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Review

Pentraxins and Collectins: Friend or Foe during Pathogen Invasion?

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Innate immunity serves as the frontline defence against invading pathogens. Despite decades of research, new insights are constantly challenging our understanding of host-elicited immunity during microbial infections. Recently, two families of humoral innate immune proteins, pentraxins and collectins, have become a major focus of research in the field of innate immunity. Pentraxins and collectins are key players in activating the humoral arm of innate immunity, taking centre stage in immunoregulation and disease modulation. However, increasing evidence suggests that pentraxins and collectins can also mediate pathogenic effects during some infections. Herein, we discuss the protective and pathogenic effects of pentraxins and collectins, as well as their therapeutic significance.

Pentraxins and Collectins: The Humoral Modulators of Innate Immunity

The innate immune system represents the front line of host defence against invading pathogens. Regulation of innate responses is sustained by the bidirectional interaction between cellular and humoral effectors of innate immunity (Figure 1). The humoral arm of innate immunity includes the complement system, as well as pattern-recognition molecules (PRMs) and pattern-recognition receptors (PRRs). Among the PRMs, members of the pentraxin and the collectin superfamilies have been studied intensively in recent years.

Pentraxins belong to an evolutionarily conserved superfamily of proteins, distinguished by the presence of a C-terminal 'pentraxin domain' of 200 amino acids and a conserved 'pentraxin signature' of an eight amino acid-long sequence (HxCxS/TWxS, where x is any amino acid) [1]. This superfamily of proteins can be further classified into short and long pentraxins. Short pentraxins have an architectural structure of five or ten identical protomers arranged into a pentameric radial symmetry [2,3]. Members of the short pentraxins include C-reactive protein (CRP) and serum amyloid P component (SAP), which are acute-phase proteins secreted mainly by hepatocytes in response to proinflammatory cytokine interleukin (IL)-6 and other stimuli [4]. During the acute phase of infection, elevated levels of CRP and SAP lead to consequential activation of the classical complement cascade via interaction with C1q [5], resulting in removal of cell debris [6].

Pentraxin 3 (PTX3) was the first long pentraxin to be described in the early 1990s and is induced by tumour necrosis factor (TNF) and IL-1 [7,8]. PTX3 has a structurally sophisticated octameric architecture, which is composed of two disulphide-linked tetramers giving rise to the asymmetry of the molecule [9]. Inflammation has been reported to induce PTX3 secretion from a broad range of cell types, but predominantly by monocytes, macrophages, and myeloid dendritic cells

Trends

The humoral arm of innate immunity is emerging as an important determinant of host-elicited defence during pathogen invasion. Pentraxins and collectins are two families of acute-phase proteins that have demonstrated immunomodulatory effector function.

Pentraxin 3 (PTX3) is a 'double-edged' sword that has demonstrated host protective roles during several fungal, bacterial, and viral infections. However, emerging evidence of pathogenic properties of PTX3 was observed during arthritogenic alphavirus infections.

Collectins and ficolins can interact with PTX3 to form heterocomplexes that may possibly affect alphavirus disease progression.

PTX3 and collectins represent promising therapeutic targets for the treatment of several pathogen infections. However, such treatment should be avoided in subjects with pre-exisiting alphavirus infection.

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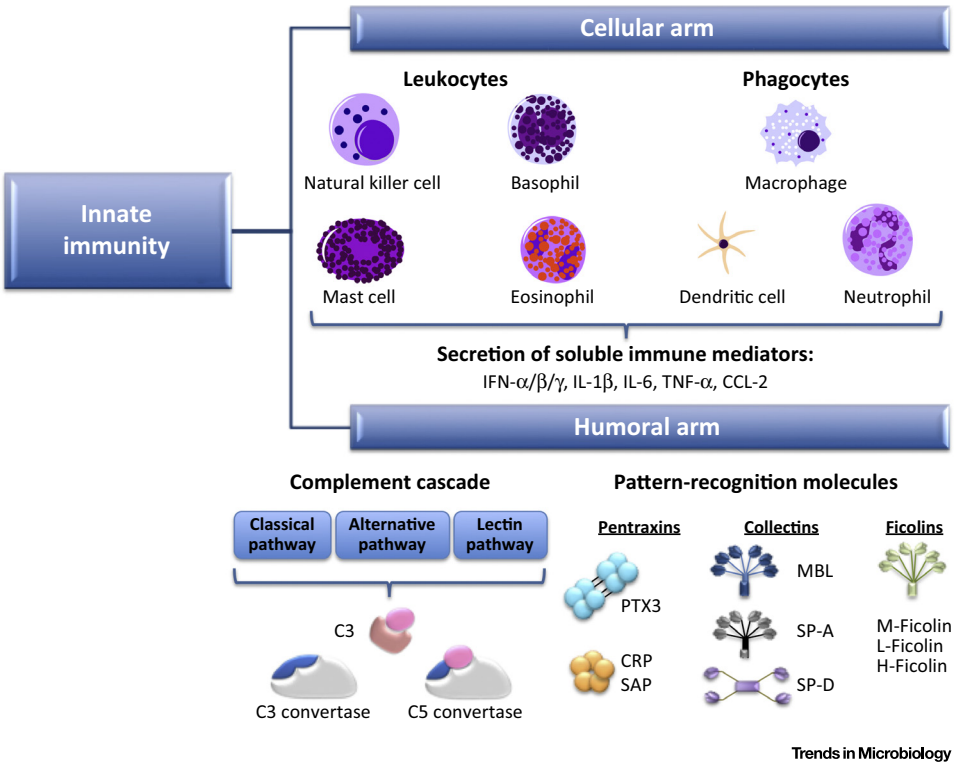

Figure 1. The Two Arms of Innate Immunity: Cellular and Humoral Responses. The cellular arm of innate immunity is composed of immune cells, such as leukocytes and phagocytes, as well as immune mediators secreted by these cells. The humoral arm is composed of the complement cascade and pattern-recognition molecules (PRMs). Crosstalk between the two arms of innate immunity is crucial to respond promptly to stimuli and facilitate adaptive immune response.

(DCs) [10]. Compared to the short pentraxins, our current understanding of PTX3 and its role in the humoral arm is limited, and has therefore been the focus of intensive research to clarify its role in a number of inflammatory and infection diseases.

Collectins are a family of collagenous Ca^{2+}-dependent (C-type) lectins that are highly conserved in evolution and also function as soluble PRMs. C-type lectins contain a collagen-like region linked to a carbohydrate recognition domain (CRD), known as the carbohydrate-binding C-type lectin domain (CTLD), which enables binding to oligosaccharide (or lipid) structures expressed on the surface of an array of microorganisms [11]. Members of this family include the well-characterized 'classical collectins' mannose-binding lectin (MBL), surfactant protein (SP)-A and SP-D. Serum MBL is produced by the liver and is constitutively expressed in the blood at a concentration of ~200 ng/ml during normal circumstances, which can be elevated to as high as ~800 ng/ml during virus infections [12,13]. MBL plays a crucial role in the activation of the lectin complement pathway via interactions with MBL-associated serine protease (MASP). In contrast, SP-A and SP-D are predominantly found within the airways where they play a number of roles in modulating inflammation and phospholipid homeostasis [14]. Recently, a growing number of 'novel collectins' have been identified, which include collectin (CL) liver 1 (CL-L1) [15], CL kidney 1 (CL-K1) [16], and CL placenta 1 (CL-P1) [17], as well as the bovine-specific collectins conglutinin [18], CL-43 [19], and CL-46 [20]. As discussed below, recognition by collectins can lead to elimination of microorganisms by a range of mechanisms, including aggregation, opsonization, activation of phagocytosis, inhibition of microbial growth, or complement activation. In addition to microbial recognition, collectins have also been implicated in modulating