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Fluid phase recognition molecules in neutrophil-dependent immune responses

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ABSTRACT

The innate immune system comprises both a cellular and a humoral arm. Neutrophils are key effector cells of the immune and inflammatory responses and have emerged as a major source of humoral pattern recognition molecules (PRMs). These molecules, which include collectins, ficolins, and pentraxins, are specialised in the discrimination of self versus non-self and modified-self and share basic multifunctional properties including recognition and opsonisation of pathogens and apoptotic cells, activation and regulation of the complement cascade and tuning of inflammation. Neutrophils act as a reservoir of ready-made soluble PRMs, such as the long pentraxin PTX3, the peptidoglycan recognition protein PGRP-S, properdin and M-ficolin, which are stored in neutrophil granules and are involved in neutrophil effector functions. In addition, other soluble PRMs, such as members of the collectin family, are not expressed in neutrophils but can modulate neutrophil-dependent immune responses. Therefore, soluble PRMs are an essential part of the innate immune response and retain antibody-like effector functions. Here, we will review the expression and general function of soluble PRMs, focusing our attention on molecules involved in neutrophil effector functions.

1. Introduction

The immune system of mammalians is composed by innate and the adaptive arms. The adaptive immune system is more recent in terms of evolution and its activation requires a set of specific receptors encoded by genes undergoing rearrangement. This system provides the basis for the immunological memory. The innate immune system constitutes the first line of defence against infections and is required for a correct activation of the adaptive immune response. The innate immune system, which is composed by a cellular and a humoral arm, uses a set of germline-encoded molecules involved in the discrimination of self versus non-self and modified-self [1,2].

The innate immunity receptors have been called pattern recognition molecules (PRMs) since they recognize motifs expressed by microorganisms and called pathogen associated molecular patterns (PAMP). In addition, PRMs can recognize a set of motifs expressed by dying cells (i.e. apoptotic cell-associated motifs (ACAMP)) and a set of alarmins, such as endogenous molecules released by necrotic cells (e.g. HMGB1) [3]. Based on their localisation, PRMs have been divided between cell-associated PRMs and soluble PRMs (Fig. 1). Cell-associated PRMs include endocytic receptors, such as scavenger receptors, and signalling receptors, which can be both membrane-associated (e.g. Toll like receptors (TLRs)) or cytoplasmic molecules (e.g. RNA helicases, such as melanoma differentiation-associated gene 5 (MDA5) and retinoic acid-inducible gene I (RIG-I), and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs)) (Fig. 1) [3]. Fluid phase PRMs are heterogeneous in terms of structure, expression and specificity and include collectins, ficolins and pentraxins [1]. These

Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; C4BP, C4b-binding protein; CL, collectin; CRD, C-terminal carbohydrate recognition domain; CRP, C-reactive protein; FHR-5, factor H-related protein 5; LPS, lipopolysaccharide; LTA, lipotechoic acid; MBL, mannose-binding lectin; MDA5, melanoma differentiation-associated gene 5; MPO, myeloperoxidase; NETs, neutrophil extracellular traps; NLR, NOD-like receptors; NOD, nucleotide-binding oligomerization domain; PAMP, pathogen associated molecular patterns; PGLYRP, peptidoglycan recognition proteins; PGRPs, peptidoglycan recognition proteins; PTX3, pentraxin 3; RIG-I, retinoic acid-inducible gene I; SAP, serum amyloid P; SP, surfactant protein; TLRs, Toll like receptors.

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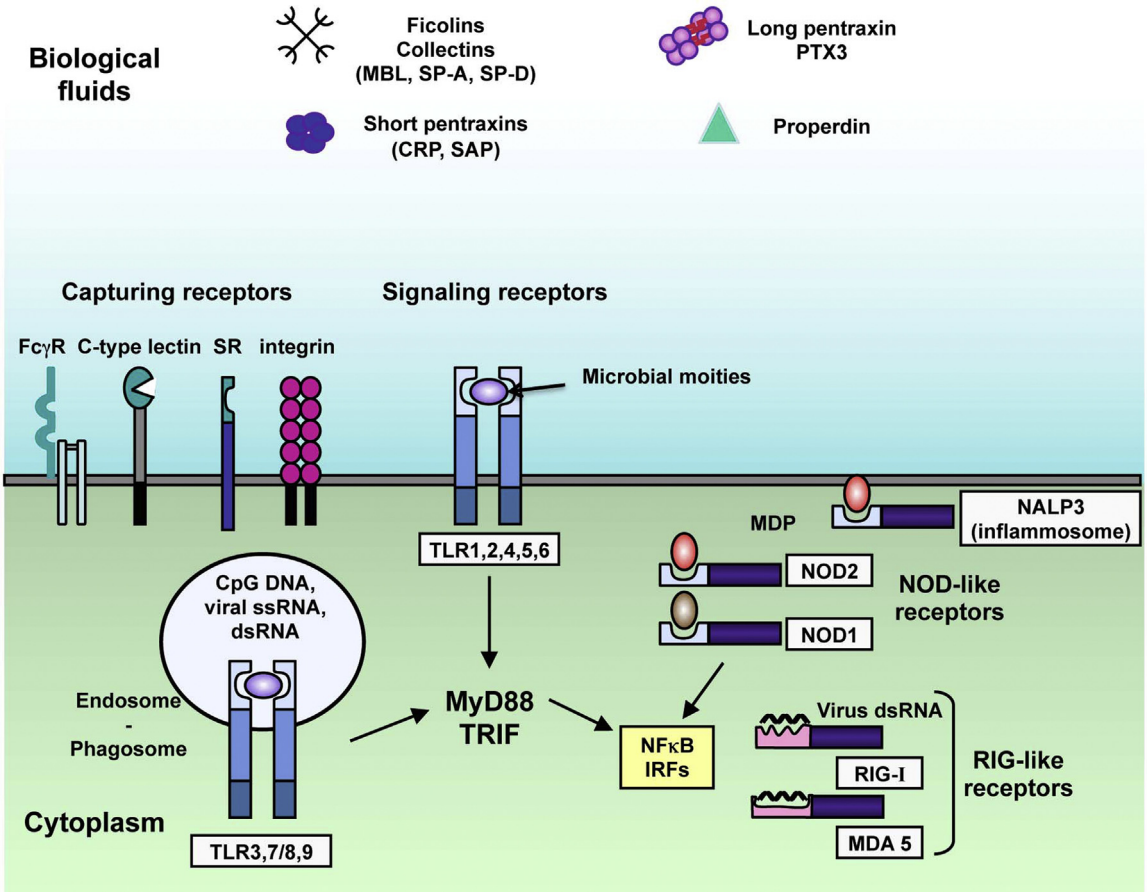

Fig. 1. Cell-associated and soluble pattern recognition molecules.
Cell associated PRMs include endocytic receptors (e.g. scavenger receptors) and signalling receptors (TLRs) and can be found on the plasma membrane (e.g. TLRs, scavenger receptors, lectin receptors), in the cytoplasm (e.g. NOD-like receptors and RIG-like receptors) or in the endosomes (e.g. TLRs). TLRs recognize microbial moieties, RIG-like receptors recognize viral double-stranded RNA and NOD-like receptors recognize muramyl dipeptide (MDP), a subunit of bacterial peptidoglycan also recognized by the component of the inflammasome NALP3. Signalling receptors induce the activation of transcription factors, including NF-κB and IRFs. Soluble PRMs include collectins (MBL, SP-A, SP-D), ficolins, pentraxins (CRP, SAP, PTX3) and properdin.

molecules are essential in the activation, regulation and effector functions of innate and adaptive immunity and are considered functional ancestor of antibodies (Table 1) [1].

Neutrophils are essential innate immune cells and the life-threatening condition of people with neutropenia or with abnormalities in neutrophil functions underlines their role in immunity and defence against pathogens [4,5]. In addition to their involvement during the acute phase of inflammation and to eliminate pathogens, neutrophils can produce cytokines, chemokines and express an important number of both cell-associated and soluble PRMs implicated in the activation and regulation of the innate and adaptive immune responses [4,6–9]. Cell-associated PRMs in neutrophils include receptors on the plasma membrane, in particular all TLRs with the exception of TLRs 3 and 7 and receptors of the C-type lectin family, such as Dectin-1, CLEC2 and CLEC4E, and receptors found in the cytoplasmic compartment, in particular NOD-1, RIG1, MDA5 and the DNA sensor interferon-inducible protein 16 (IFI16) [8,10,11]. All these receptors are involved in the activation and modulation of neutrophil effector functions (e.g. phagocytosis, expression of cytokines and chemokines, production of antimicrobial peptides and reactive oxygen species, and formation of neutrophil extracellular traps (NETs)) [8,11].

Here we will review key soluble PRMs produced by neutrophils, describing their expression, their structures and their roles in immunity, inflammation and neutrophil-dependent responses.

2. Soluble pattern recognition molecules in neutrophils

2.1. Collectins

2.1.1. Structure and expression

Collectins are oligomeric proteins where subunits are composed by three identical polypeptide chains. The degree of multimerization varies among collectins and can significantly affect protein functions [12]. The protomer of each molecule consists of a globular C-terminal carbohydrate recognition domain (CRD) linked to a collagen-like region through an alpha-helical hydrophobic neck region composed by 24–28 amino acids and a N-terminal region composed by 7–28 amino acids [13]. The collagen-like region is composed by n repetitions of the triplet Gly-Xaa-Yaa (Xaa and Yaa are mostly proline or hydroxyproline) and is involved in the stability of the molecule and the formation of triple helices, which is also stabilized by the neck region. Multimerization of the triple polypeptide chains is supported by hydrophobic interactions and stabilized by interchain disulphide bonds [1]. Mannose-binding lectin (MBL) and surfactant protein (SP)-A are formed by octadecamers of six trimeric subunits and have a polarized bouquet-like structure, whereas SP-D, conglutinin and collectin (CL)-46 are formed by dodecamers of four trimeric subunits and have a cruciform-like structure [1,12]. Based on structure and function similarities, the complement component C1q was related to this family.

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