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Hans汉斯

肥胖导致甲状腺癌发生发展的潜在机制

吕晓霞，廖　琳*

山东第一医科大学第一附属医院，山东省千佛山医院内分泌与代谢病科，山东　济南

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摘　要

近年来，甲状腺癌发病率急剧上升，与全球肥胖患病率增长同步，提示两者存在潜在关联。本文系统综述了肥胖导致甲状腺癌发生发展的多种分子机制：肥胖相关的脂肪因子紊乱，包括脂联素水平降低、瘦素水平升高及其通过AKT/mTOR/PI3K和ERK/MAPK通路促进肿瘤细胞增殖、迁移和血管生成；促炎细胞因子IL-6和TNF-α升高通过JAK/STAT通路促进上皮－间充质转化和肿瘤转移；高胰岛素血症和胰岛素抵抗通过胰岛素受体及IGF-1系统增强促甲状腺激素的有丝分裂作用；雌激素通过ER-α/ER-β失衡促进甲状腺癌细胞增殖；COX-2上调、慢性低度炎症状态及氧化应激共同构成促肿瘤微环境。此外，膳食炎症指数、癌症相关脂肪细胞与肿瘤的“串扰”以及局部异位脂肪组织沉积也在肿瘤进展中发挥重要作用。生活方式干预、减重及降低肥胖发生率对甲状腺癌的预防和治疗具有关键意义，是未来研究的重要方向。

关键词

甲状腺癌，肥胖，胰岛素抵抗，氧化应激

The Potential Mechanisms by Which Obesity Contributes to the Occurrence and Development of Thyroid Cancer

Xiaoxia Lv, Lin Liao*

Department of Endocrinology and Metabolic Diseases, Shandong Provincial Qianfoshan Hospital, The First Affiliated Hospital of Shandong First Medical University, Jinan Shandong

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Abstract

In recent years, the incidence of thyroid cancer has risen sharply, coinciding with the global increase

*通讯作者。

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in obesity prevalence, suggesting a potential association between the two. This article systematically reviews the various molecular mechanisms by which obesity leads to the occurrence and development of thyroid cancer: dysregulation of obesity-related adipokines, including decreased adiponectin levels and increased leptin levels, which promote tumor cell proliferation, migration, and angiogenesis through the AKT/mTOR/PI3K and ERK/MAPK pathways; elevated pro-inflammatory cytokines IL-6 and TNF-α promote epithelial-mesenchymal transition and tumor metastasis through the JAK/STAT pathway; hyperinsulinemia and insulin resistance enhance the mitogenic effect of thyroid stimulating hormone through the insulin receptor and IGF-1 system; estrogen promotes thyroid cancer cell proliferation through the imbalance of ER-α/ER-β; COX-2 upregulation, chronic low-grade inflammation state, and oxidative stress jointly constitute the tumor-promoting microenvironment. Additionally, dietary inflammatory index, cancer-related adipocytes, and "cross-talk" between tumors and fat cells, as well as local ectopic fat tissue deposition also play important roles in tumor progression. Lifestyle intervention, weight loss, and reduction of obesity incidence are of crucial significance for the prevention and treatment of thyroid cancer and are important directions for future research.

Keywords

Thyroid Cancer, Obesity, Insulin Resistance, Oxidative Stress

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1. 引言

癌症是全球第二大死亡原因[1]，近年来，甲状腺癌尤其是甲状腺乳头状癌(Papillary thyroid carcinoma, PTC)的患病率在全球范围内显著上升[2]。据世卫组织国际癌症研究机构 GLOBOCAN 2022 数据库统计，甲状腺癌在全球癌症新发病例中位居第七[3]。除遗传易感性、电离辐射等已知危险因素外，肥胖也被视为甲状腺癌发生发展的重要危险因素[1] [4]-[9]。甲状腺癌发病率的攀升与全球肥胖率的上升呈同步趋势[5] [6] [10]。超重和肥胖的流行率在发展中国家与发达国家均快速蔓延，在工业化国家成年人群中已达60%~70%的流行水平，且在女性及城市地区更为普遍[1]。当能量摄入超过代谢及身体活动消耗时，便会导致肥胖[11]。由于异常脂肪组织过度堆积，超出遗传和表观遗传所决定的脂肪储存容量，脂肪以异位脂肪组织形式沉积累积，进而增加多种疾病风险[8]。肥胖促进甲状腺癌发生发展的潜在机制涉及多个方面，包括高胰岛素血症与胰岛素抵抗、慢性低度炎症、细胞因子水平异常、氧化应激及激素变化等[5] [8] [12]-[14]。本文将系统阐述肥胖导致甲状腺癌发生发展的潜在机制，以期为临床治疗提供参考依据。

脂肪组织(Adipose tissue, AT)是由脂肪细胞构成的特殊结缔组织，被视为哺乳动物代谢稳态的关键调节者，也是机体内最高效的脂质储存场所[4]。作为内分泌器官，AT 能够分泌多种名为脂肪因子的活性分子，向重要器官传递信号以维持代谢平衡[4] [15]。在肥胖个体中，脂肪组织内免疫系统功能紊乱引发慢性低度炎症，表现为先天性和适应性免疫细胞浸润及活化增强，单核细胞浸润后分化为促炎性 M1 巨噬细胞，后者生成并释放大量炎症介质，干扰胰岛素信号通路，进而导致局部和全身性的促炎环境[16]-[19]。肥胖状态下，脂肪细胞的肥大化推动了 TNF-α、单核细胞趋化蛋白-1 (MCP-1)、IL-6、内皮粘附分子、C 反应蛋白以及趋化因子等促炎因子的产生[4] [20]-[22]。高水平的脂肪因子可能损害甲状腺细胞增殖并诱发肿瘤形成。

2. 脂联素

脂联素(Adiponectin, APN)是一种由脂肪组织特异性分泌的重要脂肪因子，在机体能量代谢稳态调控中发挥核心作用[23]。其最主要的生理功能在于显著增强外周组织对胰岛素的敏感性，促进葡萄糖的摄取与利用，同时抑制肝脏糖异生，从而有效维持血糖稳态[1] [6] [24]。临床流行病学研究明确显示，血浆 APN 水平的下降与胰岛素抵抗的发生发展密切相关，这一病理现象在肥胖症、2 型糖尿病、代谢综合征以及动脉粥样硬化等多种代谢性疾病中均得到广泛证实，表现为循环中 APN 浓度的显著降低[5] [25]。近年来，大量基础与临床研究表明，APN 除经典的代谢调节功能外，还具有重要的抗肿瘤生物学活性[26]。APN 可通过激活 AMP 活化蛋白激酶(AMPK)、过氧化物酶体增殖物激活受体 α (PPARα)以及 p38 丝裂原活化蛋白激酶(p38 MAPK)等多种细胞内信号级联途径，直接作用于肿瘤组织，抑制肿瘤细胞增殖、诱导细胞凋亡，并有效调控肿瘤血管生成过程，从而遏制肿瘤的恶性进展[27]-[29]。值得注意的是，肥胖作为多种恶性肿瘤的独立危险因素，其病理状态下 APN 水平显著降低，这构成了肥胖促进肿瘤发生发展的重要分子机制之一[30]。在内分泌系统肿瘤研究领域，甲状腺癌与 APN 的关联日益受到关注[31]。多项大样本临床对照研究一致证实，相较于年龄、性别匹配的健康对照人群，各类组织学亚型的甲状腺癌患者——包括乳头状甲状腺癌、滤泡状甲状腺癌以及未分化癌等——其循环 APN 水平均呈现明显偏低状态[1] [4] [31]。然而，值得注意的是，不同甲状腺癌亚型对脂联素的响应可能存在差异[32]。例如，在 PTC 中，APN 的抑癌效应更为显著，这可能与其更强的 AMPK 激活能力有关；而甲状腺滤泡状癌(Follicular thyroid carcinoma, FTC)对 APN 信号通路的依赖性较低，其潜在机制需进一步探索[32]。此外，BRAF 突变型 PTC 患者中 APN 水平降低更为明显，可能与 BRAF 信号通路的持续激活抑制了脂肪细胞的分化和 APN 分泌有关[31] [32]。

3. 瘦素

瘦素(Leptin)是一种由脂肪组织分泌的多效性激素，在肥胖的发生发展中发挥关键作用[33]。从结构上看，瘦素与白细胞介素-2 (Interleukin-2, IL-2)、白细胞介素-6 (Interleukin-6, IL-6)及粒细胞集落刺激因子等细胞因子相似，因而能够参与类似的细胞及生理过程，例如通过产生饱腹感调控摄食行为、调节能量消耗[6] [34]。肥胖患者体内长期维持较高的循环瘦素水平，可引发“高瘦素血症”或瘦素抵抗，使下丘脑对瘦素信号及机体能量储备状态的敏感性下降，而瘦素抵抗又会促使炎症反应持续[27] [35] [36]。瘦素可以通过激活细胞内信号通路如 AKT/mTOR/PI3K 和 ERK/MAPK 通路，影响细胞周期调节剂的表达、细胞增殖、转化、迁移和侵袭、刺激血管内皮生长因子、血管生成和抑制抗炎细胞因子[7] [37]-[41]。瘦素水平与身体质量指数(Body mass index, BMI)相关，BMI 高和/或体脂量大的个体瘦素水平更高[40] [42]。瘦素及其受体(OB-R)的过表达已经在许多癌症中被发现，包括甲状腺癌[4] [43]。有研究证明，瘦素及其受体在甲状腺乳头状癌细胞中过表达，诱导甲状腺乳头状癌细胞增殖并抑制凋亡，可以增强甲状腺乳头状癌细胞的迁移[44]-[46]。瘦素/OB-R 通路在 PTC 中激活程度远高于 FTC [45]。研究表明，瘦素以剂量依赖的方式，通过 PI3K/AKT 和 MEK/ERK 信号通路促进了 PTC 细胞的迁移[47] [48]。同时，瘦素也通过激活 STAT3 通路促进上皮－间质转化(Epithelial-mesenchymal transition, EMT)和肿瘤侵袭[49]。而在 FTC 中，瘦素可能更多通过 PI3K/AKT 通路促进细胞存活和抗凋亡[44]。BRAF 突变型 PTC 对瘦素诱导的迁移与侵袭增强更敏感，RAS 突变型则是以增殖驱动为主[45]。

4. IL-6 和 TNF-α

肥胖人群中常观察到细胞因子 IL-6 和 TNF-α 水平升高。这些因子与其他促炎因子共同作用，可能促进甲状腺癌的发生发展[16] [22] [50]。IL-6 可激活 JAK/STAT 信号通路，该通路参与能量消耗、胰岛素敏

感性、糖耐量、肥胖调控及细胞生长增殖等多种代谢过程[51]-[53]。体外研究显示，IL-6 经 JAK/STAT3 通路促进间变性甲状腺癌干细胞增殖，并诱导 EMT，进而推动甲状腺癌生长与转移[4] [54]-[57]。EMT 指上皮细胞向间质表型转变的过程，该过程削弱细胞间及细胞与基质的粘附能力，增强细胞迁移活性[1] [58]-[60]。肿瘤间质中的间充质细胞作为关键祖细胞，在肿瘤恶性转化中扮演重要角色[1] [61]。TNF-α 是首个被鉴定的脂肪组织源性脂肪因子，其循环水平在肥胖及胰岛素抵抗者中升高，兼具促炎特性，参与肿瘤细胞毒效应及血管生成调控[62] [63]。与良性甲状腺病变相比，乳头状甲状腺癌(PTC)组织中 TNF-α mRNA 表达显著上调[64]。尽管现有研究提示 TNF-α 与甲状腺癌存在密切关联，但证据尚不充分，仍需深入探索该细胞因子在甲状腺癌中的具体作用机制[4]。研究发现，IL-6 和 THF-α 在不同甲状腺癌亚型中的作用可能存在差异。IL-6/JAK/STAT3 在 PTC 中更易激活并驱动 EMT，FTC 则是以 TNF-α 介导的血管生成与侵袭为主[55]。此外，其他研究表明，BRAF 突变型 PTC 的 IL-6 通路活化显著强于 RAS 突变型[55]。

5. 高胰岛素血症和胰岛素抵抗

肥胖作为糖尿病的危险因素，会使个体胰岛素敏感性下降，促使胰岛 β 细胞增加胰岛素分泌，进而引发高胰岛素血症与胰岛素抵抗(Insulin resistance, IR) [65]-[67]。多项研究证实，胰岛素抵抗与甲状腺癌等多种癌症的发病风险上升存在关联[6] [7] [44] [68]。胰岛素可通过直接或间接途径促进肿瘤形成，其对靶细胞的刺激作用经由胰岛素受体或胰岛素样生长因子(Insulin-like growth factor, IGF)实现[5] [8] [69]。胰岛素能够降低 IGFBP1 及 IGFBP-2 在血液中的浓度，从而使循环 IGF 水平升高。胰岛素与 IGF 可在靶细胞中激活多种促癌机制，涵盖细胞增殖、抗凋亡、血管生成及淋巴管生成等方面[1] [70]-[72]。IGPBP 属于 IGF 的特异性高亲和力结合蛋白。乳腺癌、结肠癌、肺癌、前列腺癌、卵巢癌及甲状腺癌等众多肿瘤均高表达胰岛素受体[73]-[77]。该受体包含胰岛素受体-A (IR-A)与胰岛素受体-B (IR-B)两种剪接异构体[78]-[80]。在肿瘤组织中，异常信号通路造成剪接因子表达变化，使得 IR-A 表达上调，这可能是高胰岛素血症影响肿瘤发生的机制之一；此外，胰岛素还可增强细胞代谢活性，提升氧化应激水平，造成 DNA 损伤，进一步升高癌症发生风险[1] [76] [81] [82]。既往研究表明，胰岛素抵抗与 FTC 风险关联更强，PTC 次之[13]。RAS 突变型甲状腺癌对高胰岛素环境的增殖响应更突出，BRAF 突变型则是以抗凋亡为主[13]。

6. 胰岛素样生长因子

胰岛素样生长因子(IGFs)在正常人体生理和病理状态中发挥着关键作用[83]-[85]。IGF 系统由以下部分组成：两种生长因子(IGF-1 和 IGF-2)、细胞表面受体(IGF-1r 和 IGF-2r)、六种特异性高亲和力结合蛋白 IGFBP-1 至 IGFBP-6 以及其他 IGF 结合分子[1] [86]-[88]。IGF-1 的生物学效应由 IGF-1r 介导[8]，该受体是一种跨膜蛋白，具有酪氨酸激酶结构域，激活后会触发一系列涉及 AKT、RAF-1/MEK/ERK 蛋白的级联反应，这些蛋白是参与癌症增殖和存活的主要信号通路[89]-[91]。此外，IGF-1 通过 PI3K/AKT 细胞存活途径抑制细胞凋亡，并刺激甲状腺癌中血管内皮生长因子的合成，同时抑制性激素结合球蛋白(SHBG)的合成，增加游离性激素水平，从而促进性激素依赖性肿瘤的发生[7] [92]。IGF 轴的失调可促进甲状腺癌的发生[93]。研究表明，分化型甲状腺癌患者体内 IGF-1r 的表达水平较高[94]。胰岛素和/或 IGF-1 能够在转录水平上调控 TSH 受体基因和甲状腺球蛋白基因的表达[8]，增强促甲状腺激素(TSH)的增殖效应[95]。在甲状腺中，这两种激素被认为是 TSH 作用于甲状腺滤泡细胞所必需的辅助因子[7] [95]。促甲状腺激素是甲状腺细胞生长的主要生理性促进剂，而 IGF-1 可增强 TSH 的有丝分裂作用[4] [96]。IGF-1/IGF-1R 轴在 FTC 中活化更显著，与远处转移相关；RAS 突变型对 IGF-1 刺激更敏感，BRAF 突变型则依赖 IGF-1 介导的耐药与侵袭[72] [97]。

7. 雌激素

雌雌激素可作为良性和恶性甲状腺结节的生长因子，在女性肥胖发展中也发挥重要作用[98] [99]。脂肪组织经芳香化酶作用参与内源性类固醇的合成与转化[100]。在肥胖个体中，芳香化酶浓度增加和过度激活导致雌激素和雄激素之间的失衡，雌激素浓度增加，这可能导致甲状腺癌的发生[1] [4] [101]。雌激素属类固醇激素，主要调控生殖器官的生长、分化及功能，同时对骨骼、心血管和免疫系统产生多种生物效应[102] [103]。其作用机制包括雌激素受体介导的基因组途径与非基因组途径，核雌激素受体分为ER-α 和 ER-β 两种亚型，二者在细胞增殖与存活方面功能相拮抗：ER-α 促进细胞增殖、抑制凋亡，ER-β 则辅助细胞分化并诱导凋亡[6] [7] [104] [105]。多项研究表明，在甲状腺癌细胞中，ER-α 过度表达，ER-β 表达减少或缺失，此外 ER-α 激动剂诱导甲状腺癌细胞增殖[5] [6]，而 ER-β 表达增加或 ER-β 激动剂的使用会降低甲状腺癌细胞的增殖[4] [106] [107]。雌激素也通过调节甲状腺细胞的血管内皮生长因子分泌来促进甲状腺癌的血管生成[108]。ER-α/ER-β 失衡在女性 PTC 中更突出。在 BRAF 突变型的 PTC 中 ER-α 表达更高，对雌激素促增殖效应更敏感[104]。

8. 环氧化酶-2

环氧化酶-2 (COX-2)为诱导型酶，在细胞增殖与炎症反应过程中受多种刺激因素而上调[109]。COX-2 与多种上皮性癌症的发生发展密切相关[110] [111]。其致癌机制涉及促进前列腺素合成、促使原致癌物向致癌物转化、抑制细胞凋亡、诱导血管生成、调控炎症及免疫功能、增强肿瘤细胞侵袭性等多个方面[112]-[114]。COX-2 在甲状腺上皮性肿瘤(如乳头状癌、滤泡癌)中呈阳性表达，而正常甲状腺组织则不表达[115] [116]。超重可能导致正常黏膜中 COX-2 表达失调，肥胖所诱导的 COX-2 水平升高或许与甲状腺癌的发病相关[7] [117]-[119]。COX-2 在 PTC 中阳性率更高，与淋巴结转移相关，在 FTC 中 COX-2 主要促血管生成，与侵袭相关[115]。

9. 肥胖患者的慢性低度炎症

肥胖与低级别慢性炎症状态相关，表现为免疫系统非特异性激活及炎症因子水平升高，多种炎症因子构成的肿瘤微环境可推动癌症的发生与发展[1] [27] [120] [121]。研究表明，内脏脂肪组织中存在促炎性 T 淋巴细胞，可能在巨噬细胞浸润前即促进局部炎症细胞活化，对脂肪组织炎症的启动和持续具有重要作用[6] [122]-[124]。脂肪组织中同时存在 M1 型和 M2 型巨噬细胞：M1 型巨噬细胞经 INFγ 或脂多糖刺激后可分泌促炎细胞因子；M2 型巨噬细胞则参与体液免疫应答，能够产生抗炎细胞因子[125]。肥胖所致的局部缺氧环境可能促使 M2 型向 M1 型转化，进而增加促炎细胞因子的释放，促进甲状腺癌的发生[6] [126] [127]。PTC 以 M1 型巨噬细胞浸润为主，促炎微环境更强，而 FTC 以 M2 型为主，促血管生成与免疫抑制更显著[17]。

10. 氧化应激

氧化应激是一种以自由基和反应性代谢物过量为特征、对生物体有害的状态。自由基指原子或分子轨道上带有一个或多个未配对电子的分子，这类电子会增强分子的反应活性[128]。活性氧(ROS)由氧气衍生而来，在细胞内生成，可分为两类：自由基类如超氧阴离子(O_2^-)和羟基自由基(OH^-)，以及非自由基分子如过氧化氢(H_2O_2) [129]。生理状态下，细胞内会生成少量或适量的活性氧，这些物质对细胞内信号转导、细胞死亡调控、基因表达、宿主防御及激素合成等生物学过程不可或缺[130]。ROS 的稳态由氧化还原调节系统维持和调控，从而保护机体免受氧化应激损伤[131]。一旦抗氧化系统无法维持活性氧的平衡，过量的活性氧便会对细胞、组织及器官造成伤害，进而引发多种疾病，甲状腺癌即在其中[4]。PTC 的氧

化应激水平更高，DNA 损伤更显著；FTC 以线粒体 ROS 介导的代谢重编程为主[12]。肥胖的个体易表现出较低水平的抗氧化剂和较高水平的氧化应激[27] [132] [133]。

11. 其他

肥胖主要源于食物摄入热量与能量消耗的不平衡，不健康饮食在慢性炎症的病理生理过程中扮演关键角色，且饮食对炎症状态具有直接影响[134]。膳食炎症指数(Dietary inflammatory index, DII)是基于文献综述构建的评分工具，用于评估各类膳食成分(包括食物、营养素及类黄酮)与炎症生物标志物的关联性[135]。较高的 DII 评分代表促炎饮食模式，并与肥胖及癌症等多种慢性疾病风险上升相关[4] [136] [137]。瘤周脂肪组织可推动肿瘤生长，肿瘤－基质交界处的脂肪细胞(即癌症相关脂肪细胞，Cancer-associated adipocytes, CAAs)会转变为成纤维细胞样表型，并通过分泌多种蛋白酶和细胞因子增强侵袭能力[138]。癌症与瘤周脂肪细胞间的“相互作用”还涉及脂肪分解增强，从而为癌细胞供给能量[1]。局部脂肪组织异位可能是部位特异性癌症的一个重要的危险因素。局部异位脂肪组织与更明显的炎症环境相关，促进肿瘤的发生和进展[139]。临床观察显示，PTC 的瘤周脂肪“串扰”更显著，促侵袭能力更强；FTC 以异位脂肪沉积相关代谢紊乱为主[138]。

12. 临床启示与未来展望

肥胖与甲状腺癌的密切关联不仅揭示了深刻的生物学机制，也为临床实践和未来研究指明了方向。1) 潜在的用于风险分层的生物标志物：由于脂联素降低、瘦素升高等脂肪因子紊乱在甲状腺癌发生中的核心作用，可以将两者及其比值纳入高危人群作为筛查指标[140]。肥胖相关的慢性炎症和氧化应激是促癌微环境的重要组成部分。监测血清 IL-6、TNF-α 以及氧化应激标志物的动态变化，可为评估甲状腺结节恶变风险提供补充信息[135]。未来还应着重开发针对特定分子亚型的生物标志物。2) 针对肥胖甲状腺癌患者的潜在药物干预靶点：二甲双胍可改善胰岛素抵抗、抑制 IGF-1/AKT/mTOR 通路并诱导凋亡，适用于合并肥胖或糖尿病的分化型甲状腺癌患者[141]。IGF-1R 抑制剂可阻断 FTC/RAS 突变驱动的增殖与转移[142]。JAK/STAT 抑制剂可抑制 PTC/BRAF 相关炎症与上皮－间充质转化[54] [55]。COX-2 抑制剂可降低炎症与血管生成，减少肿瘤侵袭[115]。雌激素受体调节剂与芳香化酶抑制剂可纠正 ER-α/ER-β 失衡，降低肥胖相关高雌激素状态的促癌作用[101] [108]。3) 未来研究应填补的关键空白：开展大规模、长期的纵向队列研究，追踪肥胖人群的甲状腺癌发病情况，明确肥胖与不同甲状腺癌亚型之间的因果关系及时间动态变化。聚焦于肥胖如何影响不同甲状腺癌亚型的细胞生物学行为，展开关于肥胖促进甲状腺癌发生发展的机制的深入研究，包括但不限于代谢重编程、表观遗传修饰、肿瘤微环境重塑等方面。基于肥胖表型、甲状腺癌病理亚型和分子特征的综合分析，制定个体化的预防、筛查和治疗策略，真正实现精准医学在甲状腺癌管理中的应用。

有意减肥可以降低患癌症的风险，尤其是女性患肥胖相关癌症的风险，这强调了超重与癌症风险之间的联系[1]。通过戒烟、保持健康体重、食用坚果、水果、蔬菜和橄榄油、增加体育锻炼和减少酒精摄入量，可以预防相当比例的癌症病例[143] [144]。对肥胖相关癌症最重要的预防措施是基于生活方式的改变、导致体重减轻的饮食、医学营养治疗和减肥手术[143] [145]。

总之，肥胖与甲状腺癌的关系是一个复杂的多因素网络，涉及内分泌、免疫、代谢等多个层面。未来研究应致力于揭示其内在机制的异质性，开发精准的预测模型和靶向治疗策略，最终实现对甲状腺癌的有效预防和个性化治疗。

13. 结论

近年来，甲状腺癌，特别是甲状腺乳头状癌的患病率在全球范围内急剧增加，除了与更密集和敏感

的诊断程序有关之外，也与包括肥胖在内的各种环境因素的影响有关。事实上，肥胖被认为是仅次于吸烟的第二大可预测和可改变的癌症发展原因，在甲状腺癌的发展中也起着重要作用。肥胖与低级别慢性炎症状态有关，其特征是免疫系统的非特异性激活，炎症因子的增加以及各种细胞因子和脂肪因子的产生，这些因素可能直接或间接地决定包括甲状腺在内的各种组织的细胞增殖，促进肿瘤的发生。肥胖相关机制在 PTC 与 FTC、BRAF 突变与 RAS 突变亚型中存在显著异质性。肥胖与甲状腺癌的发生密切相关，改善生活方式、健康生活、减重及降低肥胖的发生率对未来甲状腺癌预防及治疗起着关键的作用，是未来甲状腺癌研究关注的新方向。

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