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• 综述 •

干细胞因子Nanog在肿瘤中的研究进展

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Role of Nanog in Tumorigenesis and Tumor Development

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Abstract: Nanog is a key transcription factor involved in maintaining the self-renewal and pluripotency of embryonic stem cells. The expression of Nanog is gradually decreased with cell differentiation and tissue maturation. The recent studies demonstrate that Nanog expression is restored in tumor cells. Nanog plays pleiotropic roles in tumorigenesis and tumor development. Nanog promotes tumor growth, metastasis and drug resistance via regulating tumor cell proliferation, migration and invasion, tumor stemness, as well as tumor immune escape. Nanog overexpression is an independent indicator for poor prognosis. In this review, we summarize the recent progress of Nanog in tumor and the underlying molecular mechanisms, with an emphasis on the potential of Nanog in tumor diagnosis and targeted therapy.

Key words: Nanog; Stem cell factor; Tumor; Biomarker

摘要: Nanog是维持胚胎干细胞自我更新和多能性的关键转录因子。Nanog在分化的细胞中表达逐渐降低或缺失。研究发现肿瘤细胞中Nanog异常激活, 并且与肿瘤发生、发展和转移密切相关。Nanog通过调控肿瘤细胞增殖、迁移和侵袭、肿瘤干性以及肿瘤免疫逃逸等多种机制参与肿瘤生长、转移和耐药。临床研究证据提示Nanog在肿瘤患者中异常高表达, 可作为预后评估的独立指标。本文就Nanog在肿瘤中的作用、分子机制和临床应用的研究进展作一综述。

关键词: Nanog; 干细胞因子; 肿瘤; 分子标志物

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0 引言

2003年Mitsui和Chambers等在研究胚胎干细胞(embryonic stem cells, ESCs)时发现了一种新的多能干细胞转录因子, 起初称为Ecat4 (ES cell associated transcripts 4), 随后统一命名为Nanog^[1-2]。Nanog能够不依赖于LIF (leukemia inhibitory factor) /STAT3 (signal transducer and activator of transcription 3) 参与调控胚胎干细胞自我更新和多能性维持。Nanog属于ANTP超家族NK-2型基因, 主要表达于胚泡的内细胞团^[3]。Nanog基因表达随着细胞分化逐渐降低, 直到在完全分化的细胞不表达^[4]。但是研究发现Nanog在生殖细胞肿瘤和多种实体肿瘤中高表达, 而且Nanog表达水平与肿瘤细

胞的分化程度以及肿瘤的病理分期呈正相关。研究证实Nanog参与肿瘤发生发展过程的多个环节。Nanog参与正常细胞恶性转化, 维持肿瘤干细胞自我更新, 调控肿瘤细胞增殖、迁移和侵袭, 以及促进肿瘤免疫逃逸。Nanog在肿瘤中的多重作用可能是推动肿瘤发生发展的重要因素。因此, 深入研究Nanog在肿瘤中的确切作用及其信号网络, 不仅能够揭示肿瘤分子病理机制提供新的实验证据, 同时也能够为肿瘤早期诊断、预防和治疗提供新的分子靶点。

1 Nanog分子概述

人胚胎Nanog基因(Nanog1基因)定位于12号染色体, 含有4个外显子和3个内含子, 还有11个假基因(pseudogene), 其中仅Nanog P8 (定位于15号染色体) 具有完整开放读码框, 能够编码蛋白。由于Nanog1和Nanog P8在蛋白序列、结构和功能上具有极大相似性, 目前研究将两者统称为Nanog。人Nanog蛋白含有305个氨基酸, 分为N端(1~95aa), 同源盒区(96~155aa), C端(156~305aa)。N端富含丝氨酸、苏氨酸和脯氨

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酸, 可被翻译后修饰如磷酸化调节; 同源盒区含有DNA结合序列以及出入核信号序列; C端具有转录激活作用。Nanog能促进胚胎干细胞的自我更新, 使其保持未分化特性, 还能使终末分化细胞发生重编程而显示多能性。

2 Nanog在肿瘤中的作用

早期研究认为Nanog只在多能性干细胞中表达, 在成体组织中不表达。然而最近研究发现Nanog在肿瘤细胞中高表达。由于肿瘤细胞与干细胞具有较多的相似性, 据此推测Nanog可能在肿瘤发生发展中也起着重要的作用。

2.1 Nanog与细胞恶性转化及肿瘤细胞增殖

Nanog基因转染的小鼠3T3细胞和人293细胞增殖明显加快, 并且能够在软琼脂上以非锚着依赖性方式进行克隆生长^[5-7]。Nanog基因转染的人293细胞还能够在裸鼠体内致瘤^[7], 说明Nanog过表达可能导致人293细胞发生恶性转化。Nanog过表达也可促进肿瘤细胞生长。Nanog基因转染促进乳腺癌细胞克隆形成和增殖, 而Nanog基因敲除则明显抑制乳腺癌细胞生长^[8]。Nanog过表达促进(而敲除Nanog抑制)肺癌细胞克隆形成和增殖能力^[9]。Nanog可能通过参与调控细胞周期进展发挥促增殖作用。Nanog基因敲除导致多种细胞周期相关蛋白包括cyclin D1表达下降^[10]。Nanog可结合到cyclin D1远端启动子区, 介导其转录活化, 加速细胞周期进展, 从而促进细胞增殖。

2.2 Nanog与肿瘤细胞迁移和侵袭

采用基因干扰Nanog表达抑制卵巢癌细胞迁移和侵袭。Nanog通过抑制下游基因E-cadherin和FOXJ1表达促进卵巢癌细胞迁移和侵袭^[11]。Nanog还可通过上调Slug表达诱导上皮-间质转化(epithelial mesenchymal transition, EMT)发生, 促进肺癌细胞体外迁移、侵袭和体内转移^[9]。不同肝癌细胞的迁移能力与Nanog表达水平呈正相关。在Nanog低表达肝癌细胞中过表达Nanog诱导EMT发生, 导致细胞侵袭能力增强, 体内肿瘤生长和肝内转移也明显增加。Nanog直接结合Nodal启动子并上调其表达, 激活Smad3信号通路促进肝癌细胞EMT^[12]。采用MMTV-Cre/LoxP系统体内诱导小鼠乳腺组织过表达Nanog并不能够诱导乳腺癌发生, 却可促进MMTV-Wnt1转基因小鼠乳腺癌细胞增殖和远端转移, 并发现在Wnt1/Nanog双转基因小鼠中EMT相关基因PDGF α 表达更高^[13]。在结肠癌细胞中Nanog上调Slug和Snail表达促进

EMT发生^[14]。此外, Snail也可调控Nanog表达, 表明两者直接存在正反馈调控作用^[15]。Nanog还可通过结合FAK(focal adhesion kinase)而发生磷酸化, 并且转录激活FAK表达, 形成正反馈, 促进结肠癌细胞侵袭^[16]。

2.3 Nanog与肿瘤细胞耐药

Nanog过表达可通过上调ABCB1表达水平促进肺癌细胞外排顺铂诱导耐药^[9]。在乳腺癌和卵巢癌细胞中, Nanog通过与STAT3形成核内复合物, 激活MDR1基因表达^[17]。HA与CD44相互作用激活PKC ϵ 磷酸化Nanog, 促进Nanog与STAT3结合, 激活miR-21表达而抑制PCD4表达^[18-19]。Nanog表达在紫杉醇(Paclitaxel)耐药的卵巢癌细胞中比亲代细胞表达显著增加。HA与CD44v3相互作用还能够诱导Nanog与其他干细胞因子如Oct3/4和Sox2结合, 通过转录激活miR-302抑制下游基因IAP表达, 促进化疗耐药^[20]。

2.4 Nanog与肿瘤干细胞

卵巢癌组织分离的CSC高表达Nanog, 并且具有较强化疗耐药性^[21]。MiR-214可通过调控p53/Nanog信号轴调控卵巢癌细胞耐药和干细胞形成^[22-23]。放疗诱导产生的乳腺癌CSC中Nanog表达显著增加^[24]。结肠癌CSC中Nanog基因敲除抑制体外成球和体内致瘤能力, 并且下调其他干细胞因子如Sox2和Oct3/4的表达^[25]。结肠癌CSC中Nanog表达可能受c-Jun与 β -catenin/TCF共同调控^[26]。采用醛脱氢酶1(aldehyde dehydrogenase class 1, ALDH1)、CD44作为标志物分选或采用悬浮成球培养富集的胃癌干细胞中Nanog高表达, 对化疗药物耐药性强, 并且体内致瘤能力也更强^[27]。CSC中Nanog启动子低甲基化。采用Nanog启动子控制GFP表达作为报告分子, 从Huh7干细胞中分离的GFP阳性细胞高表达Nanog, 低表达分化相关指标如ALB, 具有CSC的特征如体外成球、体内致瘤和化疗耐药能力。Nanog通过调控IGF2/IGF1R信号途径参与肝癌CSC的维持^[28-29]。在肺癌、前列腺癌和胶质瘤干细胞中Nanog表达均有显著增加^[30-32]。Siddique等报道Nanog通过诱导Aurora A激酶表达诱导NUMB蛋白磷酸化, 从而抑制NUMB-p53复合物形成, 降低p53蛋白稳定性, 最终促进肿瘤干细胞的自我更新^[33]。Chen等发现肺癌相关成纤维细胞释放的IGF2通过与IGF1R结合, 诱导Akt磷酸化, 激活Nanog表达, 参与肺癌干细胞的干性维持^[34], 表明Nanog是参与肿瘤微环境旁分泌信号作用的重要分子。

2.5 Nanog与肿瘤免疫逃逸

肿瘤细胞可通过适应机体的免疫系统而逃脱CTL细胞的杀伤作用。Noh等研究发现肿瘤免疫治疗可导致肿瘤细胞中Nanog表达增加^[35], 通过激活Tcl1a/Akt信号通路介导肿瘤细胞对CTL细胞的杀伤作用产生免疫耐受^[36]。采用siRNA干扰Nanog表达则可逆转肿瘤细胞免疫逃逸, 能够被CTL细胞识别, 最终抑制肿瘤生长。Nanog/Tcl1a/Akt通路活化不仅促进肿瘤免疫逃逸, 还能够增强肿瘤细胞的干性和转移能力。免疫逃逸后的肿瘤细胞发生EMT样转变, 体外迁移、侵袭能力和体内肺转移明显增加^[37]。

3 Nanog在肿瘤诊断和治疗中的应用价值

研究发现Nanog在多种肿瘤细胞及组织中存在表达, 并且证实这些肿瘤细胞及组织中的Nanog可能主要是来源于Nanog P8假基因的转录产物。Nanog表达与肿瘤分期、淋巴结转移和预后密切相关。与正常上皮组织相比, 胃癌组织中Nanog1和Nanog P8表达增加^[38]。Nanog高表达与淋巴结转移、肿瘤晚期分期和肿瘤分化程度低相关。Nanog高表达的胃癌患者5年存活率比低表达患者差, 表明Nanog可能是促进胃癌恶性进展的重要因子^[39]。Nanog高表达与乳腺癌患者预后不良相关。乳腺癌患者中Nanog基因表达水平与肿瘤大小、临床分期及淋巴结有无转移相关^[40-41]。在手术后经联合化疗的卵巢癌患者中, Nanog核内表达增加与卵巢癌患者耐药和生存率低相关^[11]。在I/II期卵巢癌患者中, Nanog高表达的患者中位生存时间为40月, 而Nanog低表达的患者中位生存时间为120月, 表明Nanog表达水平可作为独立的预后评估指标。多因素分析揭示Nanog表达水平增加是结肠癌预后不良的独立预测指标^[14]。Nanog表达增加与口腔鳞癌患者治疗耐药和预后差相关^[42]。Nanog高表达非小细胞肺癌患者预后明显差于低表达患者^[43-44]。Nanog高表达与疾病进展(TNM III/IV分期)相关。Nanog高表达是肝癌预后不良的分子标志物^[28]。与正常肝细胞和正常组织相比, 肝癌细胞和原代肝癌组织中Nanog1启动子甲基化程度明显降低。此外, 采用siRNA或shRNA干扰Nanog表达体内外能够显著抑制肿瘤细胞生长和转移发生^[8-9, 25, 36]。最新研究发现采用TALEN和CRISPR/Cas9基因编辑技术敲除Nanog基因具有抑制肿瘤生长、转移和增强化疗敏感度的效果^[45-46], 提示Nanog可作为肿瘤治

疗的潜在靶点。

4 展望

目前研究表明Nanog是在肿瘤中起着重要作用的干细胞因子^[47]。Nanog通过调控增殖、EMT、耐药、肿瘤干细胞以及免疫逃逸等多种机制参与肿瘤发生发展的多个环节。研究还发现多种肿瘤中激活的信号通路能够上调Nanog表达, 增强肿瘤细胞转移能力和干性^[15, 48-50]。临床研究证据亦证实Nanog表达水平可作为多种肿瘤患者的独立预后评估指标^[38-44]。实验研究结果表明Nanog基因敲除、抑制Nanog表达及功能可单独或协同发挥肿瘤治疗性作用^[36, 51-52]。尽管Nanog在肿瘤中的研究仍有一些问题尚未完全阐明^[53], 如Nanog高表达是否能够导致上皮性肿瘤发生还有待进一步研究, Nanog在肿瘤微环境中的具体作用也不甚清楚, 此外, 目前对肿瘤细胞中Nanog基因异常激活和蛋白翻译后修饰的分子机制研究也相对较少。但是相信随着对这些关键问题研究地不断深入, 将为全面揭示Nanog在肿瘤中的作用提供更多的实验证据, 同时也为肿瘤分子诊断和靶向治疗提供新的思路和方法。

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