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Lab Note

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New values of a type 2 taste receptor TAS2R14 in thyroid cancer

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Recognition of bitter substances is mediated by type 2 taste receptors (TAS2Rs) family which consists of over 20 members. Traditionally, TAS2Rs are thought to be specifically expressed in the tongue. Recent studies on TAS2R member TAS2R14 in non-gustatory tissues supported its new functions beyond the perception of bitter taste. TAS2R14 regulates resveratrol transport across the human blood-cerebrospinal fluid barrier [1], which renders hope for resveratrol to be used in the treatment of brain diseases. TAS2R14 also mediates the relaxation of smooth muscle [2], indicating its value for the development of effective tocolytics for preterm birth management. TAS2R14 also has an anti-inflammatory property. TAS2R14 can inhibit IgE-induced mast cell degranulation with anti-asthma activity when activated directly by Saikosaponin b [3], and prevent LPS-induced cytokine production in human lung macrophages [4]. Of note, TAS2R14 also has endocrine regulatory effect. It stimulates glucagon-like peptide 1 secretion in rat gastrointestinal tract [5], and may also have appetite-suppressant effects by inducing cholecystokinin secretion [6]. Of greater interest is that we found that TAS2R14 might be a receptor for bitter medicines to fight COVID-19 [7,8]. Meanwhile, TAS2R14 has recently been linked to oncology. Agonists of TAS2R14, including quercetin and naringenin, exhibit anti-cancer activities in numerous cancer types [9]. Noscapine stimulation of TAS2R14 increases apoptosis in ovarian cancer cells [10]. However, the involvement of TAS2R14 in the risk and development of cancers including thyroid cancer (THCA) has yet to be clarified.

THCA represents the most common endocrine malignancy, and its incidence has been increasing over the last few decades all over the world. Here, we aimed to elucidate the potential of TAS2R14 as a new drug target and a biomarker of diagnosis and prognosis prediction for THCA. Web of Knowledge, Embase, and PubMed were searched and assessed. Using the high-throughput sequencing big data from The Cancer Genome Atlas (TCGA) [11], we first examined the expression levels of TAS2R14 in 20 types of human cancers, including adrenocortical carcinoma (ACC), bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cervical squamous cell carcinoma (CESC), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), kidney choromophobe (KICH), kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), ovarian serous cystadenocarcinoma (OV), pancreatic adenocarcinoma (PAAD), prostate adenocarcinoma (RAD), skin cutaneous melanoma (SKCM), thyroid carcinoma (THCA), uterine corpus endometrial carcinoma (UCEC), and uterine carcinosarcoma (UCS). Then, we focused our analysis on THCA based on more than 800 cases. All the analyses were conducted following the instructions of Gene Expression Profiling Interactive Analysis (GEPIA) [12] and University of Alabama Cancer Database (UALCAN) [13].

We found that TAS2R14 expression in 20 types of tumors is decreased (Supplementary Figure S1A), despite that some other tumor types show up-regulated expression or no changes (data not shown). Furthermore, we specially examined the expression of TAS2R14 in THCA and found significantly declined expression of TAS2R14 in THCA (Supplementary Figure S1B,C). And the check of clinical sample expression analysis via qRT-PCR and western blot analysis confirmed this descended expression of TAS2R14 in THCA (Supplementary Data and Supplementary Figure S2A,B). We then examined the expression level of TAS2R14 in different populations with THCA, and found that TAS2R14 showed differential expression in different population groups. Although TAS2R14 expression in THCA showed no significant association with the stage, race, gender or age of patients (Figure 1A–D), significant expression differences were observed among different subtypes of THCA patients (Figure 1E). Expression of TAS2R14 in tall papillary thyroid cancer (PTC) is significantly distinct from that in classical PTC and follicular PTC subtypes (Figure 1E).

Then, we analyzed the association between TAS2R14 expression and survival of patients, and found that low TAS2R14 expression in THCA was significantly associated with a high overall survival rate,

and the survival rate is more than 90% for the patients with low expression level of TAS2R14 (Figure 2A). For disease free survival, high TAS2R14 expression in THCA is significantly associated with low survival rate, and the survival rate is more than 85% for patients with high expression level of TAS2R14 (Figure 2B).

Here, based on the high-through sequencing big data, we found declined expression of TAS2R14 in 20 tumor types, indicating that TAS2R14 may be a new candidate for drug development. TAS2R14 showed differential expressions in different population groups of patients with THCA; however, TAS2R14 expression showed no significant association with the stage, race, gender or age of patients. Only significant expression differences in patient's subtype were observed, that is, TAS2R14 expression in tall PTC is significantly distinct from that in classical PTC and follicular PTC subtypes. However, the expression levels of all checked tumor subtypes are significantly lower than those in the normal group,

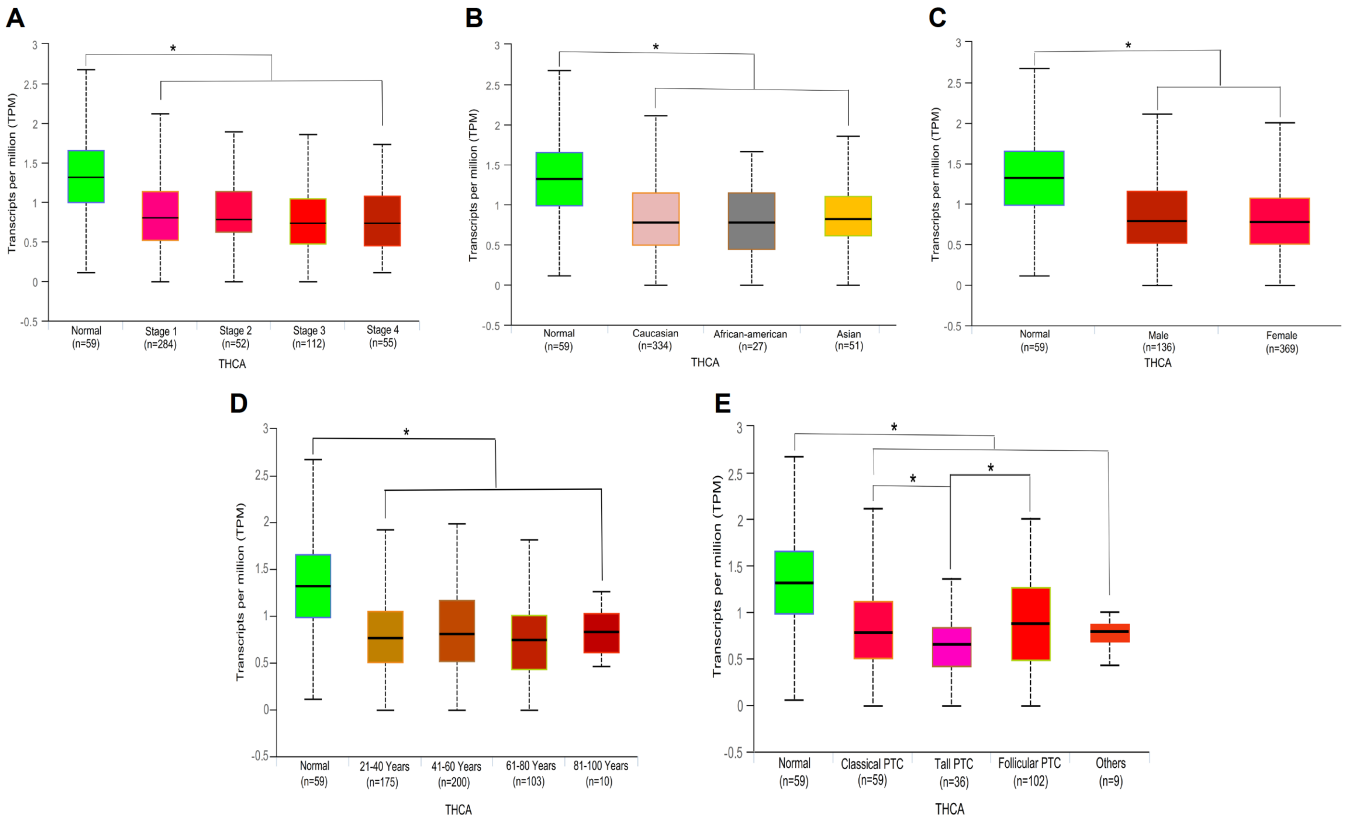

Figure 1. Obvious differences in TAS2R14 expression among different population groups with THCA (A) Differential expression of TAS2R14 in thyroid cancer patients of different stages. (B) Differential expression of TAS2R14 in thyroid cancer patients of different races. (C) Differential expression of TAS2R14 in thyroid cancer patients of different genders. (D) Differential expression of TAS2R14 in thyroid cancer patients of different age. (E) Differential expression of TAS2R14 in thyroid cancer patients with different subtypes. *$P < 0.05$.

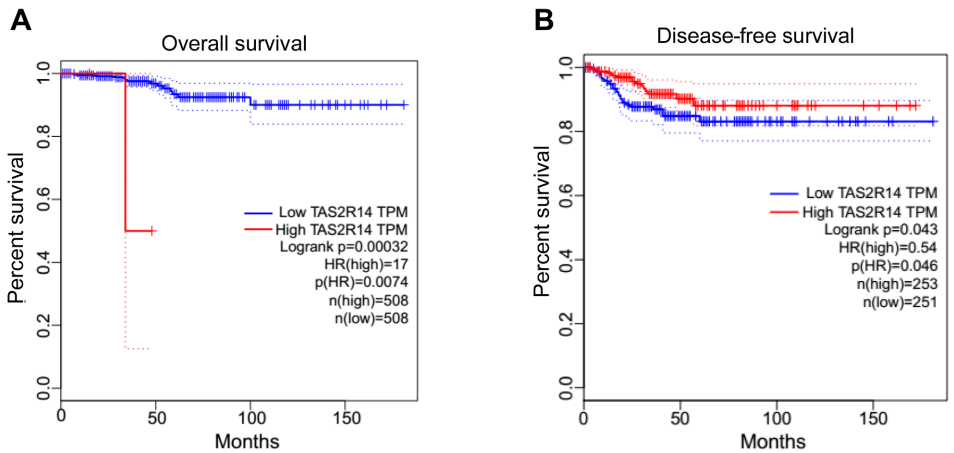

Figure 2. Survival analysis of THCA patients based on TAS2R14 expression (A) Overall survival of patients with THCA. (B) Disease-free survival of patients with THCA.

suggesting that TAS2R14 may have the diagnosis value for clinical prediction of tumors. We also found that low TAS2R14 expression in THCA is significantly associated with high overall survival, while high TAS2R14 expression in THCA is significantly associated with low disease-free survival, indicating that TAS2R14 may be a critical factor for assessing THCA patients' survival, suggesting its important prognosis significance. As such, extrapolating the molecular mechanisms from our results, TAS2R14 may inhibit THCA development. However, experiments using tumor cell and nude mice model need to be performed to confirm these preliminary results.

Collectively, TAS2R14 expression is decreased in thyroid cancer and significantly associated with tumor subtype and patient's survival. As far as we are aware, our investigation clarified the important clinical significance of TAS2R14 in cancers for the first time. Investigating the relationship between bitter taste receptors and tumors is just beginning, and much more research remains to be done.

Supplementary Data

Supplementary data is available at *Acta Biochimica et Biophysica Sinica* online.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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