Neutrophil

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Neutrophils represent about 50–70% of all white blood cells in the human circulation and are widely recognized as the first line of defense in infectious disease. However, neutrophils also have a clear modulatory role in human diseases such as cancer, respiratory disease, and autoimmunity. Infections and/or any inflammatory signals trigger a rapid influx of neutrophils from the peripheral blood to the inflammatory site, where they can utilize a broad variety of effector functions to. Neutrophils are well known phagocytic cells, engulfing microorganisms or in case of bigger targets, such as cancer cells, taking “bites” of the membrane in a process called ‘trogocytosis’. Moreover, neutrophils are armed with granules that are loaded with proteases and inflammatory mediators that are released upon activation. In addition, during a so called ‘oxidative burst’ neutrophils release high levels of reactive oxygen species (ROS), which can trigger cell death of the target cell. Finally, neutrophils can entrap foreign materials in so called ‘neutrophil extracellular traps’ (NETs), which are mainly composed of neutrophil DNA and Granular contents. The effector functions of neutrophils can be triggered by antibodies that activate neutrophils by binding to Fc-receptors (FcRs), leading to antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Although neutrophils are mainly involved in innate immunity, neutrophils contribute to adaptive immune responses.

Keywords: neutrophil ; immunity ; cancer ; Fc receptor ; antibody ; phagocytosis ; trogocytosis

1. Introduction

Neutrophils are the most prevalent cell population of the circulating leukocyte fraction of humans, with ~100 billion neutrophils being produced in the bone marrow each day [1][2]. Neutrophils belong to the polymorphonuclear cell family that also comprises basophils and eosinophils, have an average diameter of 9-15 micrometers (μm) [3], and are morphologically defined by their multilobed nucleus and highly developed intracytoplasmic granules. The lifespan of neutrophils is relatively short and has been reported to range from one day up to 5.4 days without immunologic challenge [4]. In homeostasis, the majority of neutrophils are surveilling cells that circulate through the body in resting state.

Neutrophils express a large number of pattern recognition receptors by which they recognize pathogens, such as fungi and extracellular bacteria, and can react to tissue inflammation [5][6]. Furthermore, neutrophils express various Fc receptors (FcRs) that bind antibodies leading to either the activation or inhibition of neutrophil effector functions [as reviewed by [7]]. In brief, neutrophils express the activatory immunoglobulin G (IgG)-binding FcRs CD64, CD32a and CD16a as well as the IgA-binding FcR CD89. In addition, neutrophils express the inhibitory IgG-binding FcRs CD32b and CD16b, which serve to inhibit neutrophil effector functions. Neutrophils most efficiently recognize their targets when opsonized by complement or antibodies [8]. In case of antibodies, the binding to activating FcRs will lead to antibody-dependent cellular phagocytosis (ADCP) or antibody-dependent cellular cytotoxicity (ADCC). During ADCP, the pathogen, target cell or cell debris is engulfed and subsequently eliminated; a process determined among others by particle shape, size, and deformability [9]. Notably, when the target cell is too big the neutrophil cannot completely engulf it and will take bites of the membrane instead. This process is termed ‘trogocytosis’ and can eventually lead to killing of the target cell by disruption of the cell membrane, a process termed ‘trogoptosis’ [10]. In case of ADCC, direct cytotoxicity is induced by releasing high amounts of reactive oxygen species (ROS) and/or by the release of neutrophils granule content that is comprised of proteases and inflammatory mediators [11].

2. Functions of Neutrophils

Although neutrophils were initially classified as ‘simple’ innate immune cells important for the immediate elimination of pathogens, accumulating evidence indicates that neutrophils can also be involved in the activation of adaptive immune responses. Especially in the field of virology there is evidence that neutrophils are critical players in the development of both humoral and T cell-mediated immunity against viral infections during antibody treatment and vaccination [12]. Furthermore, neutrophils are able to trigger anticancer immune responses by presenting antigens to T cells in the context

of the Major Histocompatibility Complex (MHC), leading to the proliferation and activation of cancer cell-reactive T cells [13]. Further, neutrophils and T cells interaction can upregulate co-stimulatory molecules (i.e. 4-1BBL, OX40L, CD54, CD86) on the neutrophil surface, whereby T cell proliferation and activation can be stimulated [14]. In addition, neutrophils can modulate the activity of other antigen presenting cells, such as dendritic cells, as initially demonstrated in the context of infections and Crohn's disease [15].

Thus, neutrophils are important players in first line of defense during pathogenic infections as well as in tissue inflammation. Furthermore, they have a modulatory role (both positive and negative) during human disease like cancer, respiratory disease, chronic autoimmune and inflammatory diseases, and may therefore by targeted for therapy. In the case of cancer, research has been predominantly focused on the tumor promoting role of neutrophils in the tumor micro-environment [as reviewed by [16]]. On the other hand, human neutrophils also have clear antitumor activity [as reviewed by [7]] with neutrophils from healthy human donors displaying intrinsic anticancer activity toward cancer cell lines. Furthermore, depletion of neutrophils abrogated the efficacy of antibody therapy in mice and resulted in increased tumor burden [17]. Therefore, neutrophils may also be targeted and exploited for cancer therapy. However, to date the vast majority of currently used therapeutic antibodies are of the IgG isotype, which efficiently activates monocytes and natural killer cells but does not optimally trigger neutrophil-mediated immune responses. Hereto, antibody strategies utilizing the IgA isotype are being developed in order to better trigger neutrophil cytotoxicity [18].

In conclusion, the neutrophil is an important first line of defense of the immune system and represents an underexplored target for design of immunotherapy in cancer that can not only activate innate but also aid the development of adaptive immune responses.

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