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乳腺癌骨转移发生机制和靶向治疗的研究进展

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摘 要:乳腺癌(breast cancer,BC)是全球女性中最常见的恶性肿瘤,其远处转移以骨转移最为常见。本文系统阐述了BC骨转移的五个阶段,包括转移前生态位的建立、乳腺癌细胞(breast cancer cells,BCCs)血行播散、BCCs在骨组织中的定植、BCCs的休眠与再激活以及骨转移灶的形成,为临床治疗提供理论依据。同时,本文综述了BC骨转移的经典靶点,如细胞周期蛋白依赖性激酶4/6(CDK4/6)、雌激素受体(ER)、孕激素受体(PR)、人表皮生长因子受体2(HER2),以及近年来的潜在治疗靶点,包括酪氨酸激酶SRC、白细胞介素-1β(IL-1β)、C-X-C趋化因子受体4(CXCR4)等,并介绍了相关最新临床研究进展。综上,本文旨在为克服现有靶向药物在BC骨转移治疗中存在的耐药性和副作用提供研究思路与方向。

关键词:乳腺癌;骨转移;发生机制;治疗靶点
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Progress in mechanism and targeted therapy of bone metastases in breast cancer

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Abstract: Breast cancer (BC) is the most prevalent malignancy among women worldwide, with bone representing the most frequent site of distant metastasis. This review outlines the mechanisms underlying BC bone metastasis across five stages: establishment of the pre-metastatic niche, hematogenous dissemination of breast cancer cells (BCCs), colonization within the bone microenvironment, dormancy and reactivation of BCCs, and the formation of overt bone metastatic lesions, thereby providing a theoretical framework for therapeutic development. In addition, we summarize current therapeutic strategies targeting classical molecules such as cyclin-dependent kinase 4/6 (CDK4/6), estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), and highlight recent clinical advances in emerging targets including tyrosine kinase SRC, interleukin-1β (IL-1β), and C-X-C chemokine receptor type 4 (CXCR4). Collectively, these insights may guide the development of novel therapeutic strategies aimed at overcoming drug resistance and minimizing adverse effects associated with existing targeted therapies for BC bone metastasis.

Key words: breast cancer; bone metastasis; occurrence mechanism; therapeutic target

在遗传和环境等多种因素综合作用下,乳腺癌(breast cancer,BC)已成为全球女性中发病率和死亡率均居前列的恶性肿瘤之一[1,2]。导致BC患者死亡的主要原因是肿瘤向远处转移[3],其中骨骼位

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于转移风险首位,约占BC远端转移病例的75%,且有超过2/3的BC骨转移患者死亡[4]。目前,“种子与土壤”理论被广泛认可,即循环的乳腺癌细胞(breast cancer cells,BCCs)与骨微环境之间的相互作用是BC骨转移的基础。BCCs通过核因子κB受体活化因子配体(receptor activator of nuclear factor kappa B ligand,RANKL)/RANK/骨保护素(osteoprotegerin,OPG)信号轴驱动破骨细胞活化,导致溶骨性破坏,骨破坏后释放的生长因子又促进肿瘤生长,形成恶性循环[5,6]。近年来,随着对BC骨转移发生机制研究的不断深入,转化生长因子β(transforming growth factor beta,TGF-β)、C-X-C趋化因子受体4(C-X-C chemokine receptor type 4,CXCR4)等靶点在临床前研究或Ⅰ~Ⅲ期临床试验中显示出巨大潜力,可显著延缓疾病进展、抑制骨转移灶形成。

在临床上,传统的双膦酸盐、地诺单抗(denosumab)能减少骨相关事件但不能根治转移,且面临耐药与长期毒性问题,这提示需要从机制层面寻找原因,从而制定更有效的治疗方案。为最大限度地提高患者的生存质量和生存时间,研发新型靶向药物意义重大。鉴于此,本文综述了BC骨转移的发生机制及相关靶向治疗的最新研究进展,旨在为临床治疗提供新思路。

1 发生机制

BC骨转移并非由单一因素所致,而是BCCs、骨骼结构以及骨微环境这三者之间复杂而精密的分子调控机制与细胞间相互作用的结果。BCCs在转移前即可通过分泌细胞因子或外泌体等方式,诱导骨细胞外基质(extracellular matrix,ECM)重塑及骨髓祖细胞动员,从而预先构建一个适宜肿瘤细胞定植与增殖的局部微环境,此环境被定义为转移前生态位(pre-metastatic niches,PMNs)[7]。外泌体中所携带的核酸、蛋白质等多种生物分子能够激活破骨细胞活性并抑制成骨细胞分化,破坏骨稳态平衡,使BCCs更容易通过血液循环侵入骨组织[8,9];随后,BCCs在骨微环境中通过与多种细胞的相互作用,或通过暂时休眠与再激活机制,逐步适应并持续增殖,最终形成完整的骨转移过程(图1)。

1.1 外泌体先行, 建立PMNs

在BCCs发生骨转移前,其通过分泌外泌体重塑骨微环境,从而为肿瘤细胞在骨髓中的黏附、存活与增殖创造条件。多项研究表明,来源于BCCs的外泌体进入骨组织后,可导致骨小梁数量和体积显著下降,并在骨小梁边缘富集大量破骨细胞[10]。其中,外泌体携带的miR-105能下调$CD1^+$血管内皮细胞中紧密连接蛋白ZO-1的表达,从而破坏血管内皮屏障的完整性,增加远端器官的血管通透性[11]。由此可见,外泌体介导的血管屏障破坏很可能是BCCs进入骨髓腔的关键。与此同时,整合素结合唾液蛋白(integrin-binding salivary protein,IBSP)不仅通过整合素介导的趋化作用招募破骨细胞前体并富集破骨细胞[12],还能作为外泌体的载体将miR-19a递送至破骨细胞,诱导其分化成熟。二者协同作用促进骨组织中肿瘤细胞的生长和破骨过程[13]。研究发现,$CD3^+$ T细胞表达的RANKL可先于BCCs到达骨髓并促进破骨细胞活化;而树突状细胞可协同RANKL信号,为溶骨过程提供正反馈回路;此外,该研究首次明确B细胞表达RANKL依赖于T细胞活性,B细胞与T细胞的协同作用显著诱导骨质流失,从而促进PMNs的建立[14]。

1.2 BCCs血行播散

BCCs主要依赖血液循环系统向骨组织转移,其过程依靠C-X-C趋化因子配体12(C-X-C motif chemokine ligand 12,CXCL12)和CXCR4之间的特异性相互作用,使BCCs锚定在血管周围生态位,维持BCCs的休眠状态,而新生血管的形成则可诱导其再激活并促进微转移灶的生长[15]。随着BCCs的持续增殖,它们与免疫细胞竞争氧气,同时炎症反应加剧局部耗氧。缺氧环境诱导内皮细胞表达缺氧诱导因子-1(hypoxia-inducible factor-1,HIF-1),从而大量释放血管内皮生长因子-A(vascular endothelial growth factor-A,VEGF-A),促进内皮细胞的激活、增殖和向肿瘤迁移,并招募内皮祖细胞,促进新生血管生长,为肿瘤细胞扩散提供通道[16]。此外,BCCs可分泌基质金属蛋白酶(matrix metalloproteinases,MMPs)降解ECM,突破基底膜并侵入血液循环。进入循环后的BCCs依靠E-选择素等分子黏附于血管内皮,在多种信号分子的引导下最终完成远处转移[17]。

1.3 BCCs在骨骼中定植

上皮-间充质转化(epithelial-mesenchymal transition,EMT)使BCCs获得迁移和侵袭能力,促进其早期播散。但值得注意的是,BCCs通常并非经历完全的EMT,而是处于中间状态的部分EMT,兼具上

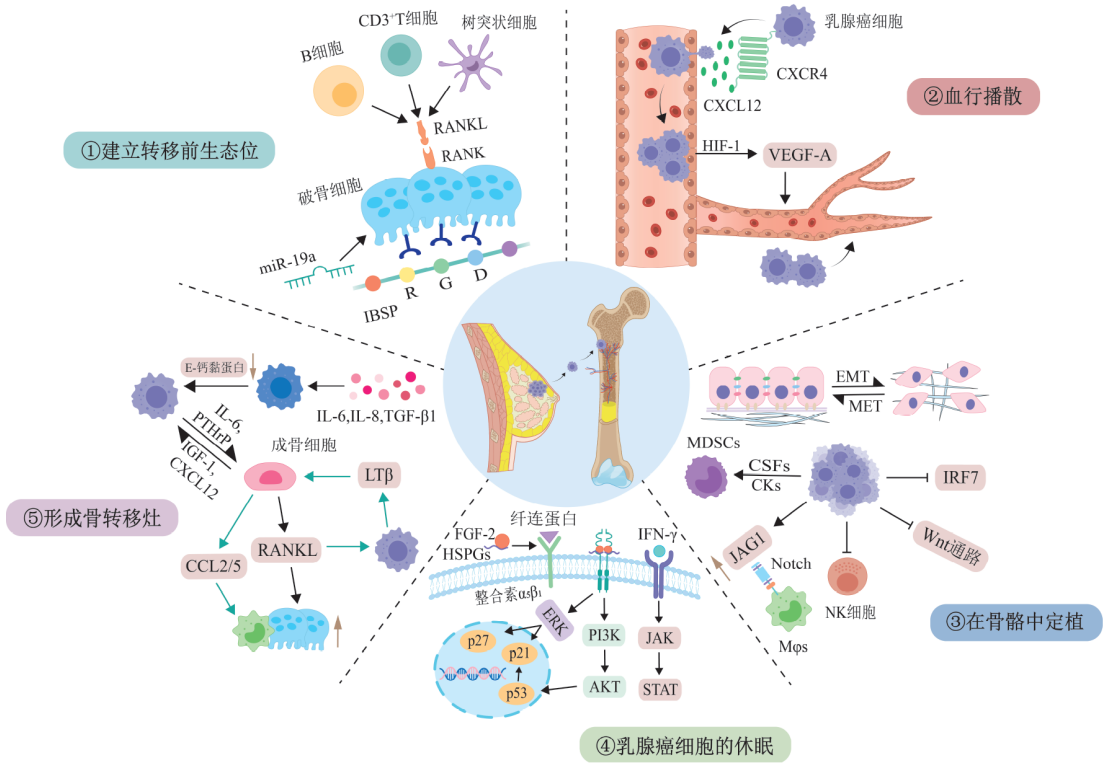

图1 BC骨转移发生机制

BC骨转移的起点是外泌体先进入骨骼中，与IBSP和RANKL协同促进破骨细胞活化进而发生溶骨，为BCCs创造合适的生存环境。然后，BCCs通过CXCL12和CXCR4进入血液循环。随着BCCs的大量增殖，血管局部逐渐变为缺氧状态，刺激内皮细胞产生VEGF-A，形成新的血管，促进BCCs转移。BCCs经血道进入骨骼后，通过MET黏附在骨髓中。此外，BCCs通过生成MDSCs、过表达JAG1等途径形成免疫抑制微环境，帮助其逃避免疫监视。同时，BCCs还与多种骨髓常驻细胞相互作用，并且在FGF-2、IFN-γ等作用下休眠，进一步适应骨微环境。休眠的BCCs被IL-6/8、TGF-β1激活后与成骨细胞相互作用，进而活化巨噬细胞和破骨细胞，促进骨转移灶形成。

Figure 1 The mechanism of bone metastasis in breast cancer

The initiation of BC bone metastasis is driven by exosomes, which first reach the bone and cooperate with IBSP and RANKL to promote osteoclast activation and subsequent osteolysis, thereby establishing a favorable niche for BCCs survival. Subsequently, BCCs enter the bloodstream through the CXCL12/CXCR4 signaling axis. As BCCs proliferate extensively, localized hypoxia develops within the vasculature, stimulating endothelial cells to secrete VEGF-A, which promotes angiogenesis and facilitates BCCs dissemination. After hematogenous dissemination to the bone, BCCs adhere to the bone marrow through MET. In addition, BCCs establish an immunosuppressive microenvironment by inducing the generation of MDSCs and overexpressing JAG1, thereby evading immune surveillance. Meanwhile, BCCs interact with multiple bone marrow-resident cell populations and enter a dormant state under the regulation of FGF-2 and IFN-γ, further adapting to the bone microenvironment. Upon reactivation by IL-6, IL-8, and TGF-β1, dormant BCCs interact with osteoblasts, leading to the activation of macrophages and osteoclasts, ultimately promoting the establishment of bone metastatic lesions.

皮与间质特征。随后，BCCs的间充质-上皮转化(mesenchymal-epithelial transition，MET)或部分逆转有助于其在骨微环境中重新建立黏附、进入休眠或恢复增殖[18]。播散到骨微环境的BCCs在早期阶段通过模拟造血干细胞(hematopoietic stem cells，HSCs)的表面分子如CXCR4竞争性结合HSCs龛位中的CXCL12，进而取代部分HSCs的位置。但在现有研究中，不同分子亚型的BC占据HSCs龛位的能力与机制差异尚未系统阐明[19]。BCCs通过分泌集落刺激因子(colony-stimulating factors，CSFs)和细胞因子(cytokines，CKs)，促进髓源性抑制细胞(myeloid-derived suppressor cells，MDSCs)生成，诱导红系前体细胞(erythroid precursor cells，EPCs)分化为MDSCs，沉默干扰素调节因子7(interferon regulatory factor 7，IRF7)通路进而下调干扰素表达，过表达Jagged 1(JAG1)进而募集并激活巨噬细胞(macrophages，Mφs)，下调自然杀伤(natural killer，NK)细胞配体并抑制Wnt通路，从而抑制免疫细胞活性，帮助BCCs逃

逸免疫监视并成功定植[15]。

BCCs通过与骨髓常驻细胞相互作用适应骨微环境，以保障自身的生存和增殖(图2)。骨微环境由多种细胞类型组成，包括间充质干细胞来源的成骨细胞、骨细胞和脂肪细胞等，HSCs来源的破骨细胞、免疫细胞等，以及内皮细胞、神经细胞等[20]。

1.3.1 BCCs与骨细胞

骨细胞是BC骨转移的关键调节因子，它通过分泌肿瘤坏死因子α(tumor necrosis factor alpha，TNF-α)抑制BCCs增殖并增强破骨细胞向BCCs定植部位的迁移能力，从而促进骨吸收。而BCCs通过释放TGF-β抑制骨细胞初级纤毛/鞭毛内转运蛋白88(intraflagellar transport protein 88, IFT88)表达，进而影响骨细胞的代谢和功能，导致骨破坏[21,22]。

1.3.2 BCCs与破骨细胞

甲状旁腺激素相关肽(parathyroid-hormone related peptide，PTHrP)被BCCs释放后，能够刺激成骨细胞分泌RANKL。随后，RANKL会与破骨细胞前体细胞表面的特异性受体相结合，进而诱导这些前体细胞分化为功能成熟的破骨细胞，增强骨吸收。而NK2同源框8(NK2 homeobox 8，NKX2-8)直接与PTHrP启动子上的组蛋白去乙酰化酶1相互作用，降低组蛋白H3K27乙酰化水平，下调BCCs中PTHrP的表达[23]。此外，破骨细胞分泌的谷氨酰胺能帮助BCCs合成谷胱甘肽，增强其对多聚腺苷二磷酸核糖聚合酶(poly(ADP-ribose) polymerase，PARP)抑制剂的耐药性，并减少DNA损伤；同时，研究发现BCCs可表达抗凋亡蛋白和细胞因子，抵御破骨细胞

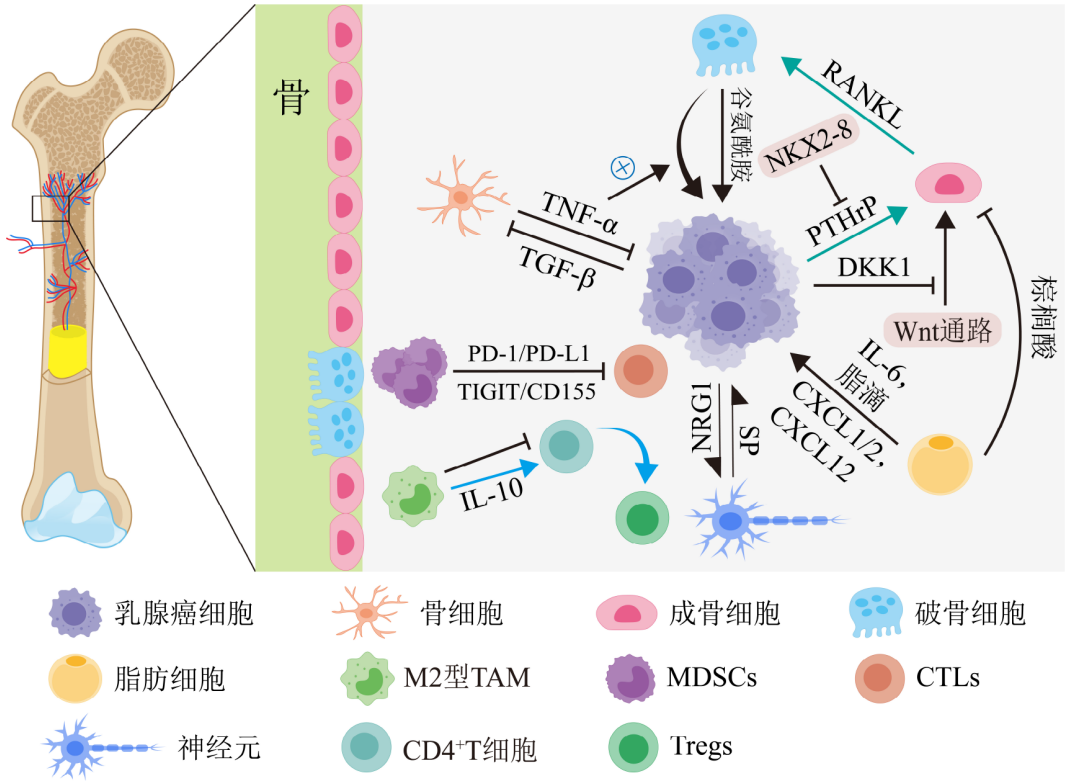

图2 BCCs适应骨微环境

BCCs和骨细胞之间存在具有相互抑制效应的串扰信号转导。PTHrP/RANKL轴调控破骨细胞生成，导致骨破坏和BCCs进一步增殖的恶性循环。BCCs通过分泌DKK1抑制Wnt信号转导，减少骨生成并加速骨破坏，脂肪细胞内储存的棕榈酸也能干扰成骨细胞成熟。此外，脂肪细胞和神经元都可以促进BCCs增殖。而$CD4^+$ T细胞、CTLs等减少和MDSCs、Tregs等增多，共同形成免疫抑制微环境，促进BCCs生存。

Figure 2 Adaptation of BCCs to the bone microenvironment

Crosstalk signaling with reciprocal inhibitory effects exists between BCCs and bone cells. PTHrP/RANKL axis regulates osteoclastogenesis, resulting in a vicious cycle of bone destruction and further BCCs proliferation. In addition, BCCs suppress Wnt signaling by secreting DKK1, thereby reducing bone formation and accelerating bone destruction. Palmitic acid stored in adipocytes also interferes with osteoblast maturation. Furthermore, both adipocytes and neurons promote BCCs proliferation. Meanwhile, reduced numbers of $CD4^+$ T cells and CTLs, together with increased populations of MDSCs and Tregs, collectively establish an immunosuppressive microenvironment that supports BCCs survival.

骨吸收过程中释放的细胞毒性物质,使其能在骨吸收微环境中存活与增殖[24]。

1.3.3 BCCs与成骨细胞

BCCs通过分泌多种骨代谢调节因子调控成骨细胞功能,从而破坏骨稳态并促进肿瘤在骨组织中的生长。其分泌的PTHrP可与成骨细胞表面受体结合,诱导信号级联反应,上调RANKL转录并抑制OPG表达,导致RANKL/OPG比值失衡,促进破骨细胞分化与骨吸收,为肿瘤定植创造有利环境[20]。此外,BCCs分泌属于TGF-β超家族的骨形态发生蛋白(bone morphogenetic protein,BMP),部分BMP亚型通过诱导成骨谱系细胞分泌RANKL或重塑基质因子,间接增强破骨活性,加速骨破坏。另一方面,Wnt通路通常有利于成骨细胞成熟并促进OPG分泌,而BCCs高表达的Dickkopf相关蛋白1(Dickkopf-related protein 1,DKK1)则抑制这一成骨信号,导致成骨活性下降并加剧骨丢失[25]。但是,现有研究对BMP在骨转移中的作用方向及其与DKK1的调控顺序仍存在分歧,在不同模型中BMP既可促进亦可抑制成骨细胞活性,这提示其作用高度依赖于亚型与骨微环境。

1.3.4 BCCs与脂肪细胞

脂肪细胞分泌的TNF-α和脂联素可抑制骨髓造血,而棕榈酸水平升高既能延长破骨细胞存活周期,又能阻碍成骨细胞成熟,从而导致骨质流失,为BCCs定植提供了有利条件[26]。其分泌的脂质及脂肪因子可上调脂肪酸结合蛋白4(fatty acid binding protein 4,FABP4)、血红素加氧酶1(heme oxygenase 1,HO1)和白细胞介素-1β(interleukin-1beta,IL-1β)等代谢与炎症相关分子,增强BCCs的侵袭性。IL-6、TNF-α和CXCL12等则促进BCCs生长并抑制凋亡,CXCL1和CXCL2进一步促进破骨细胞生成和提高BCCs存活率[27]。综上,脂肪细胞通过调控代谢和炎症过程共同推动骨微环境向促转移状态演变。然而,现有研究多聚焦于单一信号通路,对脂质代谢与骨免疫调控网络之间的互作机制仍缺乏深入探索。

1.3.5 BCCs与免疫细胞

MDSCs在肿瘤微环境中富集,通过PD-1/PD-L1轴和TIGIT/CD155轴抑制细胞毒性T淋巴细胞(cytotoxic T lymphocytes,CTLs)活性,削弱抗肿瘤免疫。IL-1β介导的粒细胞免疫抑制作用亦促进BCCs免疫逃逸与骨定植[28]。Mφs是肿瘤微环境中含量最丰富的免疫细胞,被BCCs分泌的趋化因子募集后发生表型重塑:M1型肿瘤相关巨噬细胞(tumor-associated macrophages,TAMs)分泌IL-12诱导$CD4^+$ T细胞向Th1细胞分化,Th1细胞分泌干扰素-γ(interferon-gamma,IFN-γ)进一步激活TAMs向M1型极化并增强NK细胞活性;而IL-4和IL-13诱导M2型TAMs的极化,从而抑制$CD4^+$ T细胞的增殖。M2型TAMs高表达IL-10、TGF-β,阻断CTLs活化并诱导$CD4^+$ T细胞向调节性T细胞(regulatory T cells,Tregs)分化,增强免疫抑制效应,促进BCCs免疫逃逸与转移[29]。

1.3.6 BCCs与神经细胞

社会心理因素可诱导交感神经系统(sympathetic nervous system,SNS)和下丘脑-垂体-肾上腺轴慢性激活,从而影响骨微环境,使其转化为适合BCCs转移的“肥沃土壤”。SNS信号和CXCL12共同动员HSCs进入血液循环[30]。SNS被应激激活后,会释放大量去甲肾上腺素(norepinephrine,NE),进而激活β-肾上腺素能受体(β-adrenergic receptors,β-ARs),驱动IL-6和VEGF基因表达。IL-6可直接诱导BCCs增殖,并诱导破骨细胞前体分化,形成恶性循环。而神经肽Y可通过上调VEGF的活性,促进骨髓内血管生成,为BCCs提供氧气和营养[27]。此外,BCCs分泌的神经调节蛋白1(neuregulin-1,NRG1)可与感觉神经元上的ErbB4受体结合,被激活的神经元通过P物质(substance P,SP)激活神经激肽1受体(neurokinin 1 receptor,NK1R),促进BCCs的增殖和迁移[31]。

1.4 BCCs的休眠与激活

HSCs龛位中抑制增殖的信号如TGF-β会诱导BCCs进入休眠状态,使其躲避化疗等治疗手段,为肿瘤细胞提供生存优势与免疫逃逸保护,从而成为后续骨转移复发的“种子”细胞。当龛位发生炎症、骨重塑等改变,BCCs就可能被重新激活[19]。

1.4.1 BCCs的休眠

成纤维细胞生长因子2(fibroblast growth factor 2,FGF-2)是诱导和维持BCCs休眠的关键因子。FGF-2通过与肝素硫酸蛋白多糖(heparan sulfate proteoglycans,HSPGs)结合,诱导BCCs表面整合素$\alpha_5\beta_1$表达,随后整合素$\alpha_5\beta_1$与纤连蛋白结合,使细胞形成一种非运动性、非增殖性的上皮表型,维持BCCs休眠状态[19]。在特定条件下,FGF-2通过激活细胞外信号调节激酶(extracellular signal-regulated kinase,

ERK)、磷脂酰肌醇-3激酶(phosphatidylinositol-3-kinase,PI3K),以及由TGF-β介导的细胞周期蛋白依赖性激酶抑制剂p21Waf1、p27Kip1和p15INK4b的上调、细胞周期蛋白依赖性激酶2和4的失活以及视网膜母细胞瘤蛋白(pRb)去磷酸化,抑制BCCs的增殖和对化疗的反应,促进BCCs进入休眠状态;FGF-2还可以间接上调程序性细胞死亡受体-1(programmed death receptor 1,PD-1),帮助BCCs逃避免疫监视[32,33]。

1.4.2 BCCs的再激活

骨髓基质细胞衰老后,可造成IL-6/8、TGF-β1等促炎细胞因子分泌增加,使休眠肿瘤细胞重新增殖。其中,TGF-β1不仅激活休眠细胞,还会导致细胞完全不表达雌激素受体(estrogen receptor,ER),且再激活后的细胞无法再休眠。在再激活过程中,细胞发生E-钙黏蛋白下调等EMT相关基因表达的改变,使激活后的肿瘤细胞侵袭性增强[34]。此外,炎症因子可改变乳腺癌干细胞(breast cancer stem cells,BCSCs)表面蛋白的表达,使BCSCs逃避NK细胞免疫监视,实现从休眠到激活的转变,增加复发风险。在正常情况下,NK细胞分泌的IFN-γ激活BCSCs内JAK-STAT信号通路,抑制细胞活性从而维持休眠;但NK细胞功能受损或数量减少时,原本被抑制的增殖、迁移相关基因会被激活,促使BCSCs苏醒[32]。

1.5 形成骨转移灶

骨微环境中休眠的BCCs被激活后,在骨定植部位逐渐发展为骨转移灶。成骨细胞分泌的CXCL12、胰岛素样生长因子-1(insulin-like growth factor-1,IGF-1)等因子,与BCCs表面受体结合,促进肿瘤细胞存活、增殖和迁移。同时,BCCs诱导成骨细胞分泌RANKL、IL-6等因子,导致骨吸收[35,36]。此外,RANKL诱导BCCs表达淋巴毒素β(lymphotoxin beta,LTβ),激活成骨细胞内NF-κB2信号通路,诱导C-C基序趋化因子配体2(C-C motif chemokine ligand 2,CCL2)和CCL5表达,招募Mφs,并增强破骨细胞分化,促进骨转移灶形成[37]。

2 靶向治疗

尽管双膦酸盐与Denosumab在减少骨相关事件方面取得了显著疗效,但二者主要抑制破骨细胞活性,难以阻断BC骨转移的发生与进展。加之长期使用的安全性与耐药性问题,其临床获益仍有限。鉴于骨微环境中多种细胞与信号通路的复杂互作,针对肿瘤-骨微环境关键分子和免疫代谢轴的靶向药物研发已成为当前研究的重点与突破方向。下面将从经典治疗靶点(已被指南接受或已经获批上市)和新兴治疗靶点(正处在临床前研究或Ⅰ~Ⅲ期临床试验阶段)两方面展开综述。

2.1 经典治疗靶点

2.1.1 细胞周期蛋白依赖性激酶(cyclin-dependent kinase, CDK)4/6

CDK4/6在细胞周期调控中至关重要,其异常激活会使BCCs增殖失控。临床常用CDK4/6抑制剂(cyclin-dependent kinase 4/6 inhibitor,CDK4/6i),如帕博西尼(palbociclib),阻止肿瘤细胞从G_1期进入S期[38]。在骨转移治疗中,连续使用palbociclib可显著抑制转移到骨骼中的BC生长,但治疗中断后,无论是否联合骨靶向药物唑来膦酸(zoledronic acid,ZA),BC生长都将恢复。这提示,对CDK4/6不敏感的BC的靶向替代途径仍需进一步研究[39]。目前,CDK4/6i与内分泌治疗联合是激素受体(hormone receptor,HR)阳性/人表皮生长因子受体2(human epidermal growth factor receptor 2,HER2)阴性晚期BC最重要的治疗策略[40];palbociclib与芳香化酶抑制剂联用可显著提高骨转移患者的无进展生存期(progression-free survival,PFS)和客观缓解率[41]。此外,CDK7不仅促进转录起始并参与调控转录延伸和终止[42],还激活CDK4/6从而推动细胞周期进程。研究发现,联合抑制CDK4/6和CDK7对三阴性乳腺癌(triple-negative breast cancer,TNBC)细胞迁移和侵袭的抑制效果优于单药处理[43]。

2.1.2 雌激素受体(ER)和孕激素受体(progesterone receptor, PR)

ER调控的分泌蛋白SCUBE2在骨转移生态位中高表达,通过激活间充质干细胞Hedgehog通路、驱动成骨细胞释放胶原蛋白来抑制NK细胞免疫监视功能,促进BCCs定植。研究证实,Hedgehog信号通路抑制剂Sonidegib及SCUBE2中和抗体LTMA16D5可有效阻断骨转移[44]。约75%的BC患者表达ERα,使其成为关键治疗靶点;激素治疗可抑制ERα活性,但ERα介导的骨转移常伴随耐药性。而新型药物如氟维司群、依维莫司、palbociclib,以及口服ER降解剂如AZD9496和GDC-0810,可针对*ESR1*突变相关的ERα异常激活状态发挥治疗作用,改善BCCs的耐

药性[45,46]。此外,ERα的内在无序区域能诱导促转移基因沉默,抑制骨转移进程,为靶向药物设计提供了新思路[47]。

此外,PR也是激素受体阳性BC的重要分子标志物。传统观点通常认为雌激素是BC风险的主因,而近年来研究提示孕激素及PR介导的信号通路在BC中发挥更复杂的作用。孕激素通过激活PR调控相关基因转录及乳腺上皮细胞增殖,从而影响BC发生发展过程。同时,PR表达状态也是BC分型和评估内分泌治疗反应的重要指标。因此,低剂量孕激素联用雌激素的治疗方案可能是激素替代治疗女性的安全选择[48]。

2.1.3 PARP

PARP抑制剂(PARPi)他拉唑帕利和奥拉帕利已被批准用于BRCA突变的HER2阴性晚期患者,但耐药性仍是临床难题[49]。Wang等[50]分别研究了PARPi与PI3K/蛋白激酶B(protein kinase B,AKT)通路抑制剂、免疫检查点抑制剂、HSP90抑制剂、靶向治疗药物等的联用效果,但最优方案仍待验证。现有研究显示,PARPi联合ATR/CHK1/WEE1通路抑制剂是兼顾临床获益和安全性的选择,患者的PFS和总生存期(overall survival,OS)得到明显改善,不良反应可被患者耐受。此外,研究发现破骨细胞可降低BCCs对PARPi的敏感性,这源于破骨细胞可分泌谷氨酰胺以及PARPi处理使肿瘤细胞中的关键酶GPX4表达上调,二者发挥协同作用导致肿瘤细胞耐药。而PARPi与ZA联用,可恢复BCCs对PARPi的敏感性,并协同抑制骨转移[24]。

2.1.4 HER2

HER2是一种受体酪氨酸激酶,能够激活Wnt/β-catenin信号转导通路,导致EMT相关基因被激活,促进BCCs转移[51]。曲妥珠单抗作为靶向HER2的人源化单克隆抗体,通过与NK细胞表面Fcγ受体结合触发抗体依赖性细胞毒性(antibody-dependent cellular cytotoxicity,ADCC),诱导BCCs死亡。但是,约70%的HER2阳性患者在治疗后一年内产生耐药性[52]。组蛋白去乙酰化酶抑制剂(histone deacetylase inhibitor,HDACi)——曲古抑菌素A(trichostatin A,TSA)通过上调miRNA-146a表达,可以抑制HER2过表达的BCCs;同时,TSA与酪氨酸激酶抑制剂拉帕替尼协同作用也可有效抑制BC进展,表明联合靶向HER2和HDAC的治疗策略具有较大潜力[53-55]。此外,抗体药物偶联物(antibody-drug conjugate,ADC)如恩美曲妥珠单抗、双靶点联合治疗策略以及抑制PI3K/AKT/哺乳动物雷帕霉素靶蛋白(mechanistic target of rapamycin,mTOR)通路等方法,均能有效实现针对HER2的靶向干预,并可缓解患者对曲妥珠单抗治疗产生的耐药性问题[56,57]。

2.1.5 PI3K/AKT/mTOR信号通路

PI3K/AKT/mTOR信号通路在BC骨转移中发挥关键调控作用:PI3K的激活促进下游AKT和mTOR磷酸化,驱动BCCs增殖且抑制其凋亡,同时通过调控RANKL/RANK/OPG轴及分泌IL-6、CXCL12等细胞因子重塑骨微环境,从而促进BCCs在骨中定植[58]。目前,靶向该通路的药物已在临床应用中取得显著进展:PI3K抑制剂阿培利司用于*PIK3CA*突变的$HR^+/HER2^-$晚期BC;AKT抑制剂卡培西替尼用于*PIK3CA*、*AKT1*或磷酸酶及张力蛋白同源物(phosphatase and tensin homolog,*PTEN*)突变型$HR^+/HER2^-$ BC;mTOR抑制剂依维莫司则在多项研究中被证实可延缓疾病进展并逆转内分泌耐药[59,60]。总体来看,虽然该通路的多靶点抑制策略均能改善内分泌耐药患者的PFS,但鉴于单药疗法常受限于BCCs的适应性耐药以及药物毒性,未来研究应探索PI3K/AKT/mTOR通路抑制剂与RANKL抑制剂或内分泌药物的联合应用。

2.1.6 RANKL

BCCs转移至骨后促使RANKL表达,从而激活破骨细胞引发骨破坏,破骨细胞释放的生长因子又促进BCCs生长,形成恶性循环[61]。此外,RANKL可借助RANKL/RANK信号通路,将处于循环系统中的BCCs招募至骨基质表面[62]。而全人源单克隆抗RANKL抗体(Denosumab)能够与RANK竞争性结合RANKL,进而阻断RANKL与RANK的相互作用,抑制破骨细胞形成,增加骨体积和密度[63]。在Denosumab与ZA治疗骨转移晚期癌症患者的三项Ⅲ期临床试验中,Denosumab在延迟首次骨骼相关事件中的表现优于或等于ZA[64,65]。然而,近期研究发现,突变的RANKL可抑制BCCs骨内生长、下调GDF-15表达并减少溶骨性病变数量[66],这提示该信号通路在不同分子状态下可能表现出复杂的调控特征。除单抗治疗外,天然化合物芒柄花苷(Ononin)可通过抑制ERK/JNK/p38 MAPK信号通路阻止RANKL上调,从而减少破骨细胞生成与骨吸

收,并且Ononin在成本、效益和不良反应方面比双膦酸盐和Denosumab更具优势[67],但其抗转移机制仍处于体外研究阶段,临床证据还需进一步验证。

2.2 新兴治疗靶点

2.2.1 TGF-β

TGF-β通过激活SMAD2/3和PI3K/AKT、MAPK等非SMAD途径,促进肿瘤细胞EMT进程,增强BCCs侵袭能力。当BCCs诱发骨吸收时,TGF-β以活性形式释放,造成溶骨性破坏,并释放更多的TGF-β,形成恶性循环,进一步刺激BCCs的生长和转移[68,69]。近年来,增强子甲基转移酶2(enhancer of zeste homolog 2,EZH2)与Kindlin-2被证实在调控TGF-β信号通路及骨转移中发挥关键作用。EZH2通过整合素β1/黏着斑激酶(focal adhesion kinase,FAK)轴激活TGF-β信号通路,这一过程不依赖于EZH2的甲基转移酶活性,而是通过其转录辅因子功能实现,FAK抑制剂有望成为治疗EZH2诱导的骨转移的有效手段[70]。Kindlin-2则通过稳定整合素β1和TGF-βⅠ型受体的复合体,调节整合素和TGF-β信号通路的活性,促进TNBC的进展和转移;且Kindlin-2缺失可抑制TNBC的恶性生物学行为,成为极具潜力的治疗新靶标[71]。从机制上来看,未来可探索FAK和Kindlin-2抑制剂联合用于抗骨吸收治疗的可能性。

2.2.2 酪氨酸激酶SRC

类固醇受体辅激活因子(steroid receptor coactivator,SRC)作为一类非受体型酪氨酸蛋白激酶,是调控BC骨转移的关键信号分子,通过磷酸化FAK破坏BCCs与ECM的稳定黏附,同时介导BCCs骨架重排,增强BCCs的侵袭能力,帮助其突破血管壁并进入骨组织;随后,SRC激活PI3K/AKT、MAPK等信号通路抑制BCCs凋亡,使其在骨中成功定植[72]。此外,SRC对破骨细胞的活化至关重要,SRC通过磷酸化破骨细胞内的E3泛素连接酶c-Cbl并与其结合,促进形成足体带并维持破骨细胞功能[73]。多项动物模型研究显示,SRC抑制剂能抑制破骨细胞形成、降低骨吸收;部分研究报道,在化疗耐药的TNBC模型中,达沙替尼(Dasatinib)能显著降低骨转移负荷[74]。然而,Ⅱ期临床试验显示,单用Dasatinib的客观缓解率非常有限,虽然部分患者的骨痛得到缓解且骨代谢标志物下调,但整体抗肿瘤效果不显著;此外,SRC抑制剂选择性较差,易对其他激酶产生抑制作用,不仅可能引发脱靶效应,还可能诱导肿瘤细胞启动代偿机制,从而影响治疗效果[72,75]。综上,SRC高活化状态在TNBC患者中较少见,因此在临床上要经过生物标志物筛选后再进行使用,未来的研究应探索SRC抑制剂与TGF-β、RANKL等抑制剂联用的效果。

2.2.3 分化簇47(cluster of differentiation 47, CD47)

CD47可激活整合素β3调控破骨细胞生成,促进BC骨转移。同时,CD47通过与Mφs表面的信号调节蛋白α(signal regulatory protein alpha,SIRPA)结合,发出“别吃我”信号,帮助BCCs逃避免疫监视,使其成为治疗骨转移的关键靶点[76,77]。在TNBC治疗中,虽然阻断CD47可诱导TNBC细胞被程序性清除(programmed clearance,PrCR),但疗效欠佳,而卡巴他赛可通过激活Mφs增强PrCR效果,二者联用效果更好[78]。抗CD47抗体可与靶向HER2的曲妥珠单抗联合,显著增强ADCC和抗体依赖的细胞吞噬作用,克服曲妥珠单抗耐药。此外,CD47阻断还可与放疗联合,增强癌细胞放疗敏感性[79]。为了攻克癌细胞上调CD47抑制Mφs吞噬的难题,研究者构建了基于超分子原位组装技术的CD47/CD24双靶点抑制剂,研究发现其显著抑制癌细胞侵袭和集落形成,增强Mφs对癌细胞的吞噬作用,生物安全性好且作用效果超过单靶点抑制剂,而且抑瘤效果优于双抗体联合疗法,能有效激活抗肿瘤免疫反应[80]。

2.2.4 IL-1β

IL-1β可激活BCCs内NF-κB通路,并通过间接调控环磷酸腺苷反应元件结合蛋白(cAMP response element-binding protein,CREB)通路及下游Wnt信号通路,促进BCCs的EMT进程。同时,IL-1β通过上调RANKL表达或直接作用于破骨前体细胞,加速破骨细胞分化与骨吸收过程,进而释放TGF-β,推动溶骨性转移灶的形成[81,82]。在注射或接种BCCs构建的小鼠模型中,抗IL-1β靶向治疗策略能够显著缓解骨转移相关症状,并显著提升实验小鼠的存活率,IL-1受体拮抗剂阿那白滞素联合多柔比星及ZA可协同抑制BC骨转移并延缓原发灶生长[83]。然而,IL-1β在不同位点具有双向效应:在原发肿瘤中可促进免疫细胞浸润、增强抗肿瘤反应,而在骨转移灶中则促进肿瘤定植[84]。综上,未来研究需明确IL-1β在调控免疫细胞功能和骨重塑中的具体作用机制,进而开发针对特定骨转移部位或

肿瘤发展特定阶段的靶向干预方法，避免传统的全身性治疗所导致的副作用。

2.2.5 CXCR4/CXCL12信号通路

CXCR4是一个在BCCs中广泛过表达的G-蛋白偶联受体，其配体CXCL12在骨微环境中含量丰富并形成化学梯度，进而吸引表达CXCR4的BCCs向骨迁移。CXCR4与CXCL12结合激活PI3K/AKT信号通路，维持BCCs干细胞样表型，并参与细胞周期与抗凋亡通路，导致BCCs对化疗及内分泌治疗的耐受性提高[85,86]。目前，多项临床前研究显示，靶向CXCR4的策略均能抑制骨转移、减少肿瘤细胞骨髓定植以及部分逆转化疗耐药，但单独阻断CXCR4面临骨髓内正常造血功能与细胞迁移受影响的安全性问题，因而当前更主张联合疗法[87]。此外，研究发现$CXCR4^+$ Mφs在肿瘤早期积聚，通过CXCR4/CXCL12信号轴增强肿瘤起始细胞自我更新与存活，同时分泌IL-10等因子抑制T细胞活化，形成免疫逃逸环境[88]。由此可见，靶向$CXCR4^+$ Mφs或干扰CXCR4/CXCL12轴，可能是预防BC发生或抑制早期进展的新型治疗策略。

2.2.6 DEAD-box RNA解旋酶3(DEAD-box RNA helicase 3, DDX3)

DDX3通过调控mRNA代谢和细胞周期相关基因转录或翻译，促进BCCs存活与增殖，且DDX3过表达还可通过诱导BCCs发生EMT从而增强其迁移能力[89]。同时，DDX3可促进Kirsten大鼠肉瘤病毒癌基因同源物(Kirsten rat sarcoma viral oncogene homolog，KRAS)表达进而激活ERK信号通路，解除PTEN对PI3K/AKT信号通路的抑制，促进BCCs向骨组织侵袭[90]。此外，最新研究发现DDX3协同CDK1在S616位点磷酸化动力相关蛋白1(dynamin-related protein 1，DRP1)，从而诱导线粒体分裂并增强脂肪酸氧化代谢，维持BCCs干性及侵袭能力并使其适应骨微环境[91]。基于此，研究者在BC骨转移小鼠模型中应用DDX3抑制剂RK-33，结果显示给予RK-33的实验组几乎未见骨转移形成；此外，研究发现从对照组小鼠的骨转移灶中提取的细胞系与患者来源的骨转移细胞系均对常规化疗药物产生了耐药性，但对RK-33没有耐药性[92]。综上，DDX3是一个很有潜力的干预靶点，但目前仍以临床前研究为主，其临床转化仍需更多安全性和药代动力学的探索。

2.2.7 PTHrP

PTHrP是BC骨转移中驱动溶骨“恶性循环”的核心因子。BCCs大量分泌PTHrP作用于成骨细胞上的PTHR1，诱导成骨细胞RANKL上调，从而促进破骨细胞活化，导致骨吸收[93]。除典型的旁分泌作用外，PTHrP的细胞内分泌功能可通过影响细胞周期调控蛋白、白血病抑制因子受体信号及EMT来调节肿瘤细胞的骨定植和休眠或再激活过程，且在不同时期可能发挥截然不同的作用，如在肿瘤早期主要发挥抑制作用，而在骨转移期则发挥促进作用[94]。尽管有可靠的临床前研究表明抗-PTHrP单抗能抑制骨转移进程，且人源化抗-PTHrP单抗曾进入Ⅰ/Ⅱ期试验，但直接针对PTHrP的临床研究进展有限，至今尚无获批的药物或确定的晚期临床证据[95]。目前临床干预仍以阻断破骨细胞活性为主，间接抑制由PTHrP引起的骨吸收，而并非直接抑制PTHrP本身。但PTHrP在机制上仍是极具吸引力的干预靶点，相信未来可以依据其功能设计出选择性抑制PTHrP旁分泌促溶骨而尽量不损伤其在其他组织中发挥作用的药物。

2.2.8 DKK1

DKK1是经典的Wnt信号通路抑制因子，可抑制成骨细胞分化，使骨形成减少。最新研究发现DKK1不仅作用于骨代谢，还能通过直接抑制NK细胞活性和诱导中性粒细胞呈现未成熟功能状态，使骨转移灶形成免疫抑制微环境，进而阻碍免疫检查点抑制等疗法的效应[96]。此外，DKK1也可通过细胞骨架相关蛋白4(cytoskeleton-associated protein 4，CKAP4)/AKT等非典型通路直接促进肿瘤细胞增殖与转移[97]。研究发现，血清DKK1水平在多种恶性肿瘤伴骨转移的患者中常升高，其有望成为骨转移风险的潜在生物标志物，并且抗-DKK1抗体在胃癌、结直肠癌等实体瘤的Ⅰ/Ⅱ期临床试验中展现出良好的安全性及免疫调节效应[98]。综上，靶向抑制DKK1或将成为新的联合治疗策略，但目前专门针对BC骨转移的临床证据不足，有待进一步探究。

3 展望

BC骨转移作为BC远处转移中的常见类型，其复杂的分子机制使现有临床干预手段面临巨大挑战，近年来的研究主要聚焦于BCCs在转移前预先构建PMNs以及BCCs与骨微环境的交互作用。目前，

BC骨转移的临床治疗仍主要依赖经典靶点药物,这些已获批的疗法能够延缓病程、减少骨相关事件的发生,但仍存在疗效有限、耐药性及副作用明显等瓶颈。鉴于此,未来应从如下三个方面着手进行深入研究:一方面,监测BCCs是否在塑造PMNs,以血液中DKK1浓度下降、骨组织中M2型巨噬细胞比例降低和骨基质胶原蛋白交联度恢复正常等作为指标,在骨病变形成前就阻止转移发生,而非仅治疗已形成的骨病变;另一方面,探索多靶点联合治疗,同时阻断多条促进BCCs迁移或促进溶骨的信号通路,从而增强抑制效果;此外,未来研究应加强对上述新兴治疗靶点的临床转化与验证,推动其从实验阶段迈向临床应用,提高患者生存与生活质量。

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