TRP Channels in Chemical Sensing and Environmental Disease

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The human respiratory sytem is highly sensitive to damage by hazardous chemicals and pathogens. Reflex responses such as cough, sneezing and glandular secretions are thought to protect the airways from exposures, promoting the inactivation and removal of chemical threats and pathogens from the respiratory tract. Respiratory reflexes are triggered by chemosensory trigeminal and vagal sensory nerve fibers innervating the airways. These nerve fibers are activated by a wide range of reactive electrophiles, oxidants, acids, bases, organic solvents and particulates. Only little is known about the molecular mechanisms enabling chemosensory nerves to detect such a wide variety of stimuli.

Using a combination of physiological, molecular and genetic approaches we identified TRPA1, a TRP ion channel, as a receptor for multiple reactive stimuli in airway sensory neurons. TRP (Transient Receptor Potential) ion channels are a class or sensory neuronal receptor proteins that integrate noxious chemical and physical stimuli to induce neuronal excitation (1). We found that TRPA1 mediates neuronal responses to a multitude of chemicals, including noxious isothiocyanates (such as allyl isothiocyanate, mustard oil, the pungent ingredient in mustard), acrolein, the major irritant in cigarette smoke, noxious terpenes, tear gas agents, asthma-inducing isocyanates and chlorine (2-6). In mice, chemical stimulation of nasal trigeminal nerves results in the sensory irritant response, characterized by decreased breathing frequency due to a braking at the onset of each expiration (7).Using barometric plethysmography we observed that TRPA1-deficient mice lacked respiratory irritant responses to chlorine and other oxidants, supporting a major role for TRPA1 in the initiation of respiratory reflexes (8).

TRPA1-activating stimuli such as cigarette smoke, chlorine, aldehydes and scents are frequent triggers of asthma attacks (9). Endogenous TRPA1 agonists, including reactive oxygen species, hypochlorite and lipid peroxidation products, are produced by lung-infiltrating immune cells and have been recognized as potent drivers of allergen-induced airway inflammation in asthma . TRPA1 is expressed in a subset of peptidergic sensory nerve fibers and may contribute to the release of pro-inflammatory neuropeptides such as Substance P and CGRP, two known modulators of the inflammatory response in asthma (9).

We examined the role of TRPA1 in allergic asthma in the murine ovalbumin model (10). Genetic ablation of TRPA1 prevented allergen-induced leukocyte infiltration in the airways, reduced cytokine and mucus production and almost completely abolished airway hyperreactivity to cholinergic stimuli. This phenotype was recapitulated by treatment of wild-type mice with HC-030031, a TRPA1 antagonist. HC-030031, when administered during airway allergen challenge, inhibited eosinophil infiltration and prevented the development of airway hyperreactivity. Trpa1-/- mice displayed deficiencies in chemically and allergen-induced neuropeptide release in the airways, providing a potential explanation for the impaired inflammatory response (10).

In summary, our data suggest that TRPA1 is a key integrator of interactions between the chemical environment and the immune and nervous systems in the airways, triggering acute reflex responses and driving airway inflammation following inhaled allergen challenge. TRPA1 may represent a promising pharmacological target for the treatment of cough, asthma and other inflammatory conditions.

References

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