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·综述·

脂联素及其受体与恶性肿瘤相关性研究进展

仲秀秀[1,2] 张国安[2] 综述 崔 文[3] 审校

([1] 济南大学山东省医学科学院,山东 济南 250022;[2] 济宁医学院基础学院,[3] 济宁医学院法医学与医学检验学院,山东 济宁 272067)

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脂联素(adiponectin)是脂肪细胞分泌的一种多功能脂肪因子,它具有抗糖尿病、抗动脉粥样硬化、抗炎和抗肿瘤等作用。肥胖者血脂联素浓度降低,降低的脂联素水平可能是肥胖和肿瘤发生之间的联系桥梁。

1 脂联素及其受体的概述

脂联素是脂肪细胞分泌的大分子物质,由244个氨基酸组成[1-3],是APM1的基因转录产物,位于染色体3q27,与2型糖尿病和肥胖症的基因位点相邻。血清脂联素的浓度为2～20μg/ml,循环脂联素的水平与体重指数呈反比[4]。脂联素对人体有保护作用,具有抗心血管疾病[3]、抗胰岛素抵抗[6]、抗炎和抗癌的作用[5]。

脂联素有2种受体,脂联素受体1和脂联素受体2,脂联素主要通过其受体来发挥作用。脂联素受体1主要是通过AMPK通路激活来发挥其抑制恶性肿瘤生长的作用[7]。AMPK通路是脂联素细胞内主要信号传导通路,在组织中,脂联素还可以调节其他信号感受器的上下级通路,如细胞外信号调节蛋白激酶1和2(ERk1/2)、p38激酶、激活的PPAR-α)、JNK/ERK、一氧化氮(NO)、信号传导及转录激活因子3(Signal transducers and activators of transcription3,STAT3)、核因子活化B细胞κ轻链增强子(nuclear factor kappa-light-chain-enhancer of activated B cells,NF-κB)和神经酰胺。,脂联素受体2可能与过氧化物酶增殖因子受体-α(PPAR-α)有更加密切的联系。靶向断裂实验同时显示脂联素受体1转导信号通路主要是通过AMPK通路,脂联素受体2主要是通过PPAR-α相关通路[8-12]。

2 脂联素与某些恶性肿瘤的关系

很多研究认为脂联素对各种癌症尤其是肥胖相关的癌症起保护作用[13]。最近有研究发现脂联素水平的降低与各种癌症的发病风险有关,如乳腺癌、结直肠癌、前列腺癌、甲状腺癌[14-17]。

2.1 脂联素与乳腺癌

肥胖是绝经后乳腺癌的一个危险因素,通过对706例不同种族绝经后乳腺癌病例组和706例对照组的检测发现乳腺癌的发生与脂联素无关,与瘦素和脂联素的比值增高有关[16]。Gulcelik MA等[17]在研究脂联素与乳腺癌和直肠癌的关系中选用110名患者(83名乳腺癌患者和27名直肠癌患者)作为病例组和40名健康者作为对照组,通过病例对照研究来估计血清脂联素水平与肥胖、绝经情况、受体水平和肿瘤分级之间的关系,研究结果显示癌症组乳腺癌[(8583±2095)ng/ml],直肠癌[(9513±2276)ng/ml]血清脂联素水平比对照组[(13905±3263)ng/ml]低,差异有统计学意义,乳腺癌($P<0.001$),直肠癌($P=0.023$)。脂联素水平与肿瘤的分级有关,肿瘤分期高者血清脂联素水平降低。

2.2 脂联素与甲状腺癌

甲状腺癌是最常见的内分泌恶性肿瘤,乳头状甲状腺癌和滤泡型甲状腺癌是其最常见的亚型[18]。近几年研究发现肥胖与甲状腺癌的发病呈负相关[19]。为了研究脂联素受体在甲状腺癌患者中的表达情况和生理学意义,台湾研究小组[20]选用了49名乳头状甲状腺癌患者,其中37名女性和12名男性。脂联素受体1的阳性表达率为27%,脂联素受体2为47%,并且脂联素受体阴性表达与肿瘤的边缘侵袭、多中心性、高的AJCC、TNM

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分级有关。因此脂联素受体的阴性表达与肿瘤不良预后、低无病生存率有关。而脂联素受体在乳头状甲状腺癌患者中过度表达可能与肿瘤好的预后有关。Nicholas Mitsiades 等[15]通过对 175 名甲状腺癌患者和 107 名正常人血清脂联素水平的检测、组织免疫组化、RT-qPCR 和 SW579 和 BHP7 甲状腺癌细胞系的研究。结果显示血清脂联素水平与甲状腺癌的发病风险呈负相关。人类甲状腺癌组织和细胞系均有脂联素受体的表达,但在体外实验研究中发现脂联素与甲状腺癌细胞系缺乏直接效应。

2.3 脂联素与结直肠癌

Hiyoshi 等[21]研究发现结直肠癌组织与正常结肠组织相比较,脂联素受体水平较低,从而说明在结直肠癌发展的过程中脂联素受体是下调的,可能是恶性肿瘤细胞逃避脂联素抑制效应的一个逃跑机制。Yoneda 等[22]也做了脂联素受体与直肠癌的相关研究,通过 RT-PCR、Western blotting、免疫组化方法研究脂联素受体在正常直肠黏膜和直肠癌组织中的表达情况,研究结果显示脂联素受体在正常直肠组织和癌组织中都表达,脂联素可能通过其受体来发挥作用。脂联素及其受体不仅在肿瘤组织的表达有所变化,它们的基因多态性同样与结直肠癌的发病相关。He 等[23]选用 420 名结直肠癌患者作为实验组和 555 名相同年龄和性别的正常人作为对照组进行病例对照研究,通过多变量逻辑回归分析发现,脂联素受体 1(rs12733285,rs1342387)基因多态性与结直肠癌的低发病风险有关,而脂联素(rs266729)基因多态性与结肠癌的发病风险有关但是与直肠癌没有关系。

2.4 脂联素与前列腺癌

流行病学统计分析认为血清脂联素的浓度与前列腺癌的发病风险呈负相关。为了研究血清脂联素与前列腺癌的发病风险和生存率之间的关系,有研究者[24]研究了 654 名前列腺癌患者和 644 名健康男性,通过病例对照分析研究发现,血脂联素浓度在最高 1/5 组比脂联素浓度在最低 1/5 组患前列腺癌的风险要低。脂联素很有可能在肥胖和前列腺癌之间起调节作用。然而,Beebe-Dimmer 等[25]在非裔美国人(131 例前列腺癌患者,344 例健康者)中研究发现脂联素及其受体基因的多态性与前列腺癌没有关系。

3 结语与展望

脂联素是脂肪细胞分泌的一种内分泌激素,在脂肪组织分泌的各种激素当中脂联素不仅在葡萄糖和脂类的代谢中起重要的作用,而且在各种不同癌症的发展过程中也起到很重要的作用,癌组织中脂联素及其受体的表达水平可能是肿瘤的一个新的危险因子。我们应该进行大规模和更深入的研究,以了解脂联素水平与乳腺癌和甲状腺癌的关系,明确脂联素在肿瘤发生发展中的作用机制,为肿瘤预防、早期诊断和新药研制提供新的依据。

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than that of in the system without TRS. When the concentration of TRS changed form 0.3%～0.5% the water content in the upper dense phase was reduced and the separation degree of oil and water was enhanced because of the enhanced dispersive ability of the TRS and the decreased content of the montmorillonite in OMA.

NOMENCLATURE

ζ zeta potential, mV

t separation time, min

w mass percent concentration, %

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