REVIEW ARTICLE

T2R38 Taste Receptors Can Be Affected by Cancer

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ABSTRACT

Cancer undergoes genetic changes that lead to the proliferation of uncontrolled cells. The cancer death rate in Indonesia based on WHO Globocon 2020 data is recorded as many as 273,523,621 peoples. Changes in taste and smell can occur before treatment, with the modality of other treatments, and in cancer patients. Taste perception are mediated by taste receptor cells on the dorsal and postero-lateral surfaces of the tongue, and on the surface of the oropharynx and larynx epithelials. T2R expression has been reported in various types of cells and also in the airways, gastrointestinal tract, pancreas, heart, breast, thyroid, skin, and testicles. T2R38 bitter taste receptor have been shown to be found in PBMC. To better determine the potential contribution of T2R38 receptor in adaptive immune responses. In this narrative review, we will provide an explanation of the T2R38, its function and can be affected by cancer.

Keywords: Cancer, Taste, T2R38 receptor

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INTRODUCTION

Malignant tumor is the common designation for all cancers. There is a genetic alteration that is passed on to hereditary cancer cells that cause uncontrolled cell proliferation in cancer cases (1). The prevalence of cancer in Indonesia in the last 5 years is based on data from WHO Globocon 2020 for men and women of all ages, which is 946,088 peoples out of a total population of 273,523,621 peoples, while the death rate from cancer is recorded at 234,511 peoples. Recorded cases of cancer include lung, colon liver, nasopharyngeal, prostate, breast, uterus, ovarian, thyroid, and other cancers (2). Malnutrition is common in cancer patients and is an important predictor of morbidity, death, treatment response, and toxicity. Changes in taste and smell are common and can lead to malnutrition. Previous research has focused on patients receiving chemotherapy or radio therapy for the head and neck. However, alteration in taste and smell can occur before treatment, with other treatment modalities, and in people with cancer. Taste perception is mediated by taste receptor cells on the dorsal and postero-lateral surfaces of the tongue, and on the epithelial surface of the oropharynx and larynx (3). Several studies reported on the effects of radiation on cancer patients suggest that radiation can cause an increase in bitter and metallic taste [in cancer patients] causing oral discomfort (4).

Taste type 2 receptors (T2R or Tas2R) correspond to the subfamily GPCR originally found expressed in vertebrate tongues and are dedicated to the perception of bitterness in food (5). Latterly, T2R has been found in various types of cells and in various parts of the body such as the airways, digestive tract, pancreas, white blood cells, heart, breast, thyroid, skin, testes, and adipocytes (6, 7). The T2R38 family of bitter receptors was originally identified on taste cells. The bitter taste receptor T2R38 coupled with human G-protein has recently been reported on peripheral blood neutrophils, monocytes, and lymphocytes to further determine the potential contribution of the T2R38 receptor in adaptive immune response (8). In this narrative review, we will provide an overview of T2R38, its function is primarily an immune response and can be contacted by cancer.

T2R38 TASTE RECEPTOR

Bitter taste receptors (T2Rs) are seven-transmembrane domains of guanine nucleotide binding protein (G-protein) -added receptors (GPCRs), which have about 30 different subtypes. T2Rs were initially

identified in taste papillae in the tongue and palate epithelium, where they were exclusively expressed in taste cells containing the α-gustducin G protein subunit. In vitro gustducin is an important component of the signal transduction pathway after T2R activation (9).

Some receptors can bind structurally unrelated compounds to different natural ligands, for others have not been identified. From previous reports, bitter receptors are also expressed by cells that are not part of the gustatory system, for example by airway epithelial cells, in the brain, pancreatic duct cells, or enteroendocrine cells in the colon and by myeloid cells. These receptors do not participate in taste perception, and they are responsive to a variety of unrelated structural substances, including amino acids, peptides or sugars (6).

The chemosensing protein T2R is known to have 25 types of isoforms and is expressed in several tissues, including the oral cavity and gastrointestinal tract (11). One of 25 human bitter taste receptors, the T2R38 antithyroid toxin receptor, responds to compounds containing thiourea (NC = S) moiety (8). Alongside of tr238 is that its anti-cancer effect has been shown by compounds containing N-C = S, such as allyl-isothiocyanate, have proven cancer chemo-preventive effects. It should be noted that the human T2R38 receptor is specific for compounds containing the N-C = S portion (12).

THE STRUCTURE OF THE T2R38 RECEPTOR

GPCR domain 7-transmembrane, 333 amino acids in length is the T2R38 bitter taste receptor (9). The bitter taste receptors are believed to consist of homo- or hetero-oligomeric isoforms from the taste receptor family 2 (T2R). Most of the T2R isoforms have been shown to have immunoprecipitate together with other T2R isoforms that are co-expressed in heterologous expression systems (13).

T2R38 RECEPTOR SIGNALING

Taste receptors are used as chemosensor by cells in the oral cavity and outside the oral cavity. Various biological responses under normal conditions have resulted from the activation of T2R receptors (14).

Part of the canonical T2R signal transduction cascade of common signaling molecules with sweet and umami receptors, which includes heterotrimeric G protein subunits (i.e., α-gustducin [Gnat3], Gβ3, and Gγ13), phospholipase C (PLCβ2), inositol trisphosphate receptors (InsP3R), and transient receptor potential cation channels (TRPM5; Figs. 1, A and B). The gustducin G protein separates the α, Gnat3, and βγ subunits after receptor activation. Finally, it will activate PLCβ2, which causes the release of Ca^{2+} from Ca^{2+} storage which is sensitive to InsP3 and results in the entry of Na^{+} through the TRPM5 channel. The process of cell depolarization occurs when Na^{+} enters and causes the release of the neurotransmitter ATP through gap junction hemichannels or the CAL HM1 ion channel. Finally, the released ATP activates purinergic receptors on nerves in the sense of taste, and the resulting impulses are transmitted to the taste centers in the central nervous system to initiate the perception of bitter taste (14).

On the other hand, three different mechanisms are used by nonlingual T2R to carry out a biologic role adapted to its location. These three cascades have the same initial half-life (i.e., from receptor activation to increased intracellular calcium [Ca] concentration) as the canonical T2R signaling cascade (Fig. 1 A) and then diverge to produce multiple functions in the different cell or tissue types. These mechanisms can be called autonomic regulation of cells, paracrine regulation, and endocrine regulation (14). T2R in upper respiratory cells uses most of the canonical bitter taste signal cascade including phospholipase C β2 and TRPM5 (transient cation channel potential of the 5 member M member subfamily), but of particular interest is not gustducine, the G-protein classically associated with T2R in the tongue (15).

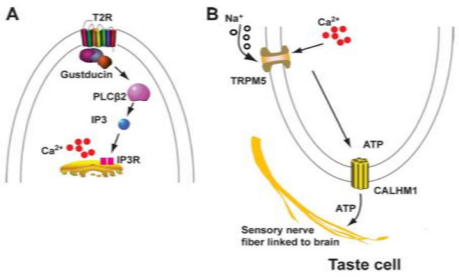

Figure 1 : Canonical T2R signaling pathway. (A) The invariant portion of T2R-mediated signaling in the tongue and extracellular/ tissue includes bitter compounds that bind (externally: not described) with receptors to increase intracellular calcium. (B) The residual component of the T2R line is taster.

THE FUNCTION OF THE T2R38 RECEPTOR IN THE IMMUNE SYSTEM

The T2R38 receptor in the respiratory tract play a role in the innate immune response. In figure 2, from left to right, the acyl-homoserin lactone (AHL) molecule is secreted by gram-negative bacteria to regulate quorum sensing. T2R38 is activated by AHL molecules expressed in human sinonasal cilia and unidentified T2R in rat nasal cilia, activation of PLCb2 is generated, which liberates IP and results in initiation of calcium (Ca^{2+}) signals which activate nitric oxide production of nitric oxide (NO) which depends on synthase (NOS) (Fig. 2). NO production has two distinct effects. The first is

activation of cellular protein kinase G (PKG), which phosphorylates ciliary protein to increase ciliary spanking and mucociliary transport. NO also diffuses directly into airway surface fluids, where it has a direct bactericidal effect (13, 16, 17).

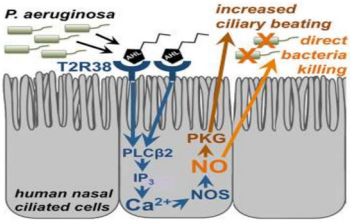

Figure 2 : Regulation of the T2R38 bitter taste receptor of the innate immunity of the airway epithelium.

The T2R38 receptor also plays a role in the digestive system, sinuses, trachea, nasal and urethral tract by the following cascade, in figure 3, (A) T2R in EEC is activated by food toxins or bitter compounds from bacteria in the intestine to release the peptide hormone CCK, which acts through the receptors. CKK2 in neighboring enterocytes to promote ABCB1 to pump bitter-tasting toxins out of enterocytes (right). In addition, the CCK released by the EEC can also be activated. The CCK1 receptors on the sensory fibers of the vagus nerve send signals to the brain to limit food intake (left). (B) The paracrine model also works in mouse SCC of the nasal or VNO organs and in the brush cells of the trachea and bladder, where the bitter compound or N-acyl homoserin lactone, the bacterial quorum sensing molecule, activates the bitter taste signal to release Ach, then activating the sensory fiber vates to (a) initiate a protective reflex, which causes a decrease in respiratory rate or an increase in bladder contraction; (b) closes the VNO tract; or (c) induce neurogenic inflammation in the nasal cavity. (C) In the bundle cells of the intestine, the parasite activates the canonical taste cascade and releases IL-25, which in turn increases the amount of ILC2 and increases secretion of the type 2 immune cytokines IL-13 and IL-4; These cytokines then increase the hyperplasia of bundle cells and goblet cells (14).

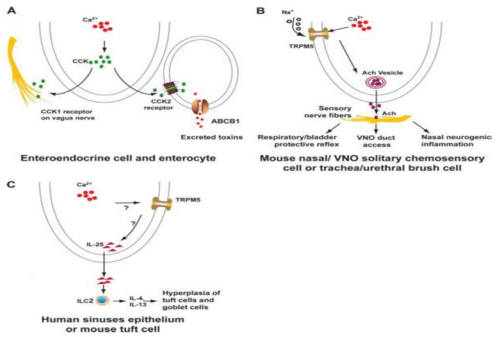

Figure 3 : A cascade of T2R38 signaling related to the immune system.

T2R38 RECEPTOR EXPRESSION IN CANCER

T2R is reported to be expressed in tumor cells or cancer cells. T2R38 is known to be expressed in tumor cells and tumor cell lines derived from pancreatic cancer patients. The phenylthiourea T2R38-specific ligand, or AHL-12 natural ligand, activates the mitogen-activated protein kinase p38 and ERK1 / 2 and increases NFATc1 in a G protein-dependent manner. T2R38-positive tumors are not associated with clinical and pathological parameters, but the T2R38 ligand increases expression of ABCB1 and appears to be associated with pancreatic cancer resistance and T2R38 (18).

Research by Gaida et. al (2016) described T2R38 expression in tumor cells in patients with pancreatic cancer and tumor-derived cell lines. T2R38 is localized mainly in intracellular contact with lipid droplets, especially with the lipid droplet membrane.

Figures 4A through D are PDAC tissue biopsies shown, stained for T2R38 (two different tumors; magnification: A, B: 100x; C, D: 200x) PDAC cells are positive for T2R38 (bold arrow), as are invaded immune cells (arrows) thin). E to F are T2R38 positive tumor cells (thick arrows) in front of the invasive tumor in the duodenal wall (magnification E: 200x; F: 400X). The lumen of the intestine is marked with an asterisk. Section G, in comparison, negative PDAC biopsy for T2R38 was shown (still with scattered positive T2R38 infiltrated immune cells marked with thin arrows; tumors marked with arrows; 200x), and in normal acinar pancreatic tissue. H section, which is negative for T2R38 (200x magnification) (6).

The results of other studies found specific patterns of TAS2R expression with TAS2R7, 16, 38, 39, 40, 41, and 42 at almost undetectable levels, TAS2R1, 8, 9, and 60 at low levels, TAS2R3, 4, 5, 10 , 13, 19, and 50 at moderate levels, and TAS2R14 and TAS2R20 (or TAS2R49) at high levels. This scheme of expression is largely bold of tissue origin and pathological conditions, except for breast cancer cells (19).

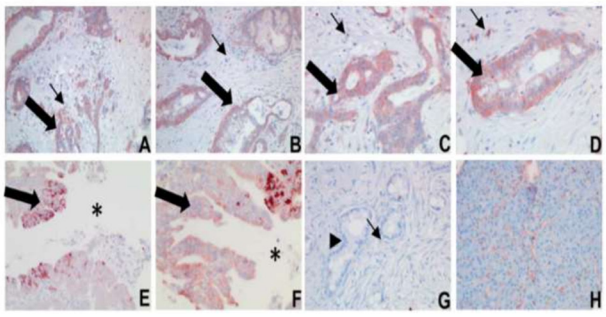

Figure 4 : Expression of T2R38 in the pancreatic tissue.

CANCER AFFECTING T2R38 MECHANISM

The AVI haplotype or AVI homo-plotted associated with the incidence of gastric cancer (GC) and colorectal cancer (CRC) has been reported by researchers (10).

Bona fide ligands can activate receptors for T2R38, phenylthiourea (PTU), and by N-acetyl-dodecanoyl homoserin (AHL-12), the quorum sensing molecule *Pseudomonas aeruginosa*, the latter being the only known natural ligand for T2R38. In response to PTU or AHL-12, key transcription factors activated include phosphorylation of MAP kinases p38 and ERK1 / 2, and upregulation of NFATc1. In conclusion, data suggest a new additional function of the T2R38 taste receptor beyond "bitter" sensing. In addition, because T2R38 can be stimulated by signaling molecules derived from bacteria, the receptors can link microbiota and cancer (6).

In fact, binding to a T2R organization results in activation of heterotrimeric G protein derived from the dissociation farm into the Gα gustucine and Gβ3/ Gγ13 subunits. The subunit activates phospholipase C-β2 (PLCβ-2), which hydrolyzes phosphatidylinositol-4,5bisphosphate (PIP2) to inositol-1,4,5-triphosphase (IP3) and diacyl glycerol (DAG). IP3 stimulates the release of Calcium from intracellular stores by acting on IP3 receptors on the endoplasmic reticulum. In human lymphocytes, eventual cell proliferation and cytokine production can result from Calcium signaling. In addition, the results showed that goitrin selectively timely anti-inflammatory response in reducing TNFalpha secretion in PBMCs with functional but non-functional T2R38 receptors (8). Besides research by Carrai et al. (2011) it was found that the non-taster group had a higher risk of colorectal cancer than the taste group when the plotype and phenotype were analyzed (20).

Psychophysical bitter sensitivity as recognized by T2R38 receptors in the tongue has also been shown to decline over life in particular. Lower levels of T2R38 in elderly immune cells can add to the disruption of adaptive immune system defense capabilities observed with age (8)

CONCLUSION

It can be concluded from literature studies that the T2R38 receptor plays a role in the innate immune system, namely in the upper respiratory system, digestive system, urinary system, and is found in PBMC. Signaling paths are generally the same, i.e. through canonical cascades or nonlingual cascades. Cancer can affect the T2R38 receptor through disruption of the signaling cascade, for example using goittrin. Changes in taste perception can result from cancer therapy.

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