Pharmacology & Therapeutics 166 (2016) 123–127

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Immune suppressive properties of artemisinin family drugs

Lifei Hou [1], Haochu Huang *

Department of Medicine, Section of Rheumatology, and Knapp Center for Lupus and Immunology Research, University of Chicago, Chicago, IL, United States

ARTICLE INFO

Available online 10 July 2016

Keywords:
Artemisinin
Germinal center B cells
Inflammation
Immune regulation
Autoimmune diseases
T cells

ABSTRACT

Artemisinin and its derivatives are the first-line antimalarial drugs, and have saved millions of lives across the globe, especially in developing world. The discovery of artemisinin by Youyou Tu was awarded the 2015 Nobel Prize in Physiology or Medicine. In addition to treating malaria, accumulating evidences suggest that artemisinin and its derivatives also possess potent anti-inflammatory and immunoregulatory properties. We recently showed that artesunate, an artemisinin analog, dramatically ameliorated autoimmune arthritis by selectively diminishing germinal center B cells. Herein, we review the immunosuppressive properties of artemisinin family drugs and the potential underlying mechanisms.

1. Introduction

Artemisinin was isolated from *Artemisia annua* L. in 1972 by Youyou Tu at the Chinese Academy of Traditional Chinese Medicine (reviewed in Tu, 2011). By the end of 1975, its unique chemical structure was elucidated, as a sesquiterpene lactone bearing a peroxy group, quite different from all other known antimalarial drugs. Soon afterwards, some artemisinin derivatives were synthesized and proved to possess better bioactivity or solubility, including dihydroartemisinin, artemether, artesunate and arteether. In recent years, by inserting new groups to the parent structure of artemisinin, a series of artemisinin derivatives were synthesized with potent in vitro immunosuppressive functions against T cell activation, including SM735, SM905, SM933 and SM934 (Yang et al., 2005, 2006; Wang et al., 2007b; Hou et al., 2009). As shown in Fig. 1, all of them share core chemical structure, a sesquiterpene lactone containing peroxide bridge, and constitute the artemisinin family drugs (reviewed in Li, 2012). Artemisinin family drugs are currently considered the most effective drug in treating cerebral malaria and chloroquine-resistant falciparum malaria (van Hensbroek et al., 1996; White, 2008). The peroxy group is essential for artemisinin family drugs to exert anti-malarial effects (Olliaro et al., 2001; Vennerstrom et al., 2004). Once the red blood cells are infected with *Plasmodium*, the intracellular energy metabolism system is activated, which results in elevated level of oxidative stress in infected red blood cells. Subsequently, heme or free iron provided by red blood cells breaks the peroxide bridge of artemisinin to form the nucleophilic radical metabolites. These alkylating artemisinin metabolites subsequently act as the free radicals to attack macromolecular bearing electrophilic groups, and finally eliminate the parasites (Robert et al., 2005). It is well established that artemisinin preferentially kills the parasite-infected red blood cells, leaving the healthy red blood cell spared (Golenser et al., 2006; Mercer et al., 2007). This distinct pharmacological mechanism endows the artemisinin distinct advantage of efficacy and safety in clinical practice. To date, in addition to anti-malarial functions, artemisinin family drugs have also been reported to have pharmacological actions against viruses, helminthes, fungi, and even a variety of cancer cells (reviewed in Ho et al., 2014). This review will focus on the anti-inflammatory and immune-regulatory functions of artemisinin family drugs, and discuss the potential application of artemisinin family drugs as novel immune-regulatory agents.

2. Artemisinin family drugs exert immune regulatory functions

2.1. Artemisinin family drugs regulate innate immune cells

In addition to their excellent clinical anti-malarial effects, experimental studies also suggest that artemisinin family drugs possess potent anti-inflammatory properties by regulating both innate and adaptive immunity. Macrophages, representing a key component of the innate immune system, can produce both pro-inflammatory cytokines, such as IL-12/23 P40 and TNFα, and anti-inflammatory cytokines, including IL-10. Most studies investigating the effect of artemisinin analogs on macrophages focused on the cell line RAW264.7, primary peritoneal macrophages, or fibroblast-like synoviocytes (Xu et al., 2007; Li et al., 2008; Wang et al., 2009; Li et al., 2010; He et al., 2011; Wang et al.,

Abbreviations: CD, cluster of differentiation; CIA, collagen-induced arthritis; EAE, experimental allergic encephalomyelitis; IL, interleukin; TCR, T cell receptor; Th, T helper; Treg, regulatory T cell.

* Corresponding author at: Department of Medicine, Section of Rheumatology, Knapp Center for Lupus and Immunology Research, University of Chicago, Chicago, IL 60637, United States. Tel.: 773 834 4482; fax: 773 702 1576.
E-mail address: hhuang@bsd.uchicago.edu (H. Huang).
[1] Current address: Program in Cellular and Molecular Medicine, Boston Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, Massachusetts.

http://dx.doi.org/10.1016/j.pharmthera.2016.07.002
0163-7258/

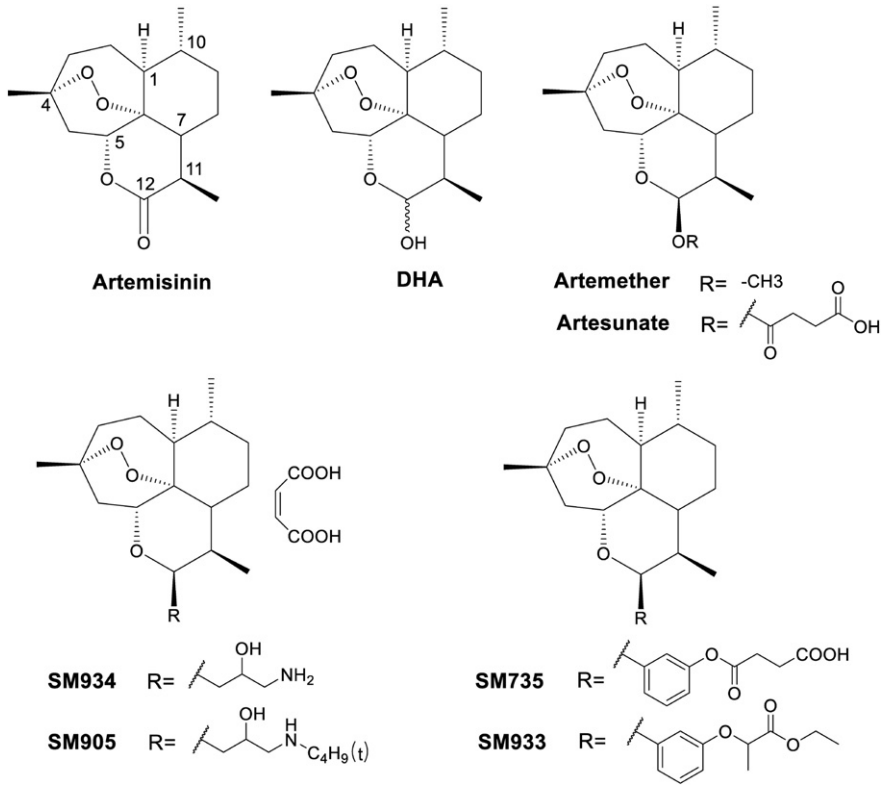

Fig. 1. Structures of artemisinin and various derivatives.

2011; Park et al., 2012; Yang et al., 2012; Li et al., 2013b). Artesunate was initially reported to reduce significantly the phagocytosis of peritoneal macrophages and the phagocytic index in vivo (Lin et al., 1995). Artemisinin family drug was also found to inhibit TNFα production from LPS-stimulated peritoneal macrophage by suppressing nuclear translocation of NF-κB (Li et al., 2006, 2013a), which was confirmed by other publications in the last decade (Xu et al., 2007; Li et al., 2008, 2010; Park et al., 2012; Li et al., 2013b). In addition to engulf and digest debris, foreign particles, and pathogens through phagocytosis, macrophages are also the critical effector cells downstream of the T cell activation in many autoimmune diseases. For example, in rheumatoid arthritis, upon the stimulation by T cell-derived interferon-γ (IFN-γ), macrophages and macrophage-like fibroblast cells are activated to produce various mediators including matrix metalloproteinases (MMPs) and nitric oxide (NO) to induce tissue damage, or to secrete IL-12/IL-23 to form the positive feedback loop to further boost the Th1/Th17 responses (Roberts et al., 2015). Besides suppressing pro-inflammatory cytokine production, artemisinin family drugs could also induce the anti-inflammatory cytokine production, such as IL-10. Hou et al. reported that SM934, an artemisinin analog, could increase IL-10 production, whereas decrease IL-12/23p40 production in primary peritoneal macrophages after IFN-γ stimulation in vitro or in vivo (Hou et al., 2012). All these studies suggest that artemisinin family drugs are able to suppress the activation of macrophage and skew the macrophage to be regulatory in autoimmune diseases.

2.2. Artemisinin family drugs regulate adaptive immune cells

T and B lymphocytes play pivotal roles in adaptive immune responses to drive cellular and humoral immunity. Upon T cell receptor (TCR) engagement with antigens presented by MHC moleculars, T cells are activated and secrete growth factor IL-2 and express its high-affinity receptor IL-2Rα chain (CD25); subsequently, by autocrine/paracrine proliferative loop, IL-2 induces clonal expansion and promotes survival of activated T cells; finally, after successful clearance of pathogen or antigen, activated T cells undergo apoptosis to maintain immune homeostasis (Alberola-Ila et al., 1997; Lea et al., 2003). Artemisinin family drugs can suppress T cell activation both in vitro and in vivo. Artemether was reported to suppress T cell proliferation and IL-2 production in response to TCR engagement or mitogens in vitro (Wang et al., 2007a). Interestingly, among all the artemisinin family drugs and derivatives, SM934 has unique properties. On one hand, similar to artemether and SM905, SM934 inhibits T cell proliferation stimulated by anti-CD3, concanavalin A, and alloantigens (mixed lymphocyte reaction). On the other hand, unlike artemether and SM905, SM934 does not affect IL-2 production from activated T cells (Hou et al., 2009). Although IL-2 is important to induce effector T cell proliferation, IL-2 is also pivotal for generating regulatory T cells (Treg), and deficiency of IL-2 or CD25 leads to severe systematic autoimmune diseases in mice (reviewed in Nelson, 2004). Clinical practices demonstrated that inhibiting T cell proliferation, rather than IL-2 production, may increase the proportion of Treg subset. For example, rapamycin, which does not inhibit IL-2 production, is used in transplantation and leads to Treg predominance (Baan et al., 2005; Coenen et al., 2006). SM934 was well characterized in regulating the balance of effector T and regulatory T cells. SM934 suppresses the differentiation and accumulation of Th1 and Th17 cells, whereas induces the differentiation and expansion of Treg cells, which was demonstrated by both in vitro T cell differentiation system and in vivo in autoimmune disease models (Hou et al., 2011, 2012; Li et al., 2013b). Similar to SM934, dihydroartemisinin and artesunate were also able to regulate the balance of effector T cells and regulatory T cells (Zhao et al., 2012; Li et al., 2013c; Hou et al., 2014). The mechanism for artemisinin family drug to enhance Treg while suppress Th1 and Th17 differentiation is still elusive. Zhao et al. reported that dihydroartemisinin works by attenuating the mTOR/Akt signaling pathway (Zhao et al., 2012). However, in a recent study, Khor et al. showed that artemisinin and other 14 novel Treg cell enhancers appear to work independently of mTOR (Khor et al., 2015). Nevertheless, accumulating evidence clearly show that most of artemisinin family drugs have potent immunosuppressive