Role of Neutrophils on the Ocular Surface

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Contributor: Young Joo Shin

Neutrophils are considered short-term and terminally differentiated phagocytes with no significant gene expression or regulatory role in adaptive immunity. However, in recent years, opinions on the role of neutrophils have been developing. Neutrophils are primarily short-term polymorphonuclear cells (PMNs) related with the first line combatant to pathogens, which can phagocytose potentially harmful antigens and trigger strong antimicrobial defenses, including the release of reactive oxygen species (ROS) such as superoxide and neutrophil extracellular traps.

Keywords: ocular surface disease ; dry eye syndrome ; neutrophil ; neutrophil extracellular trap

1. Introduction

The ocular surface of the eyeball is the part of the eye in contact with the outside world, serving as a primary barrier against external substances and pathogens [1]. The cornea is a transparent tissue that refracts light entering the eye, focusing it on the retina and acting as a barrier against the outside [2]. The conjunctiva is a mucous membrane that attaches to the cornea and becomes the surface surrounding the eyeball [3]. It forms a conjunctival sac surrounding the inner eyelid and connecting to the eyelid [2]. In addition, the conjunctiva is connected to the nasal mucosa and supplied with tears from the lacrimal gland through the lacrimal duct [2]. The mucous membrane of the conjunctiva has many blood vessels and produces a large amount of mucus from goblet cells [3]. The subconjunctival tissue contains many lymphoid tissues and the immune system [3]. The ocular surface immune system can be divided into innate and adaptive immune systems [4]. The innate immune system includes basophils, dendritic cells, eosinophils, Langerhans cells, mast cells, monocytes and macrophages, neutrophils, and natural killer cells, whereas the adaptive immune system includes T and B lymphocytes [5].

Neutrophils are members of the innate immune system and are at the forefront against infection, but they are involved in adaptive immunity through interactions with T and B cells [6]. They have been reported to play an essential role in autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and anti-neutrophil cytoplasmic antibodies-associated vasculitis (AAV) [7]. Although the ocular surface is in contact with external pathogens, both innate and adaptive immunity are involved in the pathogenesis of dry eye syndrome, characterized by tear instability and inflammation of the ocular surface [8]. Therefore, the role of neutrophils in the ocular surface is discussed in this article.

2. Neutrophils in Immunity

Neutrophil extracellular traps have been described as one of the ways in which neutrophils remove microbes [9][10]. Neutrophils release a chromatin network adorned with granular-derived antibacterial peptides and active enzymes, including cathepsin G, MPO, and neutrophil elastase [11]. Neutrophil extracellular trap formation, known as NETosis, was initially reported as an extracellular antibacterial form resisting microbe. However, recently it has been reported that neutrophil extracellular trap formation is involved in autoimmune/rheumatic and auto-inflammatory disease states beyond microbial death [12]. Neutrophil extracellular traps are released after infection with Gram (+) and (-) bacteria, especially by large-sized microbes [13]. Neutrophils generally kill small microbes through phagocytosis, but larger microbes that are not easily digested release cytoplasmic granules and promote nuclear translocation of neutrophil elastases to form neutrophil extracellular traps [9]. In addition, neutrophil extracellular trap formation is induced by nitric oxide, autoantibodies, cytokines such as interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α, hydrogen peroxide, lipopolysaccharides, phorbol-12-myristate-13-acetate, ionophores for calcium ion, and the interaction with activated platelets or vascular endothelial cells [14][15].

The three main signaling pathways of neutrophil extracellular trap formation have been discussed. First, after phorbol-12-myristate-13-acetate stimulates neutrophils through the protein kinase C (PKC) and Raf-mitogen-activated protein kinase (MEK) extracellular signal-regulated kinase signaling pathways, it induces the activation of nicotinamide adenine dinucleotide phosphate oxidase 2, triggering the associated signaling cascade and neutrophil extracellular trap formation

through the production of ROS [12][16]. ROS formation promotes the migration of two key enzymes, MPO and neutrophil elastase, stored in the neutrophil granules, to the nucleus and induces chromatin decondensation, leading to the release of nuclear neutrophil extracellular traps [12]. Hydrogen peroxide is converted to hypochlorous acid by MPO, which activates neutrophil elastase to break down the cytoskeleton and nuclear membrane, allowing neutrophil extracellular trap excretion [17]. Second, the increase in intracellular calcium levels activates the peptidylarginine deiminase 4 (PAD4) enzyme, which moves to the nucleus, leading to histone citrullination and chromatin decondensation [18]. This mechanism is independent of nicotinamide adenine dinucleotide phosphate oxidase 2 [19]. Third, another form of neutrophil extracellular trap formation is the mitoNET formation [20]. Mitochondria are degraded and release the oxidized mitochondrial DNA into the extracellular space by mitochondrial ROS production or the stimulation of toll-like receptor 4 or complement factor 5a receptor [20][21]. Neutrophil extracellular trap formation induced by nitric oxide and phorbol myristate acetate induces both nuclear and mitochondrial neutrophil extracellular trap formation [15].

Neutrophil extracellular trap is thought to be enrolled in the onset of autoimmune and autoinflammatory diseases [22]. Autoantibodies to neutrophil extracellular trap components, including the citrullinated histones with DNA, MPO-DNA complexes, and neutrophil elastase-DNA complexes, are common in several systemic autoimmune diseases [23]. Defects in the process of neutrophil extracellular trap formation, excessive neutrophil extracellular trap formation, and delayed neutrophil extracellular trap formation clearance are all associated with autoimmunity [23]. Neutrophil extracellular traps have been suggested to play a pivotal role in various autoimmune diseases, including systemic lupus erythematosus, vasculitis, rheumatoid arthritis, and chronic inflammatory bowel diseases such as Crohn's disease and ulcerative colitis [24][25][26][27]. Circulating and synovial neutrophils in patients with rheumatoid arthritis are more prone to forming neutrophil extracellular traps than in healthy controls [28][29]. Neutrophil extracellular trap formation is a source of autoantibody and stimulates inflammatory responses in rheumatoid arthritis [29]. In rheumatoid arthritis, anti-citrullinated protein antibodies are formed, associated with neutrophil extracellular trap formation and neutrophil count [30]. Neutrophil extracellular trap formation can also be provoked by neutrophil binding of anti-neutrophil cytoplasmic antibodies and anti-ribonuclear protein (RNP) antibodies [31]. As an extracellular bactericidal mechanism used by neutrophils, neutrophil extracellular traps go through steps that include ROS production, PAD4 activation, granule formation, chromatin decondensation, and active release of DNA/histone/cathelicidin antimicrobial peptide cocktail into the extracellular space [19].

Peptidyl-arginine deiminase 2 (PAD2) and PAD4 are the posttranslational modification enzymes converting protein arginine or mono-methylarginine to citrulline [32]. PAD2 and PAD4 are implicated in the pathogenesis of several autoimmune diseases [33]. Histone citrullination by PAD2 and PAD4 is essential for neutrophil extracellular trap formation [23][34][35]. Hypercitrullination in synovial fluid and anti-citrullinated protein antibodies in plasma are found in rheumatoid arthritis [36], suggesting that the hypercitrullinated molecules may serve as autoantigen. PAD2 and PAD4 are potential biomarkers and therapeutic targets of sepsis [37]. PAD4 inhibitor block neutrophil extracellular trap formation [38], reducing bleomycin fibrosis [39][40]. Simultaneous inhibition of PAD2 and PAD4 ameliorates neutrophil extracellular trap formation and reduces inflammatory cytokine production [41].

3. Endoplasmic Reticulum Stress in Neutrophils

Endoplasmic reticulum stress is involved in the pathogenesis of many diseases such as dry eye, rheumatoid arthritis, diabetes, dementia, and cancers [42][43][44][45]. It is linked to cellular dysfunction, inflammation, oxidative stress, apoptosis, and autophagy. Mitochondrial activity and endoplasmic reticulum stress are required for neutrophil differentiation [46]. Endoplasmic reticulum stress reduces during both neutrophil and macrophage differentiations, and the activities of protein kinase R-like endoplasmic reticulum kinase and activating transcription factor 6 were decreased, and that of inositol-requiring enzyme 1-α is enhanced during neutrophil differentiation [46]. The role of endoplasmic reticulum stress of neutrophils was investigated in acute lung injury [47]. Elevated endoplasmic reticulum stress levels were observed in infiltrated neutrophils in the acute lung injury mice model [47]. Sensors for endoplasmic reticulum stress, including protein kinase R-like endoplasmic reticulum kinase, activating transcription factor 6, and inositol-requiring kinase 1, were enhanced in neutrophil in acute lung injury [47]. Suppression of endoplasmic reticulum stress inhibited the inflammation [47]. Inositol-requiring enzyme 1-α is a crucial regulator of neutrophil extracellular traps through ROS generation and caspase-2 activation [48]. Endoplasmic reticulum calcium level is increased in the neutrophils in cystic fibrosis in response to endoplasmic reticulum stress response, which exaggerates the inflammation [49]. Tunicamycin-induced endoplasmic reticulum stress signaling (protein kinase R-like endoplasmic reticulum kinase/activating transcription factor 4 /CCAAT-enhancer-binding protein homologous protein signaling) aggravates airway inflammation via elevation of inflammatory cytokines (IL-6, IL-8, and TNF-α) in a murine model of neutrophilic asthma [50]. Endoplasmic reticulum stress/X-box-binding protein 1 enhances mucin secretion through the influence of neutrophil elastase [51]. Neutrophil induces apoptosis in cancer cells through an endoplasmic reticulum stress pathway [52].

4. Neutrophils in Aging

Neutrophil extracellular traps remove the old vessels to promote remodeling [53]. However, aging drives neutrophils to be pathogenic, contributing to vascular diseases [54][55]. The intestinal microtome regulates neutrophil aging by enhancing C-X-C motif chemokine receptor 4 and reducing L-selectin [56]. Interaction between neutrophils and the microbiome contributes to the maturation of the immune system and the pathogenesis of immune-mediated diseases and cardiovascular diseases [57][58]. Aged neutrophils are characterized by altered expression of surface molecules such as lymphocyte function-associated antigen-1, macrophage-1 antigen, toll-like receptor-4, platelet endothelial cell adhesion molecule-1, and higher oxidative stress levels [59]. In addition, neutrophil extracellular traps are more prone to be formed in aged neutrophils [59]. Neutrophil extracellular traps accumulation compromises organ functions and impairs revascularization and vascular repair after ischemic injuries [60]. Delayed clearance of neutrophil extracellular traps facilitates autoimmune reactivity [61].

Neutrophil aging induces chronic inflammation of vessels, affecting lacrimal glands and ocular surfaces. Since neutrophil extracellular trap formation is also easily activated on the ocular surface in the elderly, it may be one of the pathogenic mechanisms of dry eyes in elderly patients.

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