Review

Types of Cell Death and Their Relations to Host Immunological Pathways

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Types of Cell Death and Their Relations to Host Immunological Pathways

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Abstract: Host immunological pathways have been proposed including TH1, TH2, TH3, TH9, TH17, TH22, TH1-like, and THαβ immune reactions. Besides TH2 and TH9 immune responses which are against multicellular parasites, host immunological pathways against viruses, intracellular micro-organisms (bacteria, protozoa, and fungi), and extracellular micro-organisms can use programmed cell death pathways to trigger immune reactions or to execute effective strategies to eliminate these pathogens. These programmed cell deaths include apoptosis, autophagic death, pyroptosis, ferroptosis, necroptosis, and NETosis. Apoptosis is related to host anti-virus eradicable THαβ immunity. Autophagic death is related to host anti-virus tolerable TH3 immunity. Pyroptosis is related to host anti-intracellular micro-organism eradicable TH1 immunity. Ferroptosis is related to host anti-intracellular micro-organism tolerable TH1-like immunity. Necroptosis is related to host anti-extracellular micro-organism eradicable TH22 immunity. NETosis is related to host anti-extracellular micro-organism tolerable TH17 immunity.

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Introduction

Cell death is an important cellular mechanism playing roles in development or immune reactions. Apoptosis is a well-known example. Cytotoxic T cells or natural killer cells can use the mechanism of apoptosis to kill virus-infected host cells. During apoptosis, DNA fragmentation can use virus genome destroyed to eliminate viral pathogens. After the discovery of apoptosis, another cell death machineries are discovered including autophagic death, ferroptosis, pyroptosis, necroptosis, and NETosis[1]. We have proposed framework of all discovered host immunological pathways including TH1, TH2a, TH2b, TH3, TH9, TH17, TH22, TH1-like, and THαβ immune reactions[2-4]. These immune responses are combating different types of pathogens and link to four types of hypersensitivities. Cell programmed death is a very important component about host defense mechanism. Thus, different types of host immunological reactions can be related to different types of programmed cell death to defense different types of pathogens. Here, I will review these cell death pathways associated with the host immunological pathways.

Overview of cell death pathways

Apoptosis

Apoptosis is an early most discovered cell program death pathway. Unlike necrosis, which is un-programmed cell death by pathogens or physic/chemistry factors, apoptosis is a programmed cell death pathway and is tightly controlled by genetic machinery. After fertilization, embryo cells may use apoptosis machinery to delete unwanted cells during development. Besides, the mechanism of apoptosis is also used in host immune responses against pathogen infections. For example, natural killer cell antibody dependent cellular cytotoxic reaction can kill virus infected cells via the apoptosis machinery. Thus, apoptosis is also vital to self-defense reactions.

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Apoptosis can be sub-grouped into two categories: extrinsic pathway and intrinsic pathway. The extrinsic pathway is triggered by extrinsic signal molecules to stimulate the apoptosis machinery. The classical extrinsic apoptosis pathway includes FAS/Fas ligand interaction. The intrinsic pathway is triggered by intrinsic cellular signal molecules to stimulate the apoptosis machinery. The classical intrinsic apoptosis pathway is like cytochrome c release from mitochondria. Cytosolic cytochrome c initiates the apoptosis of the cell. There is a linkage of extrinsic and apoptosis cell death pathway. Thus, both extrinsic and intrinsic apoptosis lead to a common cell death pathway. The apoptosis machinery contains initiator and executor caspases to digest intra-cellular DNA and proteins. Initiator caspases include caspase 2/8/9/10 , and executor caspases include caspase 3/6/7.

Autophagic death

Autophagy is the cellular process to digest unwanted, damaged, or old organelles. Autophagy can be started during starvation or other cellular stress situation[5]. It is a process to recycle cell contents to maintain the required metabolism of cells. Special organelles involving autophagy include mitophagy, the autophagy of mitochondria, and so on. Autophagy is an important cellular process. Autophagic death is a cellular process about autophagy induced programmed cell death. This machinery also has an important cell function, especially in cell defense mechanism[6].

Pyroptosis

Pyroptosis is another kind of programmed cell death[7]. It is related to interleukin-1 and interleukin-18. It is associated with programmed cell death of macrophages. This process can help to rapidly clear intracellular pathogens. Pyroptosis usually happens in immune cells, keratinocytes, and sometimes epithelial cells. This process is triggered by the formation of an inflammasome complex (pyroptosome complex) via the stimulation of intracellular danger signals. The pyroptosome complex is related to activation of caspases 1/4/5 in humans which are different caspase sets compared to apoptosis. Caspases 1/4/5 cause the maturation of pro-inflammatory cytokines interleukin-1β as well as interleukin-18. These caspases also activate the pore-forming protein gasdermin D (GSDMD). Gasdermin D is the key effector molecule of pyroptosis. The inflammasome pathway can be canonical or noncanonical. The canonical pathway involves in activations of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) recognized by several certain endogenous pattern recognition receptors (PRRs). For example, NLRP3 or NLRC4 protein is activated by different PAMPs and DAMPs. These receptors can up-regulate pro-inflammatory cytokines including interleukin-12 via NFkB and MAPK signaling mechanism. Then, pro-IL-1β and pro-IL-18 are released to be activated via the action of cysteine-regulated caspase-1. Both NLRC4 and procaspase-1 contain a caspase activation and recruitment domain (CARD). After NLRC4 recruits pro-caspase-1, the homotypic CARD-CARD interaction will induce autocatalytic reaction to let pro-caspase-1 to become active caspase-1. Activated caspase-1 cleave pro-IL-1β and pro-IL-18 to let these two cytokines to be activated forms. Besides, caspase-1 also cleaves the intracellular gasdermin D. GSDMD will be cleaved into two fragments: N-terminal GSDMD-N and C-terminal GSDMD-C. GSDMD-N can form transmembrane pores. The transmembrane pores can let to secret IL-1β and IL-18 to extracellular spaces. These pores also impair the extracellular-intracellular ion gradients. They cause the increase of osmotic pressure with influx of water to let cell swelling and bursting leading to pyroptosis. It is worth noting that GSDMD-N can only insert itself into the inner membrane of specific lipid constitutions. And, without cleavage, GSDMD-N is autoinhibited by GSDMD-C. The noncanonical pathway involves in the interaction of bacterial lipopolysaccharide and human caspase 4/5. Binding LPS to above caspases induce the oligomerization and activation. These caspases also cleave GSDMD to become GSDMD-N to promote pyroptosis.

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Ferroptosis

Ferroptosis is a type of programmed cell death triggered by excess iron intracellularly. It is characterized by lipid peroxide accumulations. Its another term is oxytosis. Ferroptosis is triggered by failure of glutathione mediated anti-oxidation defenses. The whole pattern of ferroptosis is the iron mediated accumulations of oxidatively damaged phospholipids, especially lipid peroxides. While free radicals abstract electrons from a phospholipid, oxidation of phospholipids will occur. Typically, it affects the polyunsaturated fatty acids. The main cellular defense mechanism against ferroptosis is mediated by glutathione peroxidase 4 (GPX4). GPX4 can convert lipid peroxides into non-toxic lipid alcohol molecules. Iron is vital and necessary to generate reactive oxygen species to initiate ferroptosis. Thus, treating cells with iron chelators can stop the happening of ferroptosis. In addition, intracellular glutathione (GSH) levels are key to the function of GPX4, so depletion of GSH will lead to ferroptotic cell death. Besides, ferroptosis causes the phenotype changes of mitochondria.

Necroptosis

Necroptosis is a programmed cell death form compared to necrosis. The key cytokine mediating necroptosis is TNFα. Binding of TNFα leads to the activation of its receptor TNFR1. TNFR1 receptor binds to TNFR-associated death protein (TRADD) and TNF receptor associated factor 2(TRAF2) to activate RIPK1 which recruits RIPK3 to form necrosome (ripoptosome). During necroptosis process, anti-apoptotic protein cFLIP can inactivate caspase 8 to facilitate the necroptosis. In the absence of caspase 8, RIPK1 and RIPK3 can autophosphorylate and transphosphorylate each other to form a microfilament-like complex named necrosome. The necrosome phosphorylates pro-necroptotic protein MLKL which causes MLKL oligomerization. The oligomerized MLKL will insert plasma and organelle membranes to induce the permeability. Besides, MLKL insertion will induce the leakage of cellular contents of the damage-associated molecular patterns (DAMPs) to trigger inflammation. The necrosome also inhibits the adenine nucleotide translocase in mitochondria to lower intracellular ATP concentrations. Besides, uncoupling of mitochondria electron transport chains will lead mitochondria damages and open the mitochondria permeability transition pores to let mitochondria proteins to move to cytoplasm. The necrosome can additionally cause leaks of lysosomal enzymes into cytosol via the induction of reactive oxygen radicals by JNK, calpain activation by calcium release, and sphingosine formation. In contrast to apoptosis, the process of necroptosis does not relate to caspase activation. No apoptotic body formation is seen in necroptosis. Cells undergo necroptotic rupture to leak cellular contents to intercellular spaces.

NETosis

Neutrophil extracellular traps (NETs) are the network of neutrophil DNA derived extracellular fibers binding to extracellular pathogens[8]. NETs can let neutrophils to kill extracellular micro-organisms with least damages to the body[9]. NETs consist of DNA stretches and proteins including azurophilic granules (neutrophil elastase, cathepsin G, and myeloperoxidase), tertiary granules (gelatinase), and specific granule (lactoferrin). NETs can also form intravascularly via the regulation of platelets. Platelet TLR4 can bind to extracellular micro-organisms and activate neutrophils to initiate NETs. Thus, NETs can catch bacteria in blood vessels to stop their migration via blood circulation. NETs activation and release is usually associated with neutrophil programmed cell death, suicidal NETosis. The NETosis pathway is usually began with NADPH oxidase activation of arginine deiminase 4 (PAD4) via reactive oxygen radicals. PAD4 will induce the citrullination of histones in the neutrophil cell nuclei to result in decondensation of chromatin. Azurophilic granules (neutrophil elastase, cathepsin G, and myeloperoxidase) enter the neutrophil nucleus and result in the rupture of the nuclear envelope. Then, the uncondensed chromatin enters the cytoplasm with adding other cellular granules to become the early stage NET. NETosis is a double-edged sword which may cause complications. There is a report saying the relation of NETosis and organ injury[10].

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Overview of host immunological pathways

The immune system is a marvelously complex network, where host immunological pathways play a pivotal role in defending against diverse pathogens. These pathways are categorized based on the dominance of certain immunoglobulins, predominantly into IgG-dominant eradicable immune responses and IgA-dominant tolerable immune responses[2-4,11]. Eradicable immune responses are initiated by follicular helper T cells (Tfh) via interleukin-21, and tolerable immune responses are initiated by regulatory T cells (Treg) via TGF-β. Understanding the intricacies of these pathways is crucial in comprehending how the immune system combats various threats.

In the realm of eradicable immune responses, the action primarily revolves around combating different types of pathogens through specialized immune mechanisms. The TH1 immunity, for instance, stands guard against intracellular microorganisms such as bacteria, protozoa, and fungi. This branch mobilizes an array of defenders including M1 macrophages, IFNγ-producing CD4 T cells, iNKT1 cells, CD8 T cells (Tc1, EM4), and IgG3 B cells, forming a formidable defense line against these intruders. TH1 immunity is also intricately linked to type 4 delayed type hypersensitivity reactions, highlighting its role in specific immune responses.

In contrast, TH2 immunity gears up against parasites, presenting two distinct subtypes: TH2a and TH2b. TH2a tackles endoparasites (helminths) with its lineup of inflammatory eosinophils (iEOS), interleukin-4/interleukin-5 producing CD4 T cells, mast cells-tryptase (MCt), iNKT2 cells, and IgG4 B cells. On the other hand, TH2b focuses on combating ectoparasites (insects), marshaling basophils, interleukin-13/interleukin-4 producing CD4 T cells, mast cells-tryptase/chymase (MCtc), iNKT2 cells, and IgE B cells. These branches of TH2 immunity are instrumental in addressing parasitic threats and are associated with type 1 allergic hypersensitivity responses.

Expanding further, TH22 immunity is dedicated to countering extracellular microorganisms such as bacteria, protozoa, and fungi. Neutrophils (N1), interleukin-22 producing CD4 T cells, iNKT17 cells, and IgG2 B cells collaboratively orchestrate the defense in this domain. TH22 immunity plays a significant role in type 3 immune complex mediated hypersensitivity reactions, showcasing its specialized function in immune responses.

Moreover, THαβ immunity is specifically tailored to combat infectious particles like viruses and prions[12-15]. This immune pathway employs NK cells (NK1), interleukin-10 producing CD4 T cells, iNKT10 cells, CD8 T cells (Tc2, EM1), and IgG1 B cells to combat these minute yet potent adversaries. Its connection to type 2 antibody-dependent cytotoxic hypersensitivity underscores its significance in addressing infectious threats.

Transitioning to tolerable immune responses dominated by IgA, these pathways exemplify the system's ability to mount defenses without causing excessive damage to the host. Regulatory T cells play a crucial role in steering these responses, facilitating the switch to IgA, thereby establishing a more tolerable immune milieu.

TH1-like immunity within the tolerable response framework mirrors TH1 immunity but in a more regulated manner. It safeguards against intracellular microorganisms through M2 macrophages, TGFβ/IFNγ-producing CD4 T cells, iNKT1 cells, CD8 T cells (EM3), and IgA1 B cells, while maintaining a balance to prevent hyperactive responses that might harm the host.

TH9 immunity, targeting parasites such as insects and helminths, relies on regulatory eosinophils (rEOS), basophils, interleukin-9 producing CD4 T cells, iNKT2 cells, mast cells (MMC9), and IgA2 B cells to ensure a measured and controlled defense. This pathway, associated with type 1 allergic hypersensitivity, showcases the immune system's ability to mount responses without tipping the balance toward excessive reactions.

Continuing within the tolerable responses, TH17 immunity is specialized in combating extracellular microorganisms. Neutrophils (N2), interleukin-17 producing CD4 T cells, iNKT17 cells, and IgA2 B cells are the primary players in this pathway, illustrating a fine-tuned defense against extracellular threats while limiting immune-mediated damage through type 3 immune complex mediated hypersensitivity.

Lastly, TH3 immunity within tolerable responses gears up against infectious particles employing NK cells (NK2), interleukin-10/TGFβ-producing CD4 T cells, iNKT10 cells, CD8 T cells (EM2), and

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IgA1 B cells. This pathway showcases the immune system's adaptability, mounting responses against infectious particles while maintaining a balanced immune environment to prevent excessive host damage, closely linked to type 2 antibody-dependent cytotoxic hypersensitivity.

The intricate network of host immunological pathways, categorized into eradicable and tolerable immune responses, showcases the remarkable adaptability and specificity of the immune system in combating diverse pathogens. These pathways not only defend against various threats but also highlight the delicate balance between mounting effective responses and preventing immune-mediated damage to the host.

THαβ immune response and its relation to apoptosis

The host immunological THαβ pathway is the host immune reaction against infectious particles including viruses and prions. Viruses and prions must live intracellularly to replicate more transmissible particles. Apoptosis the most clearly investigated programmed cell death pathway. Apoptosis pathway is a key mediator regulating the virus infected cell death. During apoptosis, cell death will lead to DNA or RNA fragmentation to let intracellular virus DNA or RNA be destroyed. Thus, the virus particles can be eliminated via sacrificing virus infected cells. In addition, the activated caspases will degrade all intracellular proteins. Thus, prions is a protein composite infectious particle which will also be destroyed by activated caspases during apoptosis. THαβ related immune cells include natural killer cells and cytotoxic T cells. THαβ related immune cells also include IgG1 producing B lymphocytes. Natural killer cells can induce antibody dependent cellular cytotoxicity (ADCC) of virus infected cells via binding with IgG1 antibody[16]. Antibody dependent cellular cytotoxicity is an apoptosis mechanism. DNA and RNA fragmentations will occur during the antibody dependent cellular cytotoxicity process. Cytotoxic T cells can also cause apoptosis of virus infected cells with their DNA or RNA fragmentations to kill the viral genomes. Cytotoxic T cells mediated apoptosis is via MHC presented antigen from virus infected cells. Specific T cell receptor molecules from cytotoxic T cells can recognize viral peptides on MHC to induce apoptosis machinery. Similar mechanism can also be found in other infectious particles like prions infection. The tolerable immunity cytokine TGFβ is found to inhibit the apoptosis process[17,18]. Inhibition of TGFβ signaling can promote NK cell ADCC to cause target cell apoptosis[19]. In another study, TGFβ can suppress NK cell ADCC. TGFβ-activated kinase 1 (TAK1) can antagonize apoptosis[20]. TGFβ can inhibit Fas and caspase 8 related apoptosis[21,22]. TGFβ can also induce anti-apoptotic transcription factor to prevent apoptosis. Apoptosis related protein degradation can cause the destruction of infectious prion protein pathogens. Besides, type 1 interferon can induce caspase cascades to trigger apoptosis in malignant cell lines[23-25]. Thus, apoptosis is the THαβ related host defense mechanism against infectious particles including viruses and prions.

TH3 immune response and its relation to autophagic death

Autophagic death is the type 2 programmed cell death pathway. Autophagic death is the milder control of virus infection of host cells[26-28]. Because type 1 interferons can help to control virus infection. Research found a correlation between type 1 interferons and autophagy[24,29]. Type 1 interferon is an inducer of autophagy[30-32]. Interferon regulatory factor 1 (IRF1), which can activate interferon beta, is also related in autophagy[33]. Autophagy is related to the presentation of cytosolic antigens to the MHC class II molecules. Autophagy is also related to digest intracellularly produced viral protein antigens. Autophagy is a protective machinery against virus infection via degrading the viral particles in autolysosomes. For example: autophagy is found in the liver cells to protect from hepatic virus infection[34]. Hepatitis virus C will induce autophagy and interfere anti-viral innate eradicable immunity[35-37]. In contrast to apoptosis, autophagic death with organelle degradations induces mild host inflammation. Compared to THαβ eradicable host immune reaction, TH3 immunological pathway is the host tolerable immune response against viruses and prions. During autophagic death, organelles with residing virus particles will be degraded. Autophagic cell death is often found in chronic viral infection. The key cytokines in TH3 immunological pathway are interleukin-10 and TGF-β. However, interleukin-10 is more important to the eradicable THαβ

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immunity. Research reported that interleukin-10 can prevent from autophagy and neutralization of interleukin-10 can recover the cellular machinery of autophagy[38-40]. Previous studies found out that TGF-β can promote autophagy[41]. TGF-β can prevent caspase 8 induced apoptosis and induce cell autophagy. TGF-β is mainly produced by Treg cells, and impaired Treg activities also impair autophagy activity[42]. Thus, it implies that TH3 immune response could be related to autophagic cell programmed death pathway. Interleukin-1, a key cytokine of TH22/TH17 immunity, will increase after the TH3 associated autophagy is blocked. Another THαβ/TH3 cytokine, interleukin-27, can also promote autophagy[43,44].

TH1 immune response and its relation to pyroptosis

TH1 immunological pathway is the host eradicable immunity against intracellular micro-organisms including intracellular bacteria, protozoa, and fungi. Pyroptotic programmed cell death defends against intracellular pathogens[45,46]. The major effector cells of TH1 immune reaction are macrophages. Pyroptosis is related to the programmed cell death of macrophages. The key TH1 cytokine-interferon gamma is related to the activation of pyroptosis. The inflammasome complex in pyroptosis induces the activation of interleukin-1β and interleukin-18. Both cytokines are pro-inflammatory cytokines against micro-organisms. In addition, interleukin-18 can augment the potency of interferon gamma which is the key immune mediator of TH1 immunological pathway. The activation of interleukin-1β and interleukin-18 triggered by inflammasome further induce the production of interferon gamma. The activation of inflammasome also cause the up-regulation of NFkB, the master gene for immune activation signaling. The activation of inflammasome also inactivate interleukin-33, a mediator of TH2 immunological pathway. Pyroptosis can also trigger pore-induced intracellular traps to capture intracellular bacteria, protozoa, and fungi to lead to their clearance[47]. Caspase-1-induced pyroptosis is an innate immune effector machinery fighting against intracellular micro-organisms[46]. The tolerable immune mediator-TGFβ can suppress pyroptosis[48,49].

TH1-like immune response and its relation to ferroptosis

Ferroptosis is programmed cell death process triggered by intracellular iron overload. Iron is a key chemical element to help the survival of micro-organisms. According to more and more evidences, the happening of ferroptosis is always accompanied by the occurrence of inflammation. During the infection of micro-organisms including bacteria, protozoa, or fungi, more concentration of iron elements will cause worse infection control of host. High intracellular iron concentration will help the survival of intracellular micro-organisms. In order to reduce the availability of iron for intracellular micro-organisms, iron triggered cell death can sacrifice the infected cells and eliminate the micro-organisms. This is the underlying logical principle of ferroptosis. Chronic iron overload can drive macrophages to polarize to be M2 macrophages, the effector cells of TH1-like immune reaction[50]. During ferroptosis, iron will trigger the accumulation of lipid peroxides to cause membrane peroxidation and damage. Thus, the cell membranes of intracellular bacteria, protozoa, or fungi will be damaged and this causes the death of these micro-organisms. That is why ferroptosis is the mechanism to kill and control intra-cellular micro-organism infection. Glutathione peroxidase 4 (GPX4) which can prevent from lipid peroxidation is a protective mechanism from ferroptosis. Treg cells with their key effector cytokine-TGFβ can induce the tolerable immune response and tissue fibrosis. TGFβ could enhance ferroptosis via further GPX4 inhibition[51]. There is a linkage of ferroptosis and fibrosis[52]. Chronic inflammation can be related to ferroptosis associated tissue destruction and later on tissue fibrosis. TGFβ inhibitor can inhibit ferroptosis as well as fibrosis[53]. Previous literature suggested an association between ferroptosis and tissue fibrosis including renal fibrosis, pulmonary fibrosis, and liver cirrhosis[54]. For example: SARS-CoV2 infection on lung epithelial cells will induce ferroptosis and subsequently pulmonary fibrosis. TH1 key cytokine-interferon gamma can enhance ferroptosis in cancer cell lines and epithelial cells[55-57].

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TH22 immune response and its relation to necroptosis

TH22 immunity is the host eradicable immune reaction against extracellular micro-organisms including extracellular bacteria, protozoa, and fungi. TH22 immune response is associated with pro-inflammatory cytokines including TNFα. TNFα is the key immune cytokine of TH22 immune reaction to activate neutrophils to kill extracellular micro-organisms. TNFα is also the major mediator to conduct necroptosis. The reason for triggering necroptosis programmed cell death can be to initiate potent pro-inflammatory immune reaction to kill these invading extra-cellular micro-organisms[58]. Macrophage necroptosis is seen in acute bacterial pneumonia causing by Serratia marcescens, Staphylococcus aureus, Streptococcus pneumoniae, Listeria monocytogenes, or uropathogenic Escherichia coli (UPEC)[59]. Another reason for necroptosis is to destroy possible nutrients from host cells to prevent from the growth of extracellular micro-organisms. TNFα activates RIP kinases to form necrosome. Interferon gamma belongs to TH1 immune response, which is different from TH22/TH17 immunity, and it can down-regulate necroptosis. Type 3 innate lymphoid cells, which can help to trigger TH22/TH17 immunity, is associated with necroptosis[60]. Necroptosis can also stimulate TH22/TH17 related pro-inflammatory cytokines secretion. A research found that TGFβ–activated kinase 1 binding protein 2 (TAB2) deficiency causes dilated cardiomyopathy by enhancing RIPK1-dependent apoptosis and necroptosis[61]. TGFβ is the mediator of tolerable immunological pathways. Thus, eradicable immune mechanism like apoptosis or necroptosis can be enhanced without TGFβ signaling. Another study pointed out TGFβ-activated kinase 1 (TAK1) serves as a key survival factor in cardiac organs by directly antagonizing necroptosis[20].

TH17 immune response and its relation to NETosis

TH17 host immune reaction is the tolerable immune response against extracellular bacteria, fungi, or protozoa. Neutrophils play dominant roles in the TH17 tolerable immune response. In this situation, neutrophils cannot successfully kill and eradicate these extracellular micro-organisms. Thus, these neutrophils sacrifice themselves to stop the progression of these extracellular micro-organisms. These PMNs have condensed DNA contents in their cell nucleus, and they trigger the NETosis cell programmed death pathway. Then, these extracellular micro-organisms can be entrapped in the NET, and other alive neutrophils will go to digest these extracellular bacteria, protozoa, or fungi. Neutrophil extracellular traps can also induce TH17 immune cells[62]. The tolerable antibody IgA is found to activate NETosis. NETosis is also found to be correlated to chronic inflammation and to delay wound healing[63]. TH17 immune reaction related IgA immune complex formation is also associated with NETosis via the activation of Fcα receptor[64,65]. IgA vasculitis is also reported to be associated with neutrophil extracellular traps[66]. The central cytokine of TH17 immune response, interleukin-17, can also induce NETosis[67]. Neutrophils can release IL-17 through extracellular trap formation during psoriasis[68]. IL- 17A is expressed on neutrophil extracellular traps in ankylosing spondylitis[69]. TH22/TH17 key cytokine TNF signaling can induce NETosis of CCR5+ neutrophils[70]. Thus, TH17 host tolerable immunological pathway is associated with NETosis. TAK1 is also required for neutrophil extracellular trap formation[71]. This pointed out the significance of TGFβ in NETosis. TGFβ itself can also induce neutrophil extracellular traps[72]. Neutrophil extracellular traps can also directly trigger epithelial and endothelial cell death[73].

Conclusion

Programmed cell death pathways are related to different host immunological pathways. Apoptosis is related to host anti-virus eradicable TH$\alpha\beta$ immunity. Autophagic death is related to host anti-virus tolerable TH3 immunity. Pyroptosis is related to host anti-intracellular micro-organism eradicable TH1 immunity. Ferroptosis is related to host anti-intracellular micro-organism tolerable TH1-like immunity. Necroptosis is related to host anti-extracellular micro-organism eradicable TH22 immunity. NETosis is related to host anti-extracellular micro-organism tolerable TH17 immunity. These relations can help us to understand host defense mechanism against invading pathogens and

provide a new insight to develop better therapeutic strategies against infections or autoimmune disorders.

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