Free Radical Biology and Medicine 65 (2013) 102–116

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

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

Review Article

Sequestosome1/p62: A regulator of redox-sensitive voltage-activated potassium channels, arterial remodeling, inflammation, and neurite outgrowth

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ARTICLE INFO

Article history:
Received 17 April 2013
Received in revised form
6 June 2013
Accepted 7 June 2013
Available online 19 June 2013

Keywords:
Sequestosome1
p62
K_v channels
p56Lck
PKCζ
Nrf2
Arterial smooth muscle cells
Neointimal hyperplasia
T lymphocytes
Neurite outgrowth

ABSTRACT

Sequestosome1/p62 (SQSTM1) is an oxidative stress-inducible protein regulated by the redox-sensitive transcription factor Nrf2. It is not an antioxidant but known as a multifunctional regulator of cell signaling with an ability to modulate targeted or selective degradation of proteins through autophagy. SQSTM1 implements these functions through physical interactions with different types of proteins including atypical PKCs, nonreceptor-type tyrosine kinase $p56^{Lck}$ (Lck), polyubiquitin, and autophagosomal factor LC3. One of the notable physiological functions of SQSTM1 is the regulation of redox-sensitive voltage-gated potassium (K_v) channels which are composed of α and β subunits: $(K_v\alpha)_4$ $(K_v\beta)_4$. Previous studies have established that SQSTM1 scaffolds PKCζ, enhancing phosphorylation of $K_v\beta$ which induces inhibition of pulmonary arterial $K_v1.5$ channels under acute hypoxia. Recent studies reveal that Lck indirectly interacts with $K_v1.3$ α subunits and plays a key role in acute hypoxia-induced $K_v1.3$ channel inhibition in T lymphocytes. $K_v1.3$ channels provide a signaling platform to modulate the migration and proliferation of arterial smooth muscle cells and activation of T lymphocytes, and hence have been recognized as a therapeutic target for treatment of restenosis and autoimmune diseases. In this review, we focus on the functional interactions of SQSTM1 with K_v channels through two key partners aPKCs and Lck. Furthermore, we provide molecular insights into the functions of SQSTM1 in suppression of proliferation of arterial smooth muscle cells and neointimal hyperplasia following carotid artery ligation, in T lymphocyte differentiation and activation, and in NGF-induced neurite outgrowth in PC12 cells.

Contents

Abbreviations: AP-1, activator protein-1; ARE, antioxidant response element; CDK, cyclin-dependent kinase; EGF, epidermal growth factor; ERK1/2, extracellular regulated kinase 1/2; HNE, 4-hydroxynonenal; HO-1, heme oxygenase-1; IL-1, interleukin-1; Keap1, Kelch-like ECH associated protein 1; K_v, voltage-gated potassium channel; Lck, nonreceptor-type tyrosine kinase $p56^{Lck}$; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa beta; NGF, nerve growth factor; Nrf2, nuclear factor erythroid 2-related factor 2; oxLDL, oxidized low density lipoprotein; PDB, Pajet's disease of bone; aPKC, atypical protein kinase C; PKCλ/ι, protein kinase C rambda or iota; PKCζ, protein kinase C zeta; Prx1, peroxiredoxin 1; PASMCs, pulmonary artery smooth muscle cells; ROS, reactive oxygen species; SAP97, synapse-associated protein 97; SMCs, smooth muscle cells; SQSTM1, sequestosome1; Th2, T helper 2; TCR, T cell receptor; TXA_2, thromboxane A_2; UBA, ubiquitin association; ZIP, zeta-interacting protein

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0891-5849/$ - see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.freeradbiomed.2013.06.019

Introduction

Overview and scope of the review

Oxygen is an essential substrate in aerobic metabolism for higher organisms. Mammalians have developed or acquired numerous mechanisms for sensing O_2 tension to respond to hypoxia and for defense against oxidative damages caused by reactive oxygen metabolites. It is well known that higher vertebrates produce and utilize reactive oxygen species (ROS) for defense against infected pathogens and as intracellular signaling molecules [1,2].

Oxygen sensing by ion channels is very important in physiological responses to acute hypoxia in many specialized tissues and cell types [3]. Voltage-activated potassium (K_v) channels are known as an O_2 sensor and play a critical role in a wide variety of physiological processes including arterial vasoconstriction [4,5], T lymphocyte activation [6], and neurotransmitter release [7]. K_v channels are composed of membrane-spanning α subunits and cytoplasmic auxiliary β subunits, $(K_v\alpha)_4(K_v\beta)_4$ [8–10] (Fig. 1A). One of the interesting features of K_v channels is that the β subunit belongs to a large family of oxidoreductases [11–13]. NADPH binding is essential for optimal interaction between $K_v\alpha$ and $K_v\beta$ subunits and for $K_v\beta$-induced inactivation of K^+ currents. In excitable cells, oxidation of NADPH to $NADP^+$ in $K_v\beta$ subunit is coupled with K^+ efflux at positive membrane voltages [14]. Acute hypoxia downregulates potassium channel current, which is regulated via protein kinases in a cell-dependent manner (Fig. 1B).

Recent studies have revealed an inducible defense system against oxidative and electrophile stress regulated by a transcriptional factor nuclear factor erythroid 2-related factor (Nrf2) [15,16]. Nrf2 is stabilized and accumulated in the nucleus of cells exposed to oxidative and electrophilic stress, leading to an upregulation in the expression of detoxification enzymes and antioxidant proteins [15,16]. For example, Nrf2 regulates the expression of a group of antioxidants such as heme oxygenase 1 (HO-1), peroxiredoxin 1 (Prx1), and catalase, together with GSH-related gene products including cystine transporter xCT, GSH-*S*-transferase, GSH reductase, and multidrug resistance-associated protein1 in cultured mammalian cells [16–20] (Table 1). We previously cloned sequestosome1/p62/A170/ZIP (hereafter referred to as SQSTM1 and initially termed A170), as one of the stress-induced proteins in macrophages [21]. SQSTM1 is now recognized as a multifunctional signal modulator involved in metabolic homeostasis, but SQSTM1 is not an antioxidant enzyme and its antioxidant functions are still unknown.

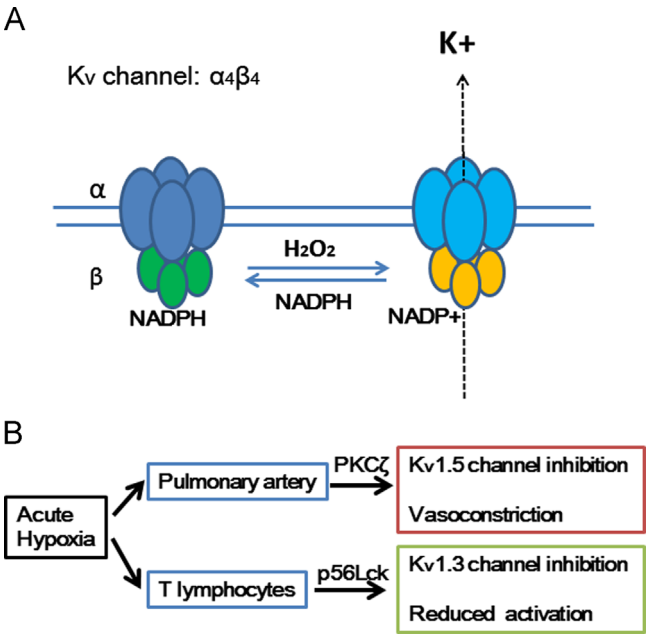

Fig. 1. Redox or oxygen sensing regulations by K_v channels. (A) Voltage-gated potassium channels (K_v) consist of 4α and 4β subunits [8–10]. The β subunit negatively modulates pore opening [10] and has aldoketo-reductase activity using NADPH as a cofactor. Oxidation of β subunit-bound NADPH to $NADP^+$ is required to open the channel by increasing the membrane potential [14]. Several family proteins and spliced variants of each of these subunits account for the wide variation in these channels. (B) K_v channels sense oxygen, and acute hypoxia downregulates the K^+ current through different mechanisms involving PKCζ in arterial smooth muscle cells [5] and tyrosine kinase p56Lck (Lck) in human T lymphocytes [6].

In this review, we critically examine the evidence that SQSTM1 plays a key role in regulation of redox-regulated K_v channels. We focus specifically on SQSTM1 as a functional partner of PKCζ and Lck and reevaluate the regulatory function of SQSTM1 in signal transduction involving K_v channels in vascular smooth muscle cells (SMCs), T lymphocytes, and PC12 cells. Lastly, we propose novel hypothesis that SQSTM1 plays various functions through