Cellular Immunology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Cellular Immunology

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

Research paper

War and peace: Factor VIII and the adaptive immune response

Maria T. Georgescu [a], Jesse D. Lai [a], Christine Hough [a], David Lillicrap [a,b,*]

[a] Department of Pathology and Molecular Medicine, Queen's University, Kingston, Ontario, Canada
[b] Kingston General Hospital, Kingston, Ontario, Canada

ARTICLE INFO

Article history:
Received 28 October 2015
Revised 27 November 2015
Accepted 28 November 2015
Available online xxxx

Keywords:
Hemophilia A
Factor VIII
Inhibitors
Adaptive immune response
B cells
Plasma cells

ABSTRACT

The development of neutralizing anti-factor VIII (FVIII) antibodies (inhibitors) remains a major challenge for FVIII replacement therapy in hemophilia A patients. The adaptive immune response plays a crucial role in the development and maintenance of inhibitors. In this review, we focus on our current understanding of FVIII interactions with cells of the adaptive immune system and the phenotype of the resultant response. Additionally, we examine both current and novel FVIII tolerance induction methods that function at the level of the adaptive immune response.

1. Introduction

Hemophilia A is an X-linked recessive bleeding disorder characterized by quantitative or qualitative defects in factor VIII (FVIII), an essential protein co-factor of the coagulation cascade. The condition is characterized by prolonged provoked bleeding, and in severe cases (<1% normal plasma FVIII levels) spontaneous bleeding into joints and soft tissues. Bleeding symptoms are ameliorated via replacement therapy with either recombinant or plasma-derived FVIII concentrates. The major complication associated with this treatment is the development of neutralizing anti-FVIII antibodies (inhibitors), a phenomenon that occurs in approximately 30% of treated severe hemophilia A patients. By binding to functionally essential regions of FVIII, inhibitors render subsequent FVIII replacement therapy ineffective, leaving patients vulnerable to bleeding symptoms and increasing the risk of morbidity.

By understanding the FVIII immune response one can potentially identify cellular targets to promote tolerance or, in cases where the anti-FVIII immune response has already been established, restore tolerance to the protein. Early events of the FVIII immune response and the protein's interactions with the innate immune system are discussed in another review in this issue. Here, we focus on interactions of FVIII with the adaptive immune system, and its role in the establishment and maintenance of inhibitors. We also introduce current and future FVIII tolerance induction methods targeted at the level of the adaptive immune response (Table 1).

2. FVIII and the cells of the adaptive immune system

2.1. The Primary Immune Response to FVIII

The primary immune response (Fig. 1A) is initiated by antigen uptake via antigen presenting cells (APCs) and subsequent antigen presentation to cognate $CD4^+$ T cells in the presence of an activating, pro-inflammatory microenvironment [1]. This process is reviewed in more detail elsewhere in this issue. In brief, activation of a $CD4^+$ T cell to an effector T cell (Teff) is dependent on antigen presentation by the APC (Signal 1), upregulation of co-stimulatory molecules CD40 and CD80/86 by the APC (Signal 2) and pro-inflammatory cytokine production (Signal 3). Following activation, Teffs migrate from the periarterial sheath to the B cell follicles of the spleen. Naïve B cells that have FVIII-specific B cell receptors (BCRs) will have endocytosed and processed the antigen to present its peptides via major histocompatibility complex (MHC) II. FVIII-presenting B cells will then interact with the TCR of the activated T cell and engage co-stimulatory molecules (CD40L and CD28 on the T cell with CD40 and CD80/86 on the B cell).

In hemophiliacs lacking FVIII production, mechanisms of central tolerance leading to deletion of T and B cell clones with reactivity to FVIII will be absent. Interestingly, these mechanisms appear to be innately incomplete, as there has been evidence of FVIII-reactive T cells and anti-FVIII antibodies even in normal individuals [2,3].

* Corresponding author at: Department of Pathology and Molecular Medicine, Queen's University, 88 Stuart Street, Kingston, ON K7L 2V6, Canada.
E-mail address: david.lillicrap@queensu.ca (D. Lillicrap).

http://dx.doi.org/10.1016/j.cellimm.2015.11.008
0008-8749/

Table 1
Novel methods for FVIII tolerance induction targeted to the adaptive immune response.

	Therapy	Mechanism of action
Anti-T Cell Strategies	Anti-CD3	Prevents formation of activating APC-T cell synapse and increases Treg:Teff ratio [42]
	Rapamycin	Increases Treg:Teff ratio [43]
	Engineered FVIII-specific Tregs	Inhibition of Teff proliferation by antigen-specific Tregs [44]
Anti-B Cell Strategies	Antigenic liposomes with CD22 ligand	B cell suppression via engagement of CD22 [45]
	B cell blasts expressing A2 and C2 IgG fusion proteins	Treg recruitment [46]
Anti-plasma Cell Strategies	Bortezomib	Non-specific eradication of plasma cells [57]

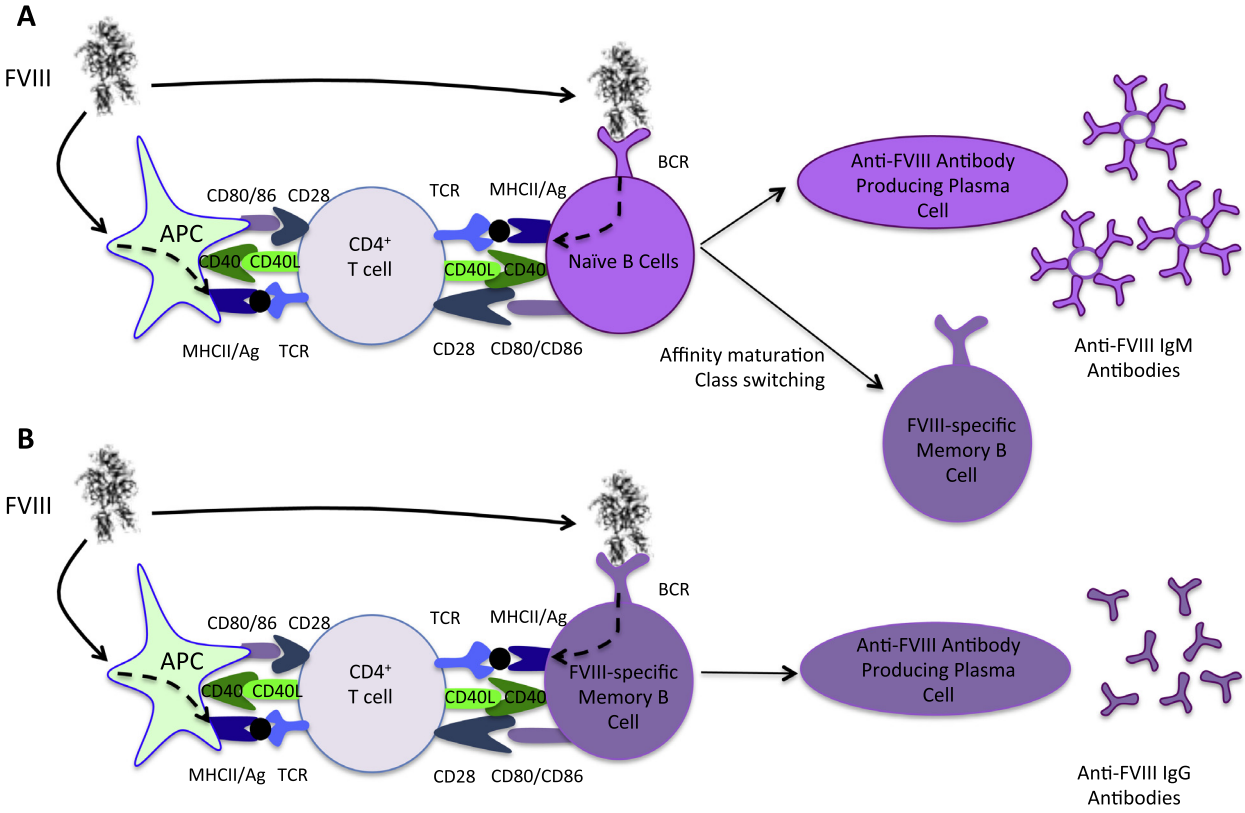

Fig. 1. A. The primary immune response to FVIII. Upon primary exposure to FVIII, APCs will endocytose the antigen and present its peptides to cognate $CD4^+$ T cells. In the presence of an activating, pro-inflammatory microenvironment (upregulation of co-stimulatory molecules CD40 and CD80/86 by the APC, production of pro-inflammatory cytokines) this results in activation of the T cell to Teff. Naïve B cells that have FVIII-specific BCRs will have also endocytosed and processed FVIII to present its peptides via MHCII. FVIII-presenting B cells will then interact with the TCR of the activated T cell and engage co-stimulatory molecules (CD40L and CD28 on the T cell with CD40 and CD80/86 on the B cell). This interaction results in B cell activation, proliferation and differentiation. A proportion of these B cells will terminally differentiate into anti-FVIII IgM antibody producing plasma cells. Others will undergo affinity maturation and class-switching to form FVIII-specific memory B cells. B. The secondary immune response to FVIII. Upon secondary exposure to FVIII, similar events to the ones in the primary immune response will be observed.

It can therefore be expected that hemophilia A patients will have some circulating cognate T and B cells capable of forming B-T cell synapses. This interaction results in B cell activation, proliferation and differentiation. A proportion of these B cells will terminally differentiate into anti-FVIII antibody producing plasma cells, while others will undergo affinity maturation and class-switching to form FVIII-specific memory B cells. These cells will play a key role in mounting a robust immune response upon subsequent re-exposure to FVIII.

2.2. The secondary immune response to FVIII

During the primary immune response, the T and B cells responsible for mounting the anti-FVIII immune response are naïve. In contrast, the secondary immune response (Fig. 1B) involves FVIII-specific memory B cells. These cells are able to mount a response to FVIII much quicker than naïve B cells, and their involvement results in the production of higher affinity neutralizing antibodies to FVIII. Studies suggest that the frequency of peripheral FVIII-specific memory B cells in hemophilia A patients with inhibitors range from <0.01 to 0.40% of total IgG positive B cells [4]. The frequency of FVIII-specific B cells appeared to be affected by the presence of recent antigenic challenge, but did not correlate with anti-FVIII antibody titers [4].

2.3. Effector T cells versus regulatory T Cells

As described, Teffs play a crucial role in the initiation and maintenance of an effective anti-FVIII immune response. The importance of this cell type was highlighted by observations derived

Please cite this article in press as: M.T. Georgescu et al., War and peace: Factor VIII and the adaptive immune response, Cell. Immunol. (2015), http://dx.doi.org/10.1016/j.cellimm.2015.11.008