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Review

Mechanical stress-initiated signal transduction in vascular smooth muscle cells *in vitro* and *in vivo*

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Abstract

Increasing evidence has been demonstrated that hypertension-initiated abnormal biomechanical stress is strongly associated with cardio-/cerebrovascular diseases e.g. atherosclerosis, stroke, and heart failure, which is main cause of morbidity and mortality. How the cells in the cardiovascular system sense and transduce the extracellular physical stimuli into intracellular biochemical signals is a crucial issue for understanding the mechanisms of the disease development. Recently, collecting data derived from our and other laboratories showed that many kinds of molecules in the cells such as receptors, ion channels, caveolin, G proteins, cell cytoskeleton, kinases and transcriptional factors could serve as mechanoceptors directly or indirectly in response to mechanical stimulation implying that the activation of mechanoceptors represents a non-specific manner. The sensed signals can be further sorted and/or modulated by processing of the molecules both on the cell surface and by the network of intracellular signaling pathways resulting in a sophisticated and dynamic set of cues that enable cardiovascular cell responses. The present review will summarise the data on mechanotransduction in vascular smooth muscle cells and formulate a new hypothesis, i.e. a non-specific activation of mechanoceptors followed by a variety of signal cascade activation. The hypothesis could provide us some clues for exploring new therapeutic targets for the disturbed mechanical stress-initiated diseases such as hypertension and atherosclerosis.

Keywords: Mechanoceptor; Mechanical stress; Signal transduction; Smooth muscle cell; Nonspecific activation

Contents

Abbreviations: AgIIR, angiotensin II receptor; cAMP, cyclic adenosine monophosphate; EC, endothelial cells; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; GPCR, G protein-coupled receptor; IGFR, insulin-like growth factor receptor; JNK/SAPK, c-*Jun* NH2-terminal protein kinase/stress-activated protein kinase; MAPK, mitogen-activated protein kinase; NO, nitric oxide; MKP-1, mitogen-activated protein kinase (MAPK) phosphatase-1; PACAP, pituitary adenylate cyclase activating peptide; PDGFR, platelet-derived growth factor receptor; PKC, protein kinase C; PKCδ−/−, PKCδ knock out; PLC, phospholipase C; RTK(s), receptor tyrosine kinases; SMC, smooth muscle cell; STRO, stromal cells expressing; TGFR, transforming growth factor receptor; TIE1/2-R, angiopoietin receptor; VWF, von Willebrand factor.

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1. Introduction

All tissues in the body are subjected to physical forces originating either from tension, created by cells themselves, or from the environment [1–5]. The role of mechanical force as an important regulator of structure and function of mammalian cells, tissues, and organs has recently been recognized. Physical stimuli must be sensed by cells and transmitted through intracellular signal transduction pathways to the nucleus, resulting in altered physiological responses or pathological conditions. In this research field, significant progress has recently been achieved, especially from studies of cardiovascular systems [6–16].

As well-known, chemical stimuli like hormone, growth factors, vasoactive peptides and neurotransmitters can specifically bind to their receptors on the cell membrane leading to changed receptor conformation, which initiates intracellular signals resulting in reprogramming of gene expression, cell hypertrophy, differentiation, proliferation and/or apoptosis etc. However, how the cells in the cardiovascular system sense and transduce the extracellular physical stimuli into intracellular biochemical signals is less known. Although intensive investigations were preformed, to date, no data have been showed specific mechanoceptors existing on the cell membranes [6,13,17,18]. On the other hand, accumulating data derived from our and other laboratories demonstrated that many kinds of molecules in the cells such as receptors [7,17], caveolin [19,20], G proteins [6,13,15,18,21,22], ion channels [6,13,23–25], cell cytoskeleton [14,26–28], kinases [6–13,17], and transcriptional factors [7,29] could sense the mechanical stimulation. Studying the mechanical behaviors of single biomolecule with the single molecule force spectroscopy methodology, it has been found that mechanical forces can modify the conformation of proteins, possibly leading to functional switches, which rely on their coupling to some independent biochemical control of the protein conformational changes [6,9,30]. Disulfide bonds have been recently proposed to act as potential redox switches [30], which couple mechanical force to deformation of cellular proteins, thus leading to an efficient and highly tuned switch for protein function, and resulting in activated signals, which can be further combined and/or modulated by processing of the molecules by intracellular signaling pathways [31]. Finally, the signal is transduced into the nuclear leading to cell responses.

Blood vessels consist of three layers: the tunica intima with one layer of endothelial cells (EC) supported by a subendothelial layer, the tunica media with smooth muscle cells (SMCs) and the tunica adventitia with connective tissue containing fibroblasts. Normally, blood with nutrients, oxygen, hormones, and neurotransmitters flows the vessels, maintaining proper tension, i.e. blood pressure. Normal blood pressure is required for development of organisms, maintenance of phenotype. However, many factors ranging from physical exertion to psychological stress lead to neuroendocrine responses including release of catecholamines into the blood circulation and activation of the renin–angiotensin system resulting in a transient rise in blood pressure [32–35]. This process is largely due to enhanced cardiac output and increased resistance of peripheral arterioles [34,35]. If the factors are persistent and the process repeated often, the arteriole walls gradually thicken resulting in chronic hypertension [32,36]. Large arteries, such as the aorta, coronary and carotid arteries, undergo adaptation or remodeling in response to chronically elevated blood pressure representing medial hypertrophy and/or intimal hyperplasia of the arterial wall [36]. Traditionally, it has been believed that SMCs in the tunica media in response to hypertension-induced mechanical stress de-differentiated from contractile into synthesizing phenotype, which synthesized an amount of extracellular matrixes, and migrated into subendothelial layer to abnormally proliferate and form neointima, where they constituted arteriosclerotic lesion, leading to stiffening and thickening of the vessel walls. However, this concept concerning source of neo-SMCs in the tunica intima has been challenged with the findings of other sources of endothelial cells and SMCs, which contribute to atherogenesis. As excellent reviews have been published concerning the source of progenitor cells, including bone marrow stem cells, adventitial stem cells and embryonic stem cells [16], the aim of the current review is to provide an update on the progress involved in mechanism underling signal pathways of mechanoceptor activation linking to SMC migration, proliferation, apoptosis, differentiation and inflammation in response to mechanical stresses. The new insights of understanding mechanotransduction in SMCs would be helpful for exploring new therapeutic targets to prevent and treat the mechanical stress-initiated diseases, such as hypertension and atherosclerosis.

2. Activation of membrane-related mechanosensors

According to Singer–Nicolsin fluid-mosaic model, cell membrane is composed of liquid-crystal membrane lipids and membrane proteins. The membrane lipids include phospholipid, glycolipid, and cholesterol, which are highly condensed assembles of caveolar and non-caveolar forms. While membrane proteins are composed of integral membrane proteins, peripheral membrane proteins and lipid-anchored membrane proteins [37–42]. Evidence has been showed that these proteins in the membrane such as receptors, caveolins, ion channels, and pumps