前列腺癌骨转移相关信号通路的研究进展

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摘要：全球前列腺癌发病率逐年升高，骨转移是前列腺癌主要的转移方式，并且与患者预后密切相关。前列腺癌骨转移相关信号通路揭示了骨转移发生的机制，可为临床治疗提供思路和指导。本文综述了与前列腺癌骨转移相关的信号通路，包括MET、VEGF、β2-肾上腺素信号通路、雄激素受体信号通路和RANKL信号通路，阐明了这些通路在骨转移发生过程中的作用及机制，并介绍了相关研究结果在临床治疗中的应用情况。

关键词：前列腺癌；信号通路；骨转移
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Research progress in bone metastasis associated signaling pathway of prostate cancer

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Abstract: The incidence of prostate cancer increased year by year in the world.Bone is the main target of metastasis of prostate cancer, which is closely related to prognosis. The mechanism of bone metastasis is revealed by some signaling pathways and provides ideas and guidance for clinical treatment. This review summarizes the signaling pathways associated with bone metastasis in prostate cancer, including MET and VEGF signaling pathway, beta 2- adrenergic signaling pathway, androgen receptor signaling pathway and RANKL signaling pathway.In this review,the role and mechanism of these pathways in bone metastases are elucidated and the application of related research results in clinical treatment are also introduced.

Keywords: prostate cancer; singling pathway; bone metastasis

在美国，前列腺癌在恶性肿瘤中死亡率位居第2[1]。随着生活水平的提高，我国前列腺癌发病率也在逐年攀升[2]。大多数前列腺癌患者在50岁后发病，这些人中有超过70%是在65岁后确诊。原发性前列腺癌的转移是导致高病死率的主要原因。局限性前列腺癌5年生存率几乎是100%，而转移后5年生存率仅为28%。在肿瘤转移前进行早期检测和治疗对于提高病人生存率至关重要。因此前列腺癌转移相关信号通路的研究对于肿瘤转移早期诊断和治疗有重要意义。

1 MET和VEGFR通路

MET基因和血管内皮生长因子(vascular endothelial growth factor，VEGF)通路在前列腺癌进展和骨转移中发挥重要作用。普通前列腺上皮基底细胞和腔细胞均可以表达MET，并且其表达水平与雄激素受体表达水平呈负相关[3-4]。MET在前列腺癌细胞中表达量较低，而去除雄激素治疗后会使其表达升高，并且增加肿瘤和间质中肝细胞生长因子(hepatocyte growth factor，HGF)的表达[4-5]。人前列腺癌细胞LNCaP和ARCaP的细胞模型实验表明，MET表达水平可以通过核因子-κB配体(receptor activator of nuclear factor kappa-B ligand，RANKL)上调，并且会增强前列腺癌细胞的骨转移能力[6]。在原发前列腺癌组织中检测到RANKL、活化的c-MET或者磷酸化的c-MET基因表达，对患者的预后预测有重大意义[7]。有研究表明，MET和HGF的表达水平与前列腺癌转移和复发具有一定相关性[8-9]。与软组织和淋巴结转移患者相比，骨转移患者MET表达水平最高[9]。而目前前列腺癌的标准内分泌治疗方法 — 去势治疗，会提高HGF/MET信号通路的表达。

VEGF信号通路的激活可以促进肿瘤新生血管生成，这对于肿瘤生长至关重要。与正常前列腺组织和高级别前列腺上皮内瘤变组织相比，前列腺癌组织内微血管密度显著增高，且密度水平与肿瘤分级和病理分期密切相关[10]。进一步研究发现，前列腺癌转移病人血清中VEGF浓度升高，其浓度可作为总生存率的独立预测因子[10-11]。另外，前列腺癌细胞中VEGF和MET信号通路可相互影响。VEGF可以经共同受体Neuropillin，通过MET依赖机制，促

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进BCL2抗凋亡蛋白家族中Mcl-1的表达[12-13]。对MET和VEGF信号通路的双重抑制可能会成为去势抵抗前列腺癌(castration resistant prostate cancer，CRPC)和骨转移患者的治疗方案，MET和VEGF信号通路在前列腺癌骨转移中的作用，为这一治疗思路提供了切实可靠的依据[14-15]。

2 β2-肾上腺素受体(β2-adrenergic receptor，ADRB2)信号通路

大多数前列腺癌转移发生在骨、淋巴结、肺和肝[16]。肿瘤的转移过程包含了多个步骤，包括肿瘤细胞从原发部位脱离、降解细胞外基质、转移到身体的其他部位、侵袭并定植形成转移灶[17]。为了适应转移过程中不断变化的周围环境，细胞要有较高的可塑性。而细胞去分化过程，如上皮细胞-间充质细胞转化(epithelial mesenchymal transition，EMT)，可以促进肿瘤细胞从原位分离、迁移、重新分化或者进行间质-上皮细胞转变，最终定植于转移部位[18-19]。

有研究表明，ADRB2的表达水平在前列腺癌转移过程中有所改变[20]。尽管前列腺癌组织与良性前列腺组织相比ADRB2表达水平上调[21]，但高侵袭性前列腺癌组织中ADRB2表达水平反而低于惰性前列腺癌组织[20]。敲低ADRB2可以导致前列腺上皮细胞EMT的发生。有实验分析表明，ADRB2敲低的细胞中波形蛋白和N-钙黏着蛋白表达上调，同时β-连环蛋白和整联蛋白β4表达降低，这表明此类细胞获得了间质细胞的表型。ADRB2敲低的细胞和使用ADRB2拮抗剂(ICI118551)处理的细胞，其迁移能力和侵袭能力均增加。相反，使用ADRB激动剂(异丙肾上腺素)处理后的细胞，其侵袭能力下降[20]。然而，在PC-3小鼠异种移植物模型中，去甲肾上腺素可以促进转移[22]，这可能与PC3收去甲肾上腺素刺激后，细胞迁移能力增强有关。

ADRB2表达水平可以影响前列腺癌细胞的表型，由此影响其迁移、侵袭和定植能力[20]。前列腺上皮细胞中ADRB2低表达与间质样表型相关[20]。这些细胞为了适应转移位点的微环境可重新分化为上皮样细胞。而转移位点的细胞中ADRB2上调和神经内分泌样肿瘤的形成在此过程中发挥的作用，目前尚未完全明了。不过已经有研究表明，肾上腺素刺激与多种肿瘤的血管生成密切相关[23-24]。这可以为肿瘤细胞从原位肿瘤脱离提供新的途径。

3 雄激素受体通路

对于已经发生转移的前列腺癌患者，去除雄激素治疗是首选疗法[25-26]。但是几乎所有的患者在经过18～24个月的雄激素剥夺治疗后最终都会进展为去势抵抗性前列腺癌，其中位生存期仅有1～2年。很多研究表明CRPC现象与复合逃逸机制有关，在这些文献中，作者对去除雄激素的雄激素信号通路进行了描述[27-29]。尽管雄激素剥夺治疗使血液循环中雄激素水平下降，但是肿瘤微环境中雄激素水平会升高[30-31]，并在调节CRPC进展过程中发挥了关键作用。研究表明，雄激素剥夺治疗并没有将肿瘤微环境中的雄激素去除，前列腺癌仍然可以在肿瘤组织分泌的雄激素诱导下逐步发展为致死性前列腺癌。肿瘤内部雄激素水平足以激活雄激素受体促进雄激素信号通路介导的下游基因表达[32-34]。因此，针对肿瘤微环境中雄激素的治疗效果可能会更好。新型雄激素合成抑制剂醋酸阿比特龙，可以通过抑制类固醇17-α-羟化酶，抑制肾上腺和肿瘤组织的雄激素分泌。另一种新型的雄激素受体拮抗剂恩杂鲁胺，能够竞争性地抑制雄激素与受体的结合，并且能抑制雄激素受体的核转运以及该受体与DNA的相互作用[35]，从而抑制前列腺癌的生长和分化。这两种新药对于CRPC的治疗有革命性意义[36]。阿比特龙由于其使用方便、毒性相对较低，在治疗转移性CRPC方面显示出了优越性[37]。尽管这两种药物取得了较好的临床结果，但是并不是对所有人都有效，部分患者对阿比特龙或恩杂鲁胺仍然存在抵抗性[38-39]；此外它们对转移性CRPC患者总体生存期仅能延长4～5个月[37]。对阿比特龙和恩杂鲁胺有抵抗性的肿瘤组织可以持续产生雄激素并使雄激素受体激活。因此，为了取得良好的治疗效果，可以考虑将信号通路靶向药物与其他治疗方式(如放疗、化疗、免疫疗法)相结合。

4 RANKL信号通路

RANKL及其相关受体RANK在破骨细胞生成中发挥关键作用[40-41]。由于破骨细胞活性升高与骨转移中骨的重塑过程有关，因此在前列腺癌和乳腺癌治疗中，针对RANKL的靶向治疗成为预防和治疗骨转移的热门方法。有研究表明，在前列腺癌、乳腺癌、肺癌、肾癌和结肠癌骨转移模型中，使用药物抑制RANKL可以预防肿瘤骨转移相关的骨质破坏[42]。另外，在一些实验模型中，使用药物阻断RANKL可以防止骨转移的发生[43-44]。这表明RNAKL在早期肿瘤定植和转移进展中扮演了种子的角色。在一项临床研究中，可以与人RNAKL高亲和力结合的IgG2抗体—狄诺赛麦，在预防和延迟前列腺癌骨转移相关并发症发生方面效果优于唑来膦酸[45]。另一项临床研究表明，与安慰剂组相比，狄诺赛麦可以延长CRPC患者无骨转移生存期[46-47]。这一研究首次成功地证明了，针对骨微环境的预防性治疗可以使骨的微环境不适合肿瘤细胞定植从而延迟骨转移的发生。

5 结语

目前的研究表明肾上腺素信号通路在前列腺癌发生、发展和骨转移过程中均发挥重要作用，但还需要进一步研究如何将其转化于临床治疗并获得预期的治疗效果。未来更多对于前列腺癌骨转移新的信号通路和潜在的治疗靶点的研究，将会进一步揭示前列腺癌的生物学特征，为前列腺癌的治疗带来更多的手段，并获得更好的疗效。

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