Advances in Applied Mathematics and Mechanics
Adv. Appl. Math. Mech., Vol. **8**, No. 1, pp. 67-81

DOI: 10.4208/aamm.2013.m234
February 2016

Dynamics of Calcium Signal and Leukotriene C_4 Release in Mast Cells Network Induced by Mechanical Stimuli and Modulated by Interstitial Fluid Flow

Wei Yao, Hongwei Yang, Yabei Li and Guanghong Ding*

Shanghai Key Laboratory of Acupuncture Mechanism and Acupoint Function, Department of Mechanics and Engineering Science, Fudan University, 220 Handan Road, Shanghai 200433, China

Received 30 May 2013; Accepted (in revised version) 14 June 2015

Abstract. Mast cells (MCs) play an important role in the immune system. Through connective tissues, mechanical stimuli activate intracellular calcium signaling pathways, induce a variety of mediators including leukotriene C_4 (LTC_4) release, and affect MCs' microenvironment. This paper focuses on MCs' intracellular calcium dynamics and LTC_4 release responding to mechanical stimuli, explores signaling pathways in MCs and the effect of interstitial fluid flow on the transport of biological messengers and feedback in the MCs network. We use a mathematical model to show that (i) mechanical stimuli including shear stress induced by interstitial fluid flow can activate mechano-sensitive (MS) ion channels on MCs' membrane and allow Ca^{2+} entry, which increases intracellular Ca^{2+} concentration and leads to LTC_4 release; (ii) LTC_4 in the extracellular space (ECS) acts on surface cysteinyl leukotriene receptors (LTC_4R) on adjacent cells, leading to Ca^{2+} influx through Ca^{2+} release-activated Ca^{2+} (CRAC) channels. An elevated intracellular Ca^{2+} concentration further stimulates LTC_4 release and creates a positive feedback in the MCs network. The findings of this study may facilitate our understanding of the mechanotransduction process in MCs induced by mechanical stimuli, contribute to understanding of interstitial flow-related mechanobiology in MCs network, and provide a methodology for quantitatively analyzing physical treatment methods including acupuncture and massage in traditional Chinese medicine (TCM).

AMS subject classifications: 92C10, 92C05, 92C42

Key words: Mast cells, Ca^{2+} signaling, LTC_4 release, interstitial fluid flow, network.

1 Introduction

MCs are an integral component of the mammalian immune system [1], which resident at

*Corresponding author.
Email: weiyao@fudan.edu.cn (W. Yao), 14110290011@fudan.edu.cn (H. W. Yang), 11210290026@fudan.edu.cn (Y. B. Li), m13564899598@163.com (G. H. Ding)

the interface between the body and the external environment (i.e., under the skin and mucosal surfaces), enabling them to respond rapidly to environmental stimuli, and making them "sentinels" of the immune system [2]. Except for the allergic responses to chemical stimuli, they usually respond to mechanical stimuli such as squeeze, friction, massage and acupuncture. These mechanical stimuli not only activate the mechano-sensitive (M-S) ion channels on MCs membrane and induce a cascade of intracellular signaling events, but also affect the microenvironment of MCs and change the interstitial fluid flow [3]. In recent studies it was found that mechanical stimulation at acupoints is associated with MCs' degranulation [4]. Single-channel activity was observed in the excised patch when negative pressure was applied to MCs [5]. Intracellular Ca^{2+} increase and histamine release were found after shear stress is applied on MCs [6]. Even though the mechanism of MCs' activation by mechanical stimuli is unknown, experimental evidences suggest that TRPV (Transient Receptor Potential Cation Channel, Subfamily V) proteins are involved in this process [7]. Western blot analysis revealed there were TRPV proteins expressed on mast cells [8]. Since TRPV proteins are sensory receptors that can regulate cations influx crossing cell membrane, they may convert external mechanical stimuli into changes in second intracellular messenger signals, particularly Ca^{2+}. Local Ca^{2+} entry activates protein kinase C (PKC) and mobilizes calcium from intracellular stores, leads to other mediators' release [9]. These mediators act in several different ways, e.g., histamine can dilate capillary vessels and increase the interstitial fluid flow [3], LTC_4 can activate MCs and produce more LTC_4 [10]. These biochemical processes change MCs' microenvironment and can sustain MCs activation over a period of time.

Mathematical models have been developed for describing biological messengers' propagation in cells network, especially for neural cells [11]. They either assumed passive diffusion through gap juncture between cells or diffusion in extracellular space (ECS) as the underlying mechanism [12, 13]. But few of them include the effect of convection. Interstitial fluid flow exists in all living tissues. Experiments and simulations have proved there were directional interstitial fluid flow in some loose connective tissues, and acupuncture can accelerate the flow rate [14, 15]. In this paper, we construct a mathematical model for describing intracellular Ca^{2+} propagation and biological messengers (i.e., LTC_4) release in MCs network induced by mechanical stimuli and modulated by interstitial fluid flow. The rest of the paper is organized as follows. In Section 2, we present the MCs network model. In Section 3, we present numerical simulations under a variety of conditions. The effects of the distance between nearby cells, interstitial flow are investigated. Discussion of our results are given in Section 4.

2 Methods

The dynamic process of MCs activation is illustrated in Fig. 1. In the first stage, mechanical stimuli activate MS ion channels on MCs membrane and allow Ca^{2+} entry; local intracellular Ca^{2+} increase activates PKC and increases the sensitivity of secretory granules