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IGF2BP2在非肿瘤与肿瘤中的作用的研究现状及进展

许晓丽，刘源静，李慧玲，宋欣玉，董　朝*

新疆医科大学附属肿瘤医院乳腺甲状腺外科，新疆　乌鲁木齐

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摘　要

IGF2BP2被认为是2型糖尿病(T2DM)相关基因，其通过对多种细胞类型中众多基因的转录后调节来调节人类代谢疾病(如糖尿病、肥胖症和脂肪肝)的细胞代谢；而作为m6A阅读器，IGF2BP2通过与不同的RNA通信，如microRNA (miRNA)、信使RNA (mRNA)和长链非编码RNA (lncRNA)参与癌症的发生和进展。我们通过综述IGF2BP2在非肿瘤与肿瘤中的作用，以望更深层次地挖掘到IGF2BP2在疾病中的作用机制。

关键词

IGF2BP2，RNA结合蛋白，m6A阅读器

Research Status and Progress of the Role of IGF2BP2 in Non-Tumor and Neoplasm

Xiaoli Xu, Yuanjing Liu, Huiling Li, Xinyu Song, Chao Dong*

Department of Breast and Thyroid Surgery, Affiliated Cancer Hospital of Xinjiang Medical University, Urumqi Xinjiang

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Abstract

IGF2BP2 is considered to be a type 2 diabetes (T2DM) related gene that regulates cellular metabolism in human metabolic diseases such as diabetes, obesity, and fatty liver through post-transcriptional regulation of numerous genes in multiple cell types. As an m6A reader, IGF2BP2 is involved in the development and progression of cancer by communicating with different RNAs, such as microRNA

*通讯作者。

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(miRNA), messenger RNA (mRNA) and long non-coding RNA (lncRNA). By reviewing the role of IGF2BP2 in non-tumor and tumor, we hope to dig deeper into the mechanism of IGF2BP2 in disease.

Keywords

IGF2BP2, RNA-Binding Proteins, m6A Reader

1. IGF2BP2 在非肿瘤中的研究进展

人胰岛素样生长因子 2 (IGF2) mRNA 结合蛋白 2 (IGF2BP2/IMP2)作为一种调节多种生物过程的 RNA 结合蛋白(RBP)，因其结合 IGF2 先导蛋白 3 mRNA 的能力而被发现[1]。IGF2BP2 在非肿瘤的代谢性疾病中的研究较为丰富[2]，IGF2BP2 通过对多种细胞类型中许多基因的转录后调节来调节糖尿病、肥胖症和脂肪肝等人类代谢疾病中的细胞代谢[3]。在小鼠模型中，在小鼠肝脏中过表达 IMP2 导致脂肪变性[4]，而 IMP2 缺失的小鼠对饮食诱导的肥胖和脂肪肝具有高度抗性，表现出超强的糖耐量和胰岛素敏感性，能量消耗增加，在寒冷暴露下对核心温度有更好的防御能力。在缺乏 IMP2 的情况下，大多数 mRNA 的翻译效率也会提高[5]。近来，在神经保护方面，miR-196a 通过抑制亨廷顿舞蹈症中的 IMP3 和上调 IGF2 来增强神经元微丝的聚合，从而通过亨廷顿舞蹈症中的神经元细胞骨架支持 miR-196a 的神经保护功能[6]。在肌细胞的增殖与分化方面，有研究表明 RNA 结合蛋白可发挥不可小觑的作用[7]；IMP 在小鼠和人类胚胎的发育中特别表达上皮、肌肉和胎盘[1]，近期也有与 IMP2 有关的报道：circIGF2BP2 促进鸡成肌细胞的增殖和分化[8]。

2. IGF2BP2 在肿瘤中的研究进展

肿瘤的发病机制复杂，其中，“细胞能量学”广受关注[9]。百年前首次详细描述了肿瘤与非增殖正常组织相比，前者对葡萄糖的消耗显着增加的结论[10]，之后在不同的肿瘤环境中都得到了证实，且证明与肿瘤预后不良密切相关[11]。IGF2 具有致癌性，其功能丧失剪接变体可预防 2 型糖尿病；作为最复杂的调节生长因子之一，它还受表观遗传改变的控制[12]。IGF2 mRNA 结合蛋白(IMPs/IGF2BPs)与 IGF2 转录本复合，介导其加工，如定位、稳定性和翻译[13]，而在缺乏 IGF2BP2 的情况下，大多数 mRNA 的翻译效率也会提高，进而限制小鼠的寿命并调节小鼠的营养和能量代谢[5] [14]。IGF2 活性通过 IGFBPs 和靶受体的差异表达来控制[15]。有研究指出，IGF2BP2 不仅仅与 IGF2 mRNA 结合[16]，它还靶向多个转录本，IGF2BP2 的这种多靶点特征与其在细胞的脂质代谢、胰岛素抵抗以及肿瘤的发生等方面的广泛生理病理功能有着紧密的联系。最近的研究揭示：IGF2BP2 是一种 N6-甲基腺苷(m6A)阅读器，通过与多种 RNA 相互作用，参与癌症的发展和进展。m6A 甲基化的修饰在表观转录组中是最丰富且研究最深入的 RNA 修饰之一，它涵盖了 mRNA 代谢的诸多环节，包括 mRNA 输出、翻译、稳定性和剪接等[17]。此外，IGF2BP2 是多种癌症类型的独立预后因素[18]。例如，在乳腺肿瘤中，与管腔或顶泌亚型相比，IGF2BP2 在基底样乳腺癌组织中过度表达，并且在乳腺癌组织中上调了自身免疫反应[19]。在胰腺肿瘤的研究中，IGF2BP2 过表达明显，其通过直接结合和稳定 GLUT1 mRNA 来促使胰腺导管腺癌细胞的有

氧糖酵解和增殖[20] [21]。在过去的几年里，越来越多的实验数据证明了 IGF2BP2 与癌症进展的联系，包括肝癌[22]、胰腺癌[23]、乳腺癌[24]、卵巢癌[25]、结直肠癌[26]和食管癌[27]等，特别是癌症干细胞的维持[14]。已发现 miRNA 作为重要的转录后调节因子参与卵巢功能的调节，包括卵泡发育、类固醇生成、细胞闭锁甚至卵巢癌发展的调节因子，gga-miR-449b-5p 可以靶向 IGF2BPs 并下调它的 mRNA 和蛋白表达，作为蛋鸡卵巢颗粒细胞中合成类固醇激素的有效调节因子，可能有助于更好地了解功能性 miRNA 在蛋鸡卵巢发育中的作用[28]。

3. 结语

无论是组织细胞的增殖分化，还是代谢的关键步骤，IGF2BP2 在各类疾病中都已有广泛的研究；肿瘤的代谢重编程是近年来的一大研究热点，IGF2BP2 在各类肿瘤细胞中高表达，且促进肿瘤细胞的增殖侵袭已有多项实验数据支持。IGF2BP2 的另一个角色：m6A 阅读器，在肿瘤的发生与进展的过程中又发挥了怎样的作用，在最近的研究中研究者们都在逐步探索。今后，将对 IGF2BP2 进行更深入的研究，有望为相关肿瘤的预防、诊疗提供可行的思路和潜在的靶标。

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