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Review

Neutrophil's weapons in atherosclerosis

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ABSTRACT

Neutrophils are important components of immunity associated with inflammatory responses against a broad spectrum of pathogens. These cells could be rapidly activated by proinflammatory stimuli and migrate to the inflamed and infected sites where they release a variety of cytotoxic molecules with antimicrobial activity. Neutrophil antibacterial factors include extracellular proteases, redox enzymes, antimicrobial peptides, and small bioactive molecules. In resting neutrophils, these factors are stored in granules and released upon activation during degranulation. These factors could be also secreted in a neutrophil-derived microparticle-dependent fashion. Neutrophils exhibit a unique property to produce neutrophil extracellular traps (NETs) composed of decondensed chromatin and granular proteins to catch and kill bacteria. Neutrophil-released factors are efficient in inactivation and elimination of pathogens through oxidation-dependent or independent damage of bacterial cells, inactivation and neutralization of virulence factors and other mechanisms. However, in chronic atherosclerosis-associated inflammation, protective function of neutrophils could be impaired and misdirected against own cells. This could lead to deleterious effects and progressive vascular injury. In atherogenesis, a pathogenic role of neutrophils could be especially seen in early stages associated with endothelial dysfunction and induction of vascular inflammation and in late atherosclerosis associated with plaque rupture and atherothrombosis. Assuming a prominent impact of neutrophils in cardiovascular pathology, developing therapeutic strategies targeting neutrophil-specific antigens could have a promising clinical potential.

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Contents

1. Introduction

Along with basophils and eosinophils, neutrophils constitute a family of polymorphonuclear leukocytes (Nathan 2006). Usually, neutrophils have a nucleus divided into 2–5 segments and multiple cytoplasmic granules. In contrast to basophils and eosinophils, after staining with

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hematoxylin, neutrophils remain neutral pink. Neutrophils are the most frequent cells among leukocytes accounting up to 75% of a total population of white blood cells (Witko-Sarsat et al., 2000). Neutrophils are highly produced by the bone marrow at average rate of 10^{11} per day. Indeed, between 55 and 65% of a hematopoietic potential of the bone marrow falls to the neutrophil generation (Edwards et al., 2005). In infection, production rate of neutrophils could rise by 10-fold (Mayadas et al., 2014).

Because neutrophils contain in granules and release upon activation of highly cytotoxic substances, their lifespan is relatively short (8–12 h in the blood and 1–2 days in tissues) (Dancey et al., 1976). These cells are very mobile and quickly respond to invasion of a broad variety of pathogens including bacteria, fungi, and protozoan parasites. Neutrophils phagocytize bacteria. From granules, neutrophils release a variety of extracellular proteases and antimicrobial factors that kill phagocytized pathogens. In addition, activated neutrophils produce large amounts of reactive oxygen species (ROS) that are released to the phagocytosome and help to inactivate engulfed microbes (Dupré-Crochet et al., 2013). However, protective activity of neutrophils is not only limited with phagocytizing and killing infectious microorganisms. Recent studies showed that a role of neutrophils in immunity is more complex since these cells were shown to communicate with other leukocytes such as dendritic cells (DCs), macrophages, natural killer (NK) cells, T cells, and B cells through cell–cell interactions and secreting soluble factors (Kolaczkowska and Kubes 2013).

Neutrophils are characterized by specific cell death properties called NETosis that is distinct from apoptosis and necrosis. Neutrophil extracellular traps (NETs) contain decondensed chromation associated with granular components (Brinkmann et al., 2004). NETs are ejected out from the neutrophil when the plasma membrane is disintegrated (Fuchs et al., 2007). NETs are able to catch pathogens within the sticky chromatin network and efficiently destroy them by high concentrations of proteases and antimicrobial peptides such as cathelicidin, α-defensins, and human neutrophil peptide 3 (HNP3) accumulated in the chromatin (Papayannopoulos and Zychlinsky 2009). Although NETosis usually leads to the death of neutrophils, some anucleated neutrophils remain able to move and kill bacteria through phagocytosis and degranulation (Yipp et al., 2012). Indeed, NETosis is a neutrophil-specific mechanism that is straightforward against infections and allows effective elimination of pathogens even after neutrophil end point. NETs could not be cleared by macrophages and are mainly degraded by exonucleases (Fuchs et al., 2007).

In many autoimmune, allergic, and inflammatory diseases, the neutrophil function could be severely compromised. In rheumatoid arthritis, inflammatory bowel disease, and other proinflammatory conditions, neutrophils account for a substantial portion of the inflammatory infiltrate. The rate of neutrophil infiltration correlated with the severity of disease (Sandborn et al., 2002; Pimentel et al., 2011). Due to the high reactivity and a rich repertoire of cytotoxic agents, neutrophils could damage host tissues and promote acute inflammation (Katano et al., 2009). The role of neutrophils in acute inflammatory response and anti-pathogenic immunity is well characterized (Mócsai 2013; Mayadas et al., 2014; Huttenlocher and Smith 2015). However, in chronic low-grade inflammation that is present in atherosclerotic disease, the role of neutrophils is frequently different from their role in pathologies accompanied with severe inflammation. Until recently, the potential involvement of neutrophils was disregarded in this pathology because they were not observed in atherosclerotic plaques. Recently only, neutrophils were observed in initial and advanced (especially vulnerable) plaques (van Leeuwen et al., 2008; Ionita et al., 2010; Rotzius et al., 2010). In atherosclerosis-associated inflammation, neutrophils play a complex and non-redundant role, which is not only restricted by the activity of neutrophils themselves but also involves their interaction with immune and non-immune cells.

As mentioned, neutrophils are heavily armored with various molecular weapons that are effectively used in the antimicrobial host defense. In normal conditions, the powerful cytotoxic and prooxidant arsenal of neutrophils is tightly regulated. However, in chronic inflammatory conditions such as atherosclerosis, this control is often deregulated leading to progressing tissue damage and oxidative stress. In this review, we will consider the input of neutrophil-derived bioactive substances to atherogenesis.

2. Antimicrobial arsenal of neutrophils and its role in atherosclerosis

In atherosclerosis, neutrophils release a variety of active substances that they normally use for eliminating infectious agents. Those include factors stored in neutrophil granules, ROS, NETs, and the content of neutrophil-derived microparticles (NMPs). Due to their high reactivity and cytotoxicity, neutrophil-derived substances actively contribute to the destruction and irreversible modification of the vascular wall components.

2.1. Neutrophil granules and their components

Neutrophils contain three types of cytosolic granules containing various enzymes and antimicrobial factors (Table 1). Azurophilic (primary) granules after staining by Romanowsky–Giemsa stain with Azure A and Azure B dyes become blue- and purple-colored due to the acidic content. Neutrophil granules contain three types of active components: extracellular proteases, redox enzymes, and antimicrobial peptides. Overall, releasing these factors upon neutrophil activation induces a powerful antimicrobial response capable to neutralize, inactivate, and kill a broad variety of pathogens (Borregaard 2010). Neutrophil-derived proteases are involved in proteolytic inactivation of bacterial virulence factors (Weinrauch et al., 2002; López-Boado et al., 2004), activation of immunoregulatory and growth factors, and processing of antimicrobial peptides (Cole et al., 2001). By degrading extracellular matrix (ECM) proteins of the basement membrane, neutrophil proteases facilitate entrance of neutrophils and other leukocytes to inflamed sites in extravascular tissues (Wang et al., 2005; Young et al., 2007). These enzymes are also involved in tissue remodeling in sites of inflammation.

However, in atherosclerosis, overproduction of neutrophil-derived proteases displays proatherogenic effects. In cell in vitro model of human neointima, neutrophils cocultured with endothelial cells (ECs) and smooth muscle cells (SMCs) underwent transendothelial migration driven by SMC-produced interleukin-8 (IL-8). Neutrophil infiltration was accompanied with increased release of elastase and matrix metalloproteinase-8 (MMP-8 or collagenase) and EC apoptosis (Dorweiler et al., 2008). In initial atherosclerotic stages, neutrophil proteases such cathepsin G and neutrophil elastase could stimulate neutrophil/monocyte adhesion to ECs and subendothelial infiltration (Woodman et al., 1993; Soehnlein et al., 2012) associated with propagation of arterial wall inflammation. Implementation of protease inhibitors reduced transmigration and proinflammatory properties of neutrophils (Woodman et al., 1993; Dunlevy et al., 2012). In neutrophil elastase-deficient mice, firm adhesion and transendothelial trafficking of leukocytes was inhibited and levels of inflammatory mediators in the circulation were reduced suggesting for a positive role of this enzyme in promoting mechanisms of leukocyte recruitment and migration (Young et al., 2004).

Leukotriene B4 (LTB4) produced by neutrophils and other leukocytes in response to inflammatory signals was found to efficiently increase surface expression of neutrophil elastase on neutrophils (Young et al., 2007). Neutrophil elastase cooperates with platelet/endothelial-cell adhesion molecule 1 (PECAM-1, CD31) and integrin α_6 in mediating neutrophil trafficking (Wang et al., 2005).

In advanced plaques, neutrophil proteases were shown to be involved in the degradation of proangiogenic factors such as angiopoietin-1, vascular endothelial growth factor (VEGF), and placental growth factor (PGF) (Le Dall et al., 2010). Indeed, this leads to the immaturity of intraplaque neovessels associated with microvascular leakage and lesional

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