This virus induces both the extrinsic and intrinsic apoptosis pathways. In a study of apoptosis of DCs derived from cord blood monocytes, Wang *et al.* [34] observed a significant decrease in membrane potential in the mitochondrial inner membrane of EBV-infected cultures. The researchers also observed that the proteins released from the mitochondria, such as cytochrome c, are involved in formation of the apoptosome and consequently increase the activity of caspase-9. Other caspases, whose activities were also increased were caspase-8, which initiates the extrinsic apoptosis pathway, and caspase-3, which is a major executive caspase responsible for chromatin condensation, degradation of DNA

and many nuclear substrates, and nuclear envelope budding. The observed changes were confirmed by a significant decrease in expression of the anti-apoptotic proteins Bcl-2 and Bcl-XL, which are responsible for regulation of inner mitochondrial membrane semi-permeability and the strong inhibition of XIAP (X-linked inhibitor of apoptosis protein) protein expression, which stops the apoptosis process by inhibition of caspase-3, -7, and -9 [35]. Li *et al.* [36] also observed that the virus inhibits the development of DCs by promoting apoptosis of their monocyte precursors, thereby preventing initiation and maintenance of the virus-specific immune response.

Many studies of the HIV virus show that numbers of both DC subsets (myeloid and plasmacytoid) were dramatically reduced in HIV-infected patients [37–41]. A study by Laforge *et al.* [42] indicates that rapid DC death occurs in both pathways – extrinsic (Fas-dependent) and intrinsic. A progressive process of apoptosis in this case is associated with an imbalance between the levels of pro- and anti-apoptotic proteins. The researchers observe that under the influence of HIV, DCs demonstrate increased expression of Bax and Bak proteins, which initiate the apoptosis process, by affecting mitochondrial pore formation, and decrease the expression of proteins that counter this process – Mcl-1 (a Bak inhibitor) and FLIP (which counteracts DISC complex formation and the activation of caspases). Moreover, it was demonstrated [42, 43] that HIV slows down the DC maturation process and impairs the ability of the cells to produce inflammatory cytokines. Both infected DCs and those not attacked by the virus are involved in the process [42].

Studies of herpes simplex virus (HSV) infections demonstrate that the virus induces rapid cell death of DCs [44–46]. However, DC apoptosis is not always associated with a state of immunosuppression. The ability of DCs to perform this process appears to be one of the anti-viral defense mechanisms of the body. Bosnjak *et al.* [46], in their work about interaction of HSV with DCs, note that rapid apoptosis of these cells under the influence of the virus has a positive effect on activation of defense mechanisms. HSV-infected immature DCs have significantly lower expression of costimulatory and adhesion molecules, reduced capacity to secrete cytokines and an inhibited maturation process. Such cells are incapable of effective presentation and T cell activation, especially cytotoxic T lymphocytes with CD8+ immunophenotype (CTLs). However, research shows that viral antigens derived from the infected DCs, which undergo apoptosis, activate CTLs much more effectively. Due to the ability of DCs to carry out cross-presentation [47] and cooperation with different cell subpopulations, it is possible to defend the body against the infection. During HSV infection, Langerhans cells are the first to be infected. Then they undergo apoptosis and release apoptotic bodies which are engulfed by another DC subset located in the mucosa. Owning to the cross-presentation process, those DCs stimulate mucosal CTLs, which become able to recognize and eliminate the virus [46].

Chronic hepatitis C virus (HCV) infection is characterized by a very weak or unstable antiviral response [48]. Zhao *et al.* [49] found that the ability of myeloid DCs to stimulate T cell responses during the infection was impaired. The researchers observed that myeloid DCs from chronic hepatitis C patients undergo apoptosis more frequently than myeloid DCs from healthy individuals. Furthermore they noted diminished activity of the NF-κB nuclear factor, which is essential for the antigen-presenting function, comprising the expression of human leukocyte antigen (HLA) class II molecules and co-stimulatory molecules, and, in addition, acts as an antiapoptotic factor for myeloid DCs [49, 50]. It was also observed that during HCV infection, the DC maturation process was blocked and was manifested by lower expression of maturation surface markers (CD80, CD86 and HLA-DR) [48, 49]. According to Sarobe *et al.* [48], expression of HCV E1 protein (CE1) in the DCs of patients with chronic hepatitis C may play a critical role in the inhibition of the maturation of these cells, which is mediated by TNF-α and CD40L. Another study by Zhao and Tyrrell [51] indicates that myeloid DCs from chronic hepatitis C patients have cytotoxic activity which is upregulated to kill T cells during HCV infection. Decreased expression of co-stimulatory molecules together with the cytotoxicity of myeloid DCs and their increased apoptosis were associated with their reduced ability to activate the T cell response and thereby facilitate HCV persistence.

However, not all viral infections promote DC apoptosis. Some studies indicate a reduction of this process in cell cultures infected with human respiratory syncytial virus (HRSV), human metapneumovirus (HMPV) and human parainfluenza virus type-3 (hPIV3), which was probably a result of the activation of Bcl-2 family proteins during the process of maturation and a minor cell infection with the virus [52]. Lundqvist *et al.* [53] suggest that two proteins, Bcl-XL and Bcl-2, may be responsible for the inhibition of apoptosis. At the same time they emphasize that Bcl-XL plays the more important role in this process. Because of its increased range of function, Bcl-XL (which is not only associated with the cell membrane, like Bcl-2, but is also present in cytoplasm) can more efficiently connect to the Bax protein (an apoptosis initiator), making it inactive.

Bacterial factors versus dendritic cells apoptosis

As with viruses, bacteria also contribute to increased DC apoptosis in most cases. *Legionella pneumophila*, causing a serious disease called legionellosis manifested by pneumonia, is a dangerous Gram-negative type of bacteria capable of infecting phagocytic cells [54]. The metabolic processes of infected DCs are imbalanced; hence, the infected cells become a place of intracellular multiplication of the bacteria and thus lose the ability to undergo apoptosis. Dendritic cells, unlike other phagocytes, have mechanisms that enable this process to proceed on two different routes. Studies on DCs [55] derived from mouse bone marrow have shown that the first pathway is associated with Naip5 receptor belonging to the group of NOD-like receptors (NLR). Stimulation of this receptor by flagellin (a bacterial protein) leads to the formation of a complex called the inflammasome [56]. At first, the complex activates caspase-1, then it directly activates caspase-7 (belonging to executive caspases), which consequently and irreversibly leads to cell death. As a result of this process, not only is bacterial replication inhibited, but also some cytokines such as IL-1β and IL-18 are secreted outside the cells. The main function of the mentioned cytokines is to attract other immune cells to the site of infection, as well as to stimulate a response directly against the bacteria [57]. The described pathway is called the pyroptosis, and it is a form of apoptosis closely related to the antibacterial response [55, 58]. The second apoptotic pathway activated during *L. pneumophila* infection is the intrinsic pathway. A study conducted by Nogueira *et al.* [55] also implicates significant participation of pro-apoptotic proteins Bax and Bak as well as caspase-3 in this process. Fast DC apoptosis in infections plays another very important function: it prevents migration of the infected cells to lymphoid organs and the spread of pathogens in the body. It should also be noted that only the virulent strains of *L. pneumophila* are able to induce apoptosis of DCs within a few hours following the infection, whereas the non-virulent strains only contribute to activation and maturation of these cells, and do not significantly affect the life of DCs [59].

Similar mechanisms of cell death, as described in *L. pneumophila*, also occur in *Salmonella typhimurium* and *Pseudomonas aeruginosa* [60–62]. Caspase-1-dependent pyroptosis leads to rapid cell death. Moreover, pro-inflammatory cytokines released under the influence of caspase-1 contribute to recruitment of other immune cells to the site of infection [58]. On the one hand, this process is positive, because it mobilizes the body to fight the pathogen, but on the other hand, it allows the bacteria to infect other cells and transports them to the spleen and liver, where it triggers a secondary infection [61].

Another bacterium which very quickly leads to rapid apoptosis of DCs is the Gram-negative *Streptococcus pneumoniae* [63–65]. Due to this strategy, the bacteria multiply rapidly in mucous membranes during initial stages of colonization, which results in weakening of the immune system. *S. pneumoniae* induces the programmed cell death of DCs via two mechanisms [63]. The first is caspase-independent and occurs with the participation of pneumolysin (a bacterial virulence factor), a protein capable of inducing hemolysis of red blood cells. The second mechanism takes place with the presence of caspases and TLR2 – the new "death receptor". The pneumolysin-dependent mechanism causes DC death within a short period of time and is associated with changes in cell membrane permeability, which are related to the ability of this protein to form pores in the cell membrane [63, 64]. Researchers investigating this subject [63] observed DNA fragmentation in DCs derived from the bone marrow of mice after 3–6 h following the infection, which is typical of the late stages of apoptosis. The pneumolysin derived from more and less virulent bacteria induces DC apoptosis at a similar level of intensity and does not require bacterial internalization into the cell. The second mechanism, unlike the first one described above, acts with a delay of about 24 h after infection, and occurs probably in mature DCs. A study [63] has shown that this process is induced by neither TNF-α nor FasL. It also does not require the direct influence of the bacteria on a cell, but only cell wall components such as peptidoglycan, lipoteichoic acid or the lipoprotein ligands of the TLR2 receptor. The receptor is not only involved in cell signaling activation, but can also initiate the apoptosis process. After binding a suitable ligand to the TLR2 receptor, the apoptosis signal is transmitted via the MyD88 adapter protein and subsequently by another adapter protein, FADD (which connects to the Fas death receptor), then caspase-8 is activated, which results in apoptosis induction [63, 66].

Yersinia enterocolitica is another example of a Gram-negative bacterium which induces DC apoptosis with a similar mechanism as *S. pneumoniae*. This apoptosis pathway is also TNF-α-independent, although it contains some elements of the TNF-α pathway. According to the researchers studying this problem [67, 68], DC death induced by *Y. enterocolitica* is dependent on caspase-8, which is activated by the atypical DISC complex, whereas the TLR4 receptor is involved in bacterial component recognition. Besides apoptosis, which is caspase-dependent, cell death might occur without the presence of caspases, and this is called

"necroptosis" or "programmed necrosis". This process, similar in effect to necrosis, is induced by connecting a suitable ligand to a death receptor, and is dependent on RIP1 protein (receptor-interacting protein 1). In the presence of caspase-8, the protein launches either the transcription of NF-κB factor, which helps cells to adapt to environmental stress, or apoptosis, whereas the inactivation of caspases leads to necroptosis [69].

There are many examples of bacteria that lead to increased DC apoptosis, but the mechanisms that induce this process have not been fully investigated. In studies on *Shigella flexneri* [70] it was observed that the OspF protein, which was secreted by the bacteria during an infection, significantly reduced the level of phosphorylation of Erk1/2 kinases (responsible for growth and differentiation), which may prevent transcription of pro-inflammatory genes and the influx of polymorphonuclear leukocytes into the site of infection, and finally lead to the apoptotic death of DCs, which is likely to have adverse consequences for the generation of adaptive immunity [70, 71].

However, the interaction of DCs with bacteria does not always lead to increased apoptosis. Studies on the influence of *Listeria monocytogenes* on DCs show that these cells, unlike macrophages, do not undergo programmed cell death after phagocytosis of the bacteria [72, 73]. It has been found that a higher pH is present in the phagosomes of DCs than in other cells, and it causes inhibition of the activity of listeriolysin O (a bacterial virulence factor), which under other conditions allows replicating bacteria to escape from the phagosome. Thereby, DCs are able to survive intracellular bacterial infection and receive appropriate signals for cell maturation as well as antigen processing and presentation to T and B lymphocytes [73].

Summary

Apoptosis is a very important element which regulates the lifespan of DCs. Therefore, all immunological processes occurring in the body are in a state of homeostasis. However, pathogens have developed a number of strategies that allow the rapid induction of apoptosis in DCs, which prevents antigen presentation to T cells and, thereby, the development of an acquired immunological response. By eliminating DCs, they improve the chances of effective colonization of the host body. However, the rapid apoptosis of DCs does not imply the weakness of the host immune system in the fight with pathogens; it is one of the body's defense strategies. The quick death of DCs by programmed cell death effectively inhibits replication of the microorganisms which invaded them. At the same time it prevents the release of a large number of pathogens into the extracellular space, since they are enclosed in apoptotic bodies, which are then ingested by phagocytes. As mentioned previously, DCs present antigens (and also stimulate CLTs) much more effectively when they are absorbed by phagocytosing the apoptotic bodies, rather than when they are in direct contact with pathogens and are infected. In addition, the apoptosis that occurs rapidly in an area of infection prevents the spread of pathogens in the body via infected DCs which migrate to lymph nodes. Otherwise, they could be a true "Trojan horse".

Conflict of interest

The authors declare no conflict of interest.

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