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·综 述·

组织微环境对肿瘤发生发展的影响

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[摘要] 肿瘤微环境与肿瘤发生发展密切相关。最近的研究证实,肿瘤形成可能是干细胞分化异常导致。而微环境是干细胞稳态调节的关键,干细胞微环境的失调在肿瘤发生中扮演了重要角色。而在肿瘤发展过程中,适宜的微环境将促进肿瘤快速增殖,改变这些特异的微环境可以抑制肿瘤的恶性表型。同时,在肿瘤迁移过程中,微环境也起到了重要作用。这些机制的研究有助于加深对肿瘤的认识,为肿瘤的预防和治疗提供新的理论基础。

[关键词] 微环境;肿瘤;干细胞;细胞增殖
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Effect of tissue microenvironment on development and progression of cancer

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[ABSTRACT] Toumor microenvironment is closely related to the development and progression of tumors. Recently, researchers suggest that abnormal differentiation of stem cells might lead to the initiation of cancer. Microenvironment is the key to homeostatic regulation of stem cells. Disregulation of microenvironment plays an important role in the carcinogenesis. And during the development of tumor, a suitable microenvironment can promote the rapid proliferation of tumor. Changing the specific microenvironment can suppress the tumorigenic phenotype of aggressive cancer. Meanwhile, microenvironment also plays an essential role in cancer metastasis. Understanding of these underlying mechanisms will enhance our knowledge of cancer and will provide a novel basis for prevention and treatment of cancer.

[KEY WORDS] microenvironment; neoplasms; stem cells; cell proliferation
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微环境是指邻近的组织细胞及其分泌的各种因子。微环境的稳定是保持细胞正常增殖、分化、代谢和功能活动的重要条件,微环境成分的异常变化可使细胞发生病变。而干细胞的微环境更是干细胞维持稳态(homeostasis)的关键,它可以通过信号分子对干细胞的自我更新和增殖进行紧密的调控[1]。

现在,肿瘤更多的被认为是一种干细胞疾病。虽然早期的肿瘤研究往往将研究重点放在肿瘤细胞本身,关注肿瘤细胞的基因突变、增殖生长、信号通路的改变等等,但随着研究的深入,肿瘤的微环境是保护和支持肿瘤发生发展以及转移复发的必要结构与功能单元[2-3]的观点得到越来越多的支持。

1 微环境在肿瘤发生中的作用

随着肿瘤干细胞研究的兴起,干细胞突变为肿瘤干细胞被认为是肿瘤发生的源头。而具有调控维持干细胞稳态的微环境,在这一转变中,也起到了重要作用。

1.1 *微环境调控维持干细胞稳态* 干细胞的微环境,又称干细胞巢(stem cell niche),主要是由一群特异性定位且具有维持干细胞特性功能的细胞所组成。它们为干细胞提供了特异性的锚定位点,并分泌黏附因子参与干细胞与干细胞巢之间干细胞与细胞外基质之间的连接[4-5]。干细胞巢分泌的许多发育调节相关的外源性因子,例如 Hh、Wnt、骨形态发生蛋白(bone morphogenetic proteins, BMPs),成纤维细胞生长因子(fibroblast growth factors, FGFs)和 Notch 等在干细

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胞的自我更新、增殖、分化以及凋亡的调控中扮演了重要的角色[1,6-7]。

通常情况下，微环境一方面提供持久性的抑制增殖分化的信号，从而维持组织干细胞的特性并阻抑肿瘤的发生；另一方面，微环境也为干细胞增殖分化提供暂时性的信号以支持必需的组织再生。维持增殖信号和抑制增殖信号之间的动态平衡是干细胞稳态调节的关键，从而使干细胞既能进行自我更新，又能支持相应组织再生[8-10]。

当干细胞巢缺失时，就会造成干细胞特性丧失。果蝇的生殖干细胞巢遗传性缺失时，生殖干细胞也相应丢失[11]。构成造血干细胞巢组分的成骨衬细胞（osteoblastic lining cells）减少，则造血组织相应减少[12]；干细胞巢的细胞数增加，则造血干细胞数量上升[13]。

1.2　*微环境失调促进肿瘤发生*　一般认为，干细胞向肿瘤干细胞转变需要细胞增殖方面的基因突变，任何一种突变使干细胞不再依赖于增殖信号或者能阻抑抑制细胞增殖的信号，都会导致干细胞增殖失控并有肿瘤发生的可能。微环境作为调控系统本身，如果促细胞增殖的信号显著大于抑制增殖的信号也很可能会造成相同的效果。

外界增殖信号的增多是造成微环境失调的原因之一。组织慢性损伤时，受损和坏死细胞释放的信号分子，激活 Hh、Wnt 等信号通路，使干细胞处于持续性激活的状态，不断地产生新的干细胞和分化的子细胞，以修复持续的组织损伤[14-16]。在这种异常微环境中，持续激活的干细胞更易成为基因事件的标靶，从而发生恶性转化，导致肿瘤发生。有研究表明，组织慢性损伤带来的炎症刺激与肿瘤发生之间显现出密切的联系[17-18]。

微环境自身改变造成的促细胞增殖的信号大量增多也有相同的效应。Chepko 等[19]的研究表明，小鼠乳腺干细胞巢的转化生长因子 α（transforming growth factor-α，TGFα）过表达会促进乳腺癌的发生。有些情况下，微环境的改变甚至是肿瘤发生必需的。Zhu 等[20]报道，某些类型的神经母细胞瘤（neuroblastoma）的形成同时需要施万细胞（Schwann cell）的突变和支持细胞的突变。

这些研究表明，微环境的改变带来增殖和抑制细胞增殖信号的失调，很可能在肿瘤发生早期起到重要作用。更好地了解其中的机制，有助于加深对肿瘤发生过程的认识。

2　微环境对肿瘤细胞的作用

肿瘤的周围显现出特异性微环境的存在。肿瘤的发生发展需要这种微环境的保护和支持[2]。而改变这种微环境，可以对肿瘤细胞起到一定的调节作用。

2.1　*适宜的微环境促进肿瘤增殖*　肿瘤的增殖受到周围微环境的很大影响，在适宜的微环境中肿瘤更容易快速增殖。Hara 等[21]将人结肠癌细胞 KM12SM 分别接种到结肠癌易转移的两个部位，小鼠的肝和肺，结果发现移植瘤在肝脏的成瘤率达到 100%，而在肺的成瘤率只有 50%。单独将人肿瘤细胞注入小鼠体内只能形成微小休眠灶，但给这些肿瘤细胞的微环境中注入 VEGF165 后，肿瘤细胞开始获得血管生成的能力，进入到生长增殖状态[22]。注入肝组织后处于休眠状态的乳腺癌细胞，从肝组织回收后重新注射入小鼠的乳腺脂肪垫，可表现出成肿瘤性[23]。

肿瘤不仅限于对微环境的适应，在发展过程中肿瘤细胞也会对微环境进行修饰使其更适宜其失控的自我更新和分化的模式。Sneddon 等[24]发现，基底细胞癌衍生出的肿瘤基质细胞会大量分泌 Gremlin1，对 BMPs 进行拮抗，从而抑制 BMPs 的促分化的作用，为肿瘤细胞的增殖提供适宜的环境。

2.2　*调节微环境可以降低肿瘤细胞的恶性程度*　由于微环境的重要性，对肿瘤细胞的微环境进行调节，可以对恶性度很高的癌细胞的生长增殖进行调控。Aguirre-Ghiso 等[25]研究发现，通过单克隆抗体封闭使尿激酶受体（urokinase-plasminogen activator receptor，uPAR）下调则可以激活 p38，同时使 ERK 失活，进而引起肿瘤细胞生长增殖暂停；而刺激 uPAR 高表达则可以引起 ERK 活性显著而持久的升高，从而使肿瘤细胞迅速增殖。

胚胎细胞特异的微环境可在干细胞的不断更新的情况下，使增殖和分化达到平衡。而肿瘤细胞的增殖则处于失控状态，分化能力降低。研究表明胚胎的微环境，尤其是胚胎干细胞可以使肿瘤细胞获得更多的分化表型，显著降低其恶性程度[2]。小鼠胚胎的微环境可以使畸胎瘤细胞基因重排得到非致瘤性的表型，并能分化为正常组织[26]。转移性黑素瘤细胞暴露在斑马鱼原肠胚形成前的胚胎微环境中，也会发生基因重排从而获得非致瘤性的表型[27]。转移性黑素瘤细胞移植到发育中的鸡胚中会遵循神经脊的迁移通路，从而失去致瘤性并表现出神经脊细胞类似的表型[28]。进一步的分子机制的研究还发现，在迁移性黑素瘤细胞和乳腺癌细胞中高表达的 Nodal 会抑制细胞分化，而胚胎干细胞的微环境中糖基化 Lefty 可以抑制 Nodal 的作用，从而显著降低肿瘤细胞的恶性程度。但由于糖基化 Lefty 是胚胎干细胞的特异性表达产物，这种抑制机制仅限于胚胎干细胞的微环境[29]。这些研究为肿瘤的“诱导分化治疗”提供了新的理论基础。

3　微环境在肿瘤转移中的作用

肿瘤转移是造成 90% 的癌症患者死亡的原因[30]，但作为一个复杂的多步骤的过程，肿瘤转移的分子机制目前了解得还比较少。但在现有的研究成果中，微环境在肿瘤转移的定向和激活中显示出了重要的作用。

3.1　*微环境参与肿瘤转移的机制与干细胞归巢相似*　微环境对肿瘤细胞侵袭转移的参与，与正常干细胞的归巢定位的机制上表现出很大的相似性。基质金属蛋白酶（matrix metalloproteinase，MMPs）家族的成员是肿瘤细胞转移的关键性分子[31-34]，MMP9 则是造血干细胞的激活和动员中必需的[35-37]。整联蛋白（integrin）与肿瘤细胞迁移相关[38-39]，同时在造血和神经系统的干细胞迁移中也必不可少[40]。骨桥蛋白（osteopontin）对乳腺癌骨转移至关重要，又可负性调节骨髓中造血干细胞池的大小[41-44]。缺少钙离子感受受体的 HSC 不能定位于骨内膜微环境[45]，而乳腺癌细胞中钙离子感受受体表达的增多使其向骨髓的转移显著增多[46]，而骨髓微环境中钙离子的浓度很有可能作为化学引诱剂使肿瘤

细胞向骨髓转移。

3.2　CXCL12-CXCR4 在肿瘤转移中的作用　CXCL12/SDF-1 及其受体 CXCR4 参与肿瘤转移的机制目前研究较多。在正常组织中,CXCL12-CXCR4 之间的作用在造血干细胞和免疫系统的调节中相当重要,并与组织再生修复密切相关[47-52]。而在肿瘤组织中,CXCL12-CXCR4 在肿瘤细胞迁移定位中起着至关重要的作用。高表达 CXCR4 的乳腺癌,往往转移到 CXCL12 高表达的组织,如肺、肝、骨髓和局部淋巴结等部位[53-57],而这些部位也与前列腺癌[58]、小细胞肺癌[59-60]等很多肿瘤的转移复发密切相关。而且,许多 $CXCR4^+$ 的肿瘤转移细胞对 CXCL12 梯度有应答反应[55]。CXCR4表达水平的高低也与乳腺癌的转移性密切相关。HER2/neu 可以通过抑制 CXCR4 的下调,增强 CXCR4 的表达,而高表达 HER2/neu 的乳腺癌患者极易发生转移,预后很差[61]。而通过使用抗 CXCR4 的单抗进行治疗,则可以抑制乳腺癌细胞向靶器官的转移[62]。

微环境对肿瘤转移和干细胞迁移的影响在分子机制上的相似性,使干细胞迁移的研究对肿瘤转移的研究提供了很大的借鉴意义。

4　展　望

微环境在肿瘤发生发展以及转移复发中都显示出重要的意义。而微环境对干细胞的调控为微环境对肿瘤的作用机制的研究提供很大的借鉴意义。例如,微环境对干细胞的维持如此重要,而相同的机制也在肿瘤细胞中有所表现,那么肿瘤干细胞是否也需要相应的微环境进行维持? 同时,探索肿瘤细胞的生长和迁移等过程中的分子机制与正常干细胞的不同之处,有利于发现新的治疗方法,以特异性地杀死肿瘤细胞而不影响正常干细胞的自我更新。这方面的研究工作将加深我们对肿瘤的认识,为探讨预防肿瘤发生和治疗肿瘤的方法提供新的方向。

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