International Immunopharmacology 36 (2016) 180–186

Contents lists available at ScienceDirect

International Immunopharmacology

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

The dual nature of retinoic acid in pemphigus and its therapeutic potential: Special focus on all-trans Retinoic Acid

Soheil Tavakolpour [a,b,*], Maryam Daneshpazhooh [b], Hamid Reza Mahmoudi [b], Kamran Balighi [b]

[a] Iran University of Medical Sciences, Tehran, Iran
[b] Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Received 15 February 2016
Received in revised form 17 April 2016
Accepted 20 April 2016
Available online 5 May 2016

Keywords:
Pemphigus
All-trans-Retinoic Acid
Regulatory T cells
Regulatory B cells
Retinoic acid

ABSTRACT

The efficient treatment of pemphigus with no certain side effect remained a controversial issue. Although there are various options for controlling disease severity, the majority of them may cause serious side effects. Retinoic acid (RA), an active metabolite converted from vitamin A, plays an active role in immune functions. Effects of RA, especially all-trans-Retinoic Acid (ATRA) on different types of cells involved in immune responses were analyzed *in vitro* and *in vivo*. RAs could affect the differentiation of T helper (Th) cells, B cells responses, stabilization of both natural regulatory T cells (nTregs) and regulatory B cells (Bregs) populations, and regulating the expression of critical genes in immune responses. The role of RA, based on major immune cells involved in pemphigus has not been addressed so far. In this study, we sought to determine the possible effects of RA, with a special focus on ATRA in pemphigus. All the evidences of ATRA effects on the immune system were collected and their association with the pemphigus was analyzed. According to the previous results, ATRA causes a decline in Th17 populations; increase in CD4+ induced regulatory T cells (iTregs), stabilization of nTregs, and promotion of suppressive B cells, which are critical in the improvement of pemphigus. Nevertheless, it also causes shifting of the Th1:Th2 balance toward Th2 cells, which is not favorable for pemphigus patients. In conclusion, ATRA acts *via* different ways in pemphigus. Due to increase in the suppressive function *via* iTregs, nTregs, and Bregs, it is suggested that patients with pemphigus may benefit from systemic ATRA therapy. To clarify this issue, further studies, such as clinical trials are needed.

Contents

1. Introduction

Pemphigus is an autoimmune blistering disease, which involves skin and mucous membrane and is potentially life-threatening in the absence of efficacious treatments. Although there are several recognized

* Corresponding author at: Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail address: soheil.tavakolpour@gmail.com (S. Tavakolpour).

http://dx.doi.org/10.1016/j.intimp.2016.04.031
1567-5769/

subtypes of this disease, the two major groups are pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Despite the few differences at the level of acantholysis, it was suggested that both PV and PF may share the same clinical course [1]. It is generally accepted that in pemphigus, circulating autoantibodies, which are directed against desmoglein (Dsg)1 and/or Dsg3 are responsible of blisters development. In PV, the passive transfer of serum immunoglobulin (Ig)G to Dsg3 into the newborn mice led to induction of blister formation, which can confirm this fact [2]. Interaction between the antigen specific T cells and B cells is postulated for the production of these destructive autoantibodies. Each occurrence that causes any alteration in the immune responses, especially differentiation and responses of T and B cells, can result in changing of the disease course. This may be helpful or harmful, depending on induced signaling pathways.

Naïve T cells can differentiate into the several subsets, driving *via* the cytokines and signals in the environment of T cell activation. First, it was assumed that there are only two subsets of these differentiated T cells, T helper (Th)1 cells and Th2 cells. Less than a decade ago, other types of T cells that could be differentiated from the naïve T cell were identified. These subsets were called Th17 and T follicular helper (Tfh), and were followed by other newly recognized subtypes, including T regulatory cell (Treg), Th9, and Th22. Subsequently, the role of each of these T cells was described for different types of diseases, such as infections, inflammatory diseases, autoimmune diseases, and cancer. During the different autoimmune diseases, changes in the number of T cells and their cytokines levels were observed. Multiple studies on pemphigus patients confirmed a decrease in the Th1 populations or associated responses, while elevation of Th2 cells populations and their cytokines levels was associated with this disease [3,4]. In addition, there is a paucity of data to support that Th17 and Tregs are other critical players in pemphigus. In fact, increase in Th17 and decrease in Tregs populations were suggested as the other alteration in immune system during pemphigus [5–7].

Vitamin A metabolite retinoic acid (RA) influences various cellular functions. The critical roles of vitamin A and RA in the homeostatic control of the immune system have been known for decades. It has both direct and indirect effects on proliferation, differentiation, and apoptosis in a variety of immune cells [8]. Thus, it should be an effective factor in induction or inhibition of several immune responses in autoimmune diseases. The role of RA was previously discussed in various autoimmune diseases, including multiple sclerosis (MS), rheumatoid arthritis (RhA), asthma and type 1 diabetes (T1D) [9–12].

Despite the high potential of RA in alteration of immune responses and its beneficial effects in several autoimmune diseases, there is no comprehensive study on the possible effects of systemic RA therapy in treatment of pemphigus. Thus, considering the last findings on the roles of RA, we highlighted the possible effects of RA and hypothesized that it could be a therapeutic potential to treat cases with refractory pemphigus. This study tried to reveal the potential effects of RA (with focus on all-trans RA) on pemphigus based on the available molecular mechanisms that could be modulated by RA. Finally, the benefits and detriments of the oral administration of RA for pemphigus patients have been discussed.

2. Immune cells involved in pemphigus and their responses during disease

Various types of cells contribute in initiation and progression of pemphigus. Despite previous findings, the exact cellular and molecular mechanisms in pemphigus remained unclear [13]. According to the last studies, this disease is governed by T cells and B cells responses [14]. Various types of T cells, which may act in opposite ways are deeply involved in pemphigus. These T cells could promote or suppress B cells responses, which are critical players in pemphigus. It is suggested that Th2 activity is associated with the active stage of PV, while in individuals with normal immune responses; there is a balance between the Th1 and Th2 cells and their associated cytokines [15]. Interleukin (IL)-4 and IL-10 are the major cytokines secreted by Th2 cells. High level of these cytokines in pemphigus patients was reported in multiple studies. IL-4 serves as an autocrine growth and differentiation factor and, as a consequence inducer of naïve T cells differentiation into the Th2 cells [16]. This cytokine could also play a substantial role in B cell isotype switching. In addition to IgE, there are different evidences that it may act as a switch factor in the production of IgG1 and IgG4 [17–19], which are the two most involved IgG subclasses in pemphigus. Similar to several recognized targets in autoimmune diseases [20], identification of this type of IL-4 and the other complex interactions with other cells has led to emergence of the idea of inhibiting IL-4 in pemphigus in order to reduce diseases severity [21,22]. IL-10 is another known switch factor for IgG4 production [23]. Although IL-10 contributes in the increase of autoantibodies in pemphigus, it has a crucial role in Tregs promotion as well as regulatory B cells (Bregs). Indeed, it can be considered as a double-edged sword in pemphigus [24]. Th17, which is known as a critical player in several autoimmune diseases, may also promote disease progression in pemphigus [25]. It seems that it acts *via* the inhibition of iTregs promotion as well as secretion of cytokines, which cause IgG isotype switching and reprogramming of nTregs into the Th17 cells. The high level of IL-17 in serum and lesion of pemphigus patients were reported, which highlights the critical role of Th17 in pemphigus [26,27]. In addition, imbalance of Th17 and Tregs populations in pemphigus patients was reported [5]. Recently, IL-21 was identified as another player in pemphigus [28].

Another subset of T cells that play major role in autoimmune diseases, such as pemphigus is Tregs. This type of cell can be categorized into two general subgroups, including natural Tregs (nTregs) and inducible Tregs (iTregs). The latter group can be classified into at least into 3 major subgroups, including CD8 + Tregs, Type 1 regulatory T cells (Tr1), Th3 cells. nTregs are developed in the thymus during the selection process whereas iTregs are developed in the periphery from naïve T cells. Dysfunction of Tregs or reduction in their number was observed in several autoimmune diseases [29–31]. Initiation and promotion of autoantibodies in autoimmune diseases may be due to failure of Tregs functions, which are responsible for the suppression of immune responses. Regarding the role of Tregs in pemphigus, it was demonstrated that Tregs can control anti-Dsg3 antibody production in PV mice model [32]. There is also some evidence that implied reduction of Tregs in pemphigus patients [5,7]. The roles of Tfh, Th9, and Th22 still remained unclear in this complex disease.

In addition to the T cells, B cells are involved in pemphigus [14]. It was found that immature B cells can also differentiate into suppressive B cells (also known as Bregs); the cells that can be a critical players in several autoimmune diseases [33]. Recently, dysfunction of Bregs was confirmed in patients with pemphigus [34]. Many studies have introduced induction of different types of suppressive cell, including iTregs, nTregs and Bregs as the new weapons against the aberrant immune responses in autoimmune diseases [33,35].

3. Involvement of retinoic acid in immune cells regulation

Vitamin A is considered as a deeply involved vitamin in the T cells differentiation as well as responses of different types of T cells. Furthermore, effects of this vitamin in other types of cells, including B cells, natural killer T (NKT) cells, and natural killer (NK) cells were reported in various studies. In fact, all-trans Retinoic Acid (ATRA), which is derived from retinol or vitamin A causes these changes, by itself. ATRA is a RA in which all four exocyclic double bonds have E- (trans-) geometry. ATRA can be produced from several sources. Dendritic cells (DCs) may be a major source of ATRA that can promote the induction of transcription factor forkhead box protein 3 (Foxp3) Tregs [36].

There is some evidence implying the critical role of RA in the T cell differentiation, the migration of T cells into tissues as well as the proper development of T cell-dependent antibody responses. The primary