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Review

Transient receptor potential (TRP) channels as molecular targets in lung toxicology and associated diseases

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ABSTRACT

The lungs as the gateways of our body to the external environment are essential for gas exchange. They are also exposed to toxicants from two sides, the airways and the vasculature. Apart from naturally produced toxic agents, millions of human made chemicals were produced since the beginning of the industrial revolution whose toxicity still needs to be determined. While the knowledge about toxic substances is increasing only slowly, a paradigm shift regarding the proposed mechanisms of toxicity at the plasma membrane emerged. According to their broad-range chemical reactivity, the mechanism of lung injury evoked by these agents has long been described as rather unspecific. Consequently, therapeutic options are still restricted to symptomatic treatment. The identification of molecular down-stream effectors in cells was a major step forward in the mechanistic understanding of the action of toxic chemicals and will pave the way for more causal and specific toxicity testing as well as therapeutic options. In this context, the involvement of **T**ransient **R**eceptor **P**otential (**TRP**) channels as chemosensors involved in the detection and effectors of toxicant action is an attractive concept intensively discussed in the scientific community. In this review we will summarize recent evidence for an involvement of TRP channels (TRPA1, TRPC4, TRPC6, TRPV1, TRPV4, TRPM2 and TRPM8) expressed in the lung in pathways of toxin sensing and as mediators of lung inflammation and associated diseases like asthma, COPD, lung fibrosis and edema formation. Specific modulators of these channels may offer new therapeutic options in the future and will endorse strategies for a causal, specifically tailored treatment based on the mechanistic understanding of molecular events induced by lung-toxic agents.

Contents

Abbreviations: 4αPDD, 4α-Phorbol 12,13-didecanoate; 5,6 EET, 5,6-Epoxy-eicosatrienoic acid; AA, arachidonic acid; ADPr, ADP-ribose; AITC, allyl isothiocyanate; BALF, bronchial aveolar lavage fluid; BBA, Bisandrographolide A; cADPr, cyclic ADP-ribose; CaM, calmodulin; DAG, diacylglycerol; DEP, diesel exhaust particles; EC, electrophilic components; ECHA, European Chemical Agency; FSGS, focal segmental glomerulosclerosis; H_2O_2, hydrogen peroxide; ILD, interstitial lung diseases; IPF, idiopathic pulmonary fibrosis; NHERF, Na^+/H^+ exchanger regulatory factor; NO, nitric oxygen; NOX, NADPH-oxidase; O_2, oxygen; O_3, ozone; PA, phosphatidic acid; PDZ, PSD95/SAP90-Discs-large-Zonula-occludentes-1 domain; PIP_2, phosphatidylinositol 4,5-bisphosphate; PKG, protein kinase G; PLC, phospholipase C; PM, particulate matter; REACH, registration evaluation authorization and restriction of chemicals; SVHC, substances of very high concern; RTX, Resinferatoxine; SOD, superoxide dismutase; TRK, tyrosine receptor kinase; TRP, transient receptor potential; TRPA, ankyrin family of transient receptor potentials; TRPC, classical/canonical transient receptor potential; TRPV, vanilloid family of transient receptor potentials; TRPM, melastatin family of transient receptor potentials.

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1. Introduction

All organisms in the living world are constantly exposed to toxic agents, which are inhaled, ingested or diffuse via the skin into the body. While animals produce venoms to kill prey and plants expose toxins mainly as their defense strategy, millions of man-made chemicals were produced since the beginning of the industrial revolution whose toxicity still needs to be determined. These substances are used daily on the body as cosmetics or for cleaning purposes in millions of domestic homes. Along these lines, approximately 15 million tons of chlorine are produced annually in the United States to be used for water purification, pharmaceutical and disinfectant purposes [1]. Others are produced as toxicants for plants (herbicides) and animals (e.g. insecticides) to increase the harvest of agricultural products and some were invented for chemical warfare in World War I and are now used during the civil war in Syria as well as in terrorist attacks. Of note, during World War II, large amounts of chemicals were produced and stockpiled but never used. They have been dumped in the Baltic Sea after the war and still represent a potential environmental and health risk [2]. Moreover, during the production of these chemicals intermediates and industrial pollutants with unknown characteristics form and may be released into the environment. A tragic example was the disaster in Bophal/India. More than 40 tons of methyl isocyanate gas leaked from a pesticide plant in 1984 immediately killing at least 3800 people and causing significant morbidity and premature death for many thousands more [3]. To tackle possible health risks of all these products of the chemical industry the **E**uropean **C**hemical **A**gency (**ECHA**) started the **REACH** program which stands for **r**egistration **e**valuation **a**uthorization and **r**estriction of **c**hemicals. In January 2017, 169 chemicals of compounds in Europe were identified as **s**ubstances of **v**ery **h**igh **c**oncern (**SVHC**) (see https://echa.europa.eu/candidate-list-table). However, the list is still growing and it is unclear, if the program can be completed in 2020 as originally anticipated. Moreover, particles produced during combustion by traffic or smoking are still not adequately characterized and the biological effects following exposure are incompletely defined.

While the knowledge about toxic substances is only slowly increasing, a paradigm shift regarding the proposed mechanisms of toxicity emerged. Hitherto, the toxic action at the plasma membrane has been mainly attributed to unspecific cell damage caused by reactions of toxicants with biomolecules. In particular, oxidation of membrane lipids and alterations of DNA bases is scenarios which have been suggested to mediate their toxicity. In line with this point of view, therapeutic interventions adopted so far are mainly symptomatic, i.e. application of steroids and β-adrenergic agonists as anti-inflammatory and broncho-spasmolytic agents, respectively, or administration of anti-oxidant molecules like e.g. *N*-acetyl cysteine [4,5]. Recently, the identification of molecular down-stream effectors in cells was a major step forward in the mechanistic understanding of the action of toxic chemicals and will pave the way for more causal and specific toxicity testing [6] as well as therapeutic options.

Therefore, the involvement of **T**ransient **R**eceptor **P**otential (**TRP**) channels as chemosensors in the detection and as effectors mediating the action of toxicants is an attractive concept intensively discussed in the scientific community. In this short review article which updates our previous publication [7] we will focus on TRPA1, TRPC4, TRPC6, TRPM2, TRPM8 as well as TRPV1 and TRPV4 channels expressed in the lung. The respiratory system has to cope with the exposure to toxicants from two sides, i.e. from the airways and the vasculature. We summarize recent data supporting the role of TRP channels as molecular targets in lung toxicology.

2. The candidates: members of the TRP channel family as chemosensory detectors and effectors in the lung

This chapter will introduce TRP proteins predominantly expressed in lung tissues and summarize activation mechanisms and proposed function of these channels. TRP channels were first described in the fruit fly *Drosophila melanogaster*. Characterization of a mutant fruit fly with a short-lived depolarizing current as a visual defect termed *transient receptor potential (TRP)* led to the identification of Ca^{2+} permeable channels named TRP channels [8–10]. By homology screening in expressed sequence tag (EST) data bases, the first mammalian channel and founding member of the classical or canonical TRP family (**TRPC**) was identified. Therefore all seven TRPC channels have high homology to drosophila *trp* and can be subdivided into subfamilies on the basis of amino acid similarity. While TRPC1 and TRPC2 are almost unique, TRPC4 and TRPC5 share ~64% amino acid identity. TRPC3, 6 and 7 form a structural and functional subfamily displaying 65 to 78% identity at the amino acid level. All TRPC family members harbor an invariant sequence, the TRP box (containing the amino acid sequence: EWKFAR), in its C-terminal tail as well as ankyrin repeats in the N-terminus (see TRPC4 and TRPC6 in Fig. 1). They are composed of intracellular N- and C-termini, six membrane-spanning helices (S1-S6), and a presumed pore forming loop (P) between S5 and S6 (Fig. 1). For a functional TRPC ion channel complex, either four monomers of the same type in a homotetrameric complex or of four different TRPC monomers forming a heterotetrameric channel are essential as illustrated in Fig. 3. All TRPC channels except TRPC1 whose role as ion channel or channel regulator is still a matter of debate [11] share a common activator i.e. diacylglycerol (DAG) [12,13] and are involved in complex cellular signal transduction cascades (Fig. 3). DAG is produced from phosphatidylinositol 4,5-bisphosphate (PIP_2) by phospholipase C-isozymes activated after agonist binding to appropriate receptors (see Fig. 3). In recent years, however, direct and indirect activation of these channels by O_2^- and hydrogen peroxide (H_2O_2) (see Fig. 3) as well as nitric oxygen (NO) species (TRPC4 in Fig. 1) as important second messengers produced after toxin exposure became evident. Therefore, unselective TRPC cation channels serve as effectors and indirect chemosensors to mediate influx of Ca^{2+} ions, which reduce cell barrier function and increase edema formation as well as cell death (Fig. 3). TRPCs are expressed in almost all tissues. Human and mouse **TRPC6** cDNAs were originally isolated from pancreas [14,15]. The protein is highly expressed in lung and therefore an important candidate for mediating lung toxicity. As mutations of the TRPC6 channel were identified in patients with focal segmental glomerulosclerosis (FSGS) an important role in kidney function is also apparent (reviewed in [16]). TRPC6 is also regulated by phosphorylation. Posttranslational modification by Fyn, a member of the Src family of protein tyrosine kinases, increases TRPC6 activity [17], while the channel is negatively regulated after phosphorylation of Thr 69 by PKG [18]. Most interestingly, this phosphorylation is essential for anti-hypertrophic effects of phosphodiesterase 5 inhibitors [19–21], which are important therapeutics for pulmonary hypertension [22].

TRPC4 is mainly found in endothelial cells, vascular smooth muscle cells and also in mast cells (see [23] for a detailed expression pattern). In contrast to other TRPC channels TRPC4 and TRPC5 currents are potentiated by La^{3+} (10–100 μM) ions [24]. Remarkably, an exchange of three glutamate residues in TRPC5 close to transmembrane segments S5 and S6 and conserved in TRPC4 (see Fig. 1) results in inhibition of ionic currents by La^{3+} [25]. In contrast to TRPC3, TRPC6 and TRPC7 which are constitutively and directly activated by DAG, TRPC4 and TRPC5 channels are only DAG sensitive after a conformational change by depleting inhibitory PIP_2 and dissociation of the Na^+/H^+ exchanger regulatory factor (NHERF) from