Vision Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vision Research

journal homepage: www.elsevier.com/locate/visres

# Diabetic retinopathy and dysregulated innate immunity

Heping Xu *, Mei Chen

*Centre for Experimental Medicine, School of Medicine, Dentistry & Biomedical Science, Queen's University Belfast, UK*

ARTICLE INFO

*Article history:*
Received 22 December 2016
Received in revised form 12 April 2017
Accepted 13 April 2017
Available online xxxx

*Keywords:*
Innate immunity
Diabetic retinopathy
Neutrophils
Macrophages
Complement
Blood retina barrier

ABSTRACT

Diabetic retinopathy (DR) is the progressive degeneration of retinal blood vessels and neurons. Inflammation is known to play an important role in the pathogenesis of DR. During diabetes, metabolic disorder leads to the release of damage-associated molecular patterns (DAMPs) both in the retina and elsewhere in the body. The innate immune system provides the first line of defense against the DAMPs. In the early stages of DR when the blood retinal barrier (BRB) is intact, retinal microglia and the complement system are activated at low levels. This low-level of inflammation (para-inflammation) is believed to be essential to maintain homeostasis and restore functionality. However, prolonged stimulation by DAMPs in the diabetic eye leads to maladaptation of the innate immune system and dysregulated para-inflammation may contribute to DR development. In the advanced stages of DR where immune privilege is comprised, circulating immune cells and serum proteins may infiltrate the retina and participate in retinal chronic inflammation and retinal vascular and neuronal damage. This review discusses how the innate immune system is activated in diabetes and DR. The view also discusses why the protective immune response becomes detrimental in DR.



## 1. Introduction

The immune system consists of innate and adaptive immunity. Innate immunity provides an early, non-specific, first line of defense against almost any substance that threatens the host, whereas adaptive immunity offers pathogen or antigen specific protection. The immune system protects the host from both exogenous pathogens, such as the pathogen-associated molecular patterns (PAMPs) (Newton & Dixit, 2012; Mogensen, 2009) and endogenous danger molecules (known as damage-associated molecular patterns, DAMPs) (Miller et al., 2011) including oxidized or glycated proteins, mis-located proteins/antigens, and intracellular contents (e.g., uric acid, DNA, RNA, etc.) released by necrotic cells. Innate immune cells express various receptors (pattern recognition receptors, PRRs) for recognizing PAMPs and DAMPs (Tang, Kang, Coyne, Zeh, & Lotze, 2012), which induce both rapid defense and more delayed cellular responses. The common PRRs responsible for PAMP/DAMP detection include toll-like receptors (TLRs) Rock, Hardiman, Timans, Kastelein, & Bazan, 1998, C-type lectin receptors (CLR) Richardson & Williams, 2014, receptor for advanced glycation end-products (RAGE) Ramasamy et al., 2005, NOD-like receptors (NLRs), and RIG-like receptors (RLRs) Carneiro, Magalhaes, Tattoli, Philpott, & Travassos, 2008.

During diabetes, insulin-dependent cells may suffer malnutrition; whereas insulin-independent cells may be stressed from the sustained hyperglycemic environment. Metabolic disorder can generate both intracellular (e.g., accumulation of unfolded/misfolded proteins) and extracellular (e.g., advanced glycation end-products, AGE) DAMPs. The intracellular DAMPs may be sensed by the PRRs in the cytosol and induce cell autonomous inflammatory response (Chen & Xu, 2015), whereas the extracellular DAMPs are often detected by cell surface PRRs and induce inflammatory response at tissue level or even systemic inflammation. The physiological role of the immune response is to remove the DAMPs and maintain homeostasis. Compelling evidence suggests that chronic inflammation in diabetes contributes to the pathogenesis of various complications, including diabetic retinopathy (DR). This review discusses how the hyperglycemic condition affects the innate immune system and explores why the protective innate immune response becomes detrimental in diabetic complications such as DR.

## 2. The effect of diabetes on the innate immune system

### 2.1. Dysregulated innate immune cell activation in diabetes

The innate immune cells consist of polymorphonuclear leukocytes (i.e., neutrophils, basophils, mast cells and eosinophils),

* Corresponding author at: Centre for Experimental Medicine, The Wellcome-Wolfson Building, Queen's University Belfast, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland, UK.
*E-mail address:* heping.xu@qub.ac.uk (H. Xu).

http://dx.doi.org/10.1016/j.visres.2017.04.013
0042-6989/

macrophages, natural-killer (NK) cells, and NK T cells. Phagocytosis of pathogens and the release of cytotoxic molecules are two main mechanisms that the innate immune cells use to eliminate pathogens. It is well recognized that infectious diseases are more prevalent in individuals with diabetes (Casqueiro, Casqueiro, & Alves, 2012). This may be attributed to the hyperglycemic environment mediated enhancement of virulence of some pathogens. The dysfunction of the innate immune system, including innate immune cells and the complement system may also contribute to increased infection. Phagocytosis and bactericidal activity of polymorphonuclear cells are reduced in diabetes patients (Cutler, Eke, Arnold, & Van Dyke, 1991; Krause, Brachmann, Losche, Hoffmann, & Gangler, 1992; Lecube, Pachon, Petriz, Hernandez, & Simo, 2011). Neutrophils from diabetes patients have reduced ability to migrate towards pathogens and chemokines (Cutler et al., 1991; Krause et al., 1992).

Despite reduced phagocytosis and bactericidal activity, neutrophils and monocytes from diabetic patient are more active than those from healthy control. For example, increased adhesion molecule expression (Bouma, Lam-Tse, Wierenga-Wolf, Drexhage, & Versnel, 2004; Devaraj, Jialal, Yun, & Bremer, 2011) and proinflammatory cytokine production (Bradshaw et al., 2009; Hatanaka, Monteagudo, Marrocos, & Campa, 2006) has been observed in monocytes and neutrophils from type 1 and type 2 diabetes (T1D and T2D) patients (Hatanaka et al., 2006; Josefsen, Nielsen, Lorentzen, Damsbo, & Buschard, 1994; Wierusz-Wysocka et al., 1987). The increased innate immune cell activation is often associated with diabetic complications. We have shown that circulating CD11b monocytes from diabetic mice are more active and express higher levels of chemokine receptor CCR5 (Serra et al., 2012). They are preferentially trapped in retinal microvasculature and may contribute to diabetic retinal vasculopathy(Serra et al., 2012). Min et al. reported increased $CD45^{+}CD14^{+}$ classical monocytes but decreased $CD16^{+}$ non-classical monocytes in T1D and T2D patients with microvascular or macrovascular complications compared with patients without complications (Min et al., 2012). In addition, increased PRR, such as TLR2 and TLR4 expression has been observed in monocytes from T2D patients (Dasu, Devaraj, Zhao, Hwang, & Jialal, 2008), and is known to be involved in various diabetes-induced complications (Devaraj et al., 2011; Szasz, Wenceslau, Burgess, Nunes, & Webb, 2016), including DR (Wang et al., 2014) (see below). Higher levels of TLR2/TLR4 were also reported in the NOD mice (a model of T1D) and the expression is positively correlated with the transcription factor, nuclear factor kappa B (NF-κB) expression and inflammation (Mohammad et al., 2006). In addition, activation of the NLRs, in particular NLRP3 is known to be involved in obesity and T2D (Wada & Makino, 2016).

The decreased phagocytosis and bactericidal activity and increased TLR expression and proinflammatory cytokine production by monocytes and neutrophils are somewhat controversial, but are typical signs of dysregulated innate immune function in diabetes (Fig. 1). Dysfunction of innate immune cells is believed to be involved in various diabetes related complications. Future study should focus on the underlying mechanism of diabetes mediated neutrophil and macrophage dysfunction.

### 2.2. Dysregulated complement activation in diabetes

The complement system is an important part of the innate immune system, consisting of over 30 proteins that are produced predominately by the liver. In the absence of infection, complement proteins circulate in an inactive form. Upon stimulation, they are cleaved by relevant proteases resulting in amplifying cascades

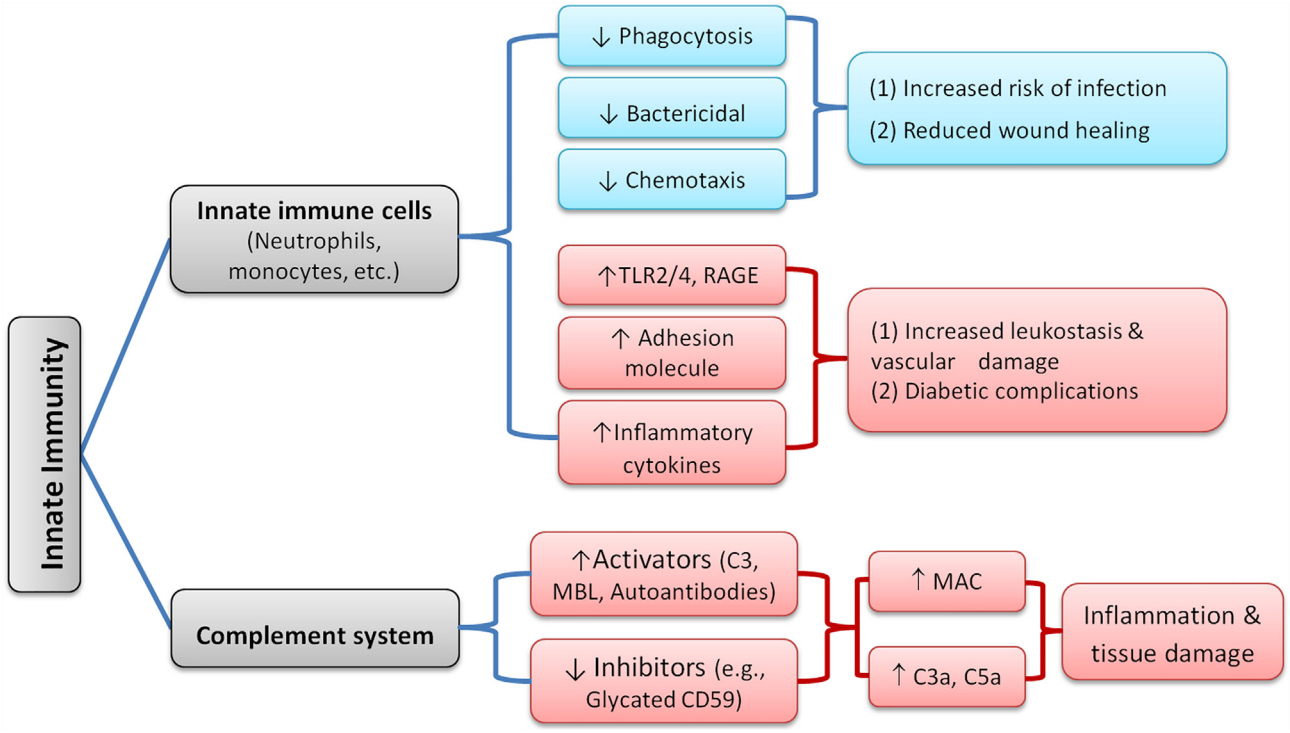


**Fig. 1.** Systemic innate immune dysregulation in diabetes. The innate immune system constitutes innate immune cells and the complement system. During diabetes, hyperglycemia reduces the phagocytosis, bactericidal activity, and chemotaxis of neutrophils and monocytes, leading to increased risk of infection and reduced wound healing. On the other hand, the metabolic intermediates stimulate neutrophil and monocyte activation resulting in inflammatory cytokine production and adhesion molecule expression. Activated neutrophils and macrophages contribute to tissue damage in various diabetes related complications. During diabetes the levels of complement activators, including C3, MBL and autoantibodies are increased, whereas the activity the regulators such as CD59 are reduced by non-enzymatic glycation. Together this leads to increased complement activation, which may also contribute to tissue damage in diabetic complications.

Please cite this article in press as: Xu, H., & Chen, M. Diabetic retinopathy and dysregulated innate immunity. *Vision Research* (2017), http://dx.doi.org/10.1016/j.visres.2017.04.013