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Wnt/β-catenin信号通路与多发性骨髓瘤上皮间质转化表型的关系

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摘　要

多发性骨髓瘤是血液系统最常见的恶性肿瘤之一，其复发难治的特点是治疗的一个难点。骨髓瘤患者易发生髓外浸润，患者预后极差。现有大量的研究表明，常发生于实体瘤中的上皮间质转化特征，也在间质肿瘤中发生，比如胶质瘤。多发性骨髓瘤作为一个侵袭性很强的血液肿瘤，我们猜测上皮间质转化在其转移与侵袭中也发挥着作用。Wnt/β-catenin信号通路与肿瘤侵袭转移研究较多，于是我们在本综述中归纳总结了关于骨髓瘤上皮间质转化的研究，并讨论Wnt/β-catenin信号通路在其中的作用。

关键词

多发性骨髓瘤，上皮间质转化，Wnt/β-catenin信号通路

Relationship between Wnt/β-Catenin Signaling Pathway and Epithelial Mesenchymal Transformation Phenotype in Multiple Myeloma

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Abstract

Multiple myeloma is one of the most common hematological malignancies, and its recurrence is

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difficult to treat. Patients with myeloma are prone to extramedullary infiltration and have a poor prognosis. A large number of studies have shown that epithelial-mesenchymal transformation features, which are common in solid tumors, also occur in mesenchymal tumors, such as gliomas. Multiple myeloma is a highly aggressive hematologic tumor, and we suspect that epithelial-mesenchymal transformation may also play a role in its metastasis and invasion. There are many studies on Wnt/β-catenin signaling pathway and tumor invasion and metastasis, so in this review, we summarize the studies on epithelial-mesenchymal transformation in myeloma and discuss the role of Wnt/β-catenin signaling pathway in it.

Keywords

Multiple Myeloma, Epithelial Mesenchymal Transformation, Wnt/β-Catenin Signaling Pathway

1. 引言

多发性骨髓瘤(multiple myeloma, MM)是一种恶性克隆性浆细胞疾病，在血液系统恶性肿瘤发病率中排名第二位，其细胞遗传学、分子生物学、临床表现及预后等方面均存在很大的异质性，目前仍是一种无法治愈的疾病[1]。过去的 20 年里，随着新药(如蛋白酶体抑制剂、免疫调节剂、单克隆抗体等)和干细胞移植技术的应用[2] [3] [4]，MM 患者的生存时间得到了极大的提高，患者生存期从 4 年延长至 8 年左右[5]，但大部分患者最终都会复发。多数 MM 表现为骨髓累及的“液体肿瘤”，少数则发生“实体瘤”特征的髓外浆细胞瘤，又被称为髓外病变。髓外病变在整个病程中都可能出现，在新药时代之前，尸检显示骨旁的髓外病变发生率高达 70%，肝脏累及率 40%，说明髓外病变可能是 MM 进展的自然结局[6] [7]。而且随着疾病进展，累及不同部位的浆细胞，其克隆演变也不同[8]。因此，深入研究 MM 的生物学异质性和侵袭机制，对开发特异性治疗靶点、优化一线治疗方案的选择、提高完全缓解率、改善患者预后具有重要意义。

1.1. 上皮－间质转化(Epithelial-Mesenchymal Transition, EMT)与 MM

EMT 是胚胎发育的基础，多种生物过程参与其中，与肿瘤细胞的局部浸润和远处转移密切相关。EMT 是指上皮细胞在特定生理或病理情况下向间质细胞转化，并伴随明显基因和表型改变的一个多阶段过程。在肿瘤细胞发生 EMT 的过程中，细胞的形态、极性、迁移侵袭能力等形态学和生物学行为会出现变化，还有一些分子标志物也会发生改变：如细胞膜蛋白 E-钙黏蛋白(E-cadherin)等上皮标志物表达减低和功能缺失，细胞膜蛋白 N-钙黏蛋白(N-cadherin)、细胞骨架蛋白(β-catenin)、波形蛋白(vimentin)等间质细胞标志物过量表达，以及某些转录因子 Snail、Twist 和 ZEB1 等表达和/或功能上调[9]。因此，EMT 在上皮细胞肿瘤中研究较多，在非上皮细胞肿瘤中研究较少，因为非上皮细胞肿瘤缺乏上皮细胞的形态特点。但近几年，研究显示在非上皮细胞肿瘤中，如脑部肿瘤、血液系统肿瘤、骨肉瘤中存在类 EMT 现象[10] [11] [12] [13]，与细胞的微环境和信号级联激活有关而非上皮细胞本身。从本质上讲，EMT 是一个可逆的过程，细胞可以通过间质－上皮转化(mesenchymal to epithelial transition, MET)恢复到上皮状态，这似乎是肿瘤细胞在远处定植所必需的，是转移过程中的关键一步。所以，肿瘤细胞在 EMT/MET 过程中，可能具有这两种相反状态的中间特征，同时表达上皮和间质标记物。上皮/间质的

混合细胞表型，比完全的 EMT，更能促进肿瘤细胞的侵袭性，细胞的粘附性更弱，迁移性增高，循环肿瘤细胞增多，增强了干细胞特征和耐药[14]。Azab 等的研究发现低氧环境可以激活 EMT 相关蛋白活化，下调 E-cadherin 的表达，从而促进骨髓瘤细胞向远处侵袭、转移[15]。Yang 等发现在 MM 合并骨旁髓外病变患者中 TWIST1 表达升高，且与较低的无进展生存率相关，证实间质转化参与了 MM 的疾病播散[16]。另有研究证实 CXCR4 增强了 MM 细胞中 EMT 样表型的获得，表型转化为侵袭型，通过 EMT 转录激活，促进 MM 髓外病变的发生[17]。间充质干细胞(mesenchymal stem cells, MSCs)是肿瘤微环境中的一种重要细胞成分，在肿瘤的发生和发展中具有重要作用，能使实体肿瘤细胞发生 EMT 及获得干性特征[18]。骨髓间充质干细胞(bone marrow mesenchymal stem cells, BM-MSCs)通过激活 Wnt 和转化生长因子-β 信号通路使胃癌细胞获得并维持干细胞特性[19]。Ibraheem 等研究发现，BM-MSCs 胞外基质与多发性骨髓瘤 EMT 样表型相关[20]。Zhou 等研究发现 BM-MSCs 源性外泌体激活骨髓瘤细胞 EMT 相关的信号通路，增加了 MM 细胞的侵袭性，导致髓外病变的发生[21]。最近的研究发现通过沉默核转录因子 Snail1 可以增加硼替佐米耐药 MM 的化疗敏感性，提示 EMT 转录因子在治疗耐药 MM 方面有很大潜力[22]。肿瘤 EMT 的调控机制仍不明确，PI3K/AKT、NF-κB、Wnt/β-catenin 和 MAPK 等多种信号通路可促进肿瘤细胞 EMT 的发生[23]。

1.2. Wnt/β-catenin 信号通路与 MM

传统 Wnt 信号转导通路在调节细胞增殖、分化、迁移和干细胞自我更新过程中起着关键作用，与疾病的多个方面有关[24]。Derksen 最先发现原代骨髓瘤细胞中 β-catenin 的表达明显高于健康对照，且通过促进 β-catenin 聚积及核内转移，进而促进骨髓瘤细胞的增殖[25]。Wnt 信号在 MM 中的相关性首先被认为是其在骨稳态中的调节作用。骨髓中的恶性浆细胞分泌的 Wnt 拮抗剂严重破坏了骨骼的稳态，导致溶骨性骨病。在 MM 中，Wnt 信号通路通过直接和间接机制调节骨形成成骨细胞和骨吸收破骨细胞之间的平衡[26]。Huang 等研究证明类泛素化通过促进泛素－蛋白酶体介导的 β-catenin 降解来下调 Wnt 通路，β-catenin 类泛素化是 MM 细胞增殖失调的重要机制，且异常激活的类泛素化与 MM 患者不良预后密切相关[27] [28]。另有研究发现，重组 Wnt 配体进行的额外治疗导致 MM 对来那度胺耐药性进一步增加，而 β-catenin 敲低极大地增强了药物敏感性，Wnt 通路靶基因 CD44 可作为 MM 中介导的来那度胺抗性的下游效应分子[29] [30]。以上的研究表明，靶向 Wnt 通路可能是治疗 MM 的一个有趣的新途径：1) 增加 MM 细胞的凋亡，从而减少肿瘤生长；2) 减少 MM 细胞分泌的 Wnt 拮抗剂，从而减少骨溶骨病；3) 减少 MM 获得的耐药，从而提高对现有治疗方案的应答。

1.3. β-catenin 在 Wnt/β-catenin 信号通路和 EMT 中的双重作用

经典的 Wnt/β-catenin 信号通路激活的关键是细胞骨架蛋白 β-catenin 的降解障碍，大量的 β-catenin 从胞浆转移至细胞核内，进而调控下游靶基因的表达[31]。而同时 β-catenin 又属于 EMT 的细胞骨架蛋白标志物，正常情况下，β-catenin 与细胞表面蛋白 E-cadherin 相互作用，从而实现上皮细胞相互粘附连接。在肿瘤发生发展的过程中，细胞表面 E-cadherin 的表达降低，以至于 E-cadherin/β-catenin 复合体不稳定，E-cadherin 和 β-catenin 发生解离，使释放入胞浆内的游离 β-catenin 增多[31]。β-catenin 进入核内，可以激活 Wnt 通路下游的 vimentin 基因转录及上调 Twist、Snails、ZEB1 等转录因子的表达，来诱导肿瘤细胞的 EMT 进程[31]。各种分子或药物通过调控 Wnt 信号通路来调控 EMT 过程已在胃癌、肝癌、肺癌等肿瘤中被证实[32] [33] [34]。Wnt 信号通路能够调节肿瘤的 EMT 变化已是事实，最新研究发现，miR-744-5p 能够通过靶向 Wnt/β-catenin 信号通路抑制多发性骨髓瘤的 EMT 表型[35]。我们期待更多的研究来证实 Wnt 通路与 MM 中 EMT 表型的联系，并发掘更多的治疗靶点来促进 MM 细胞对药物的应答。

2. 展望

Wnt/β-catenin 信号通路是诱导 EMT 的关键通路之一。大量实验表明，Wnt/β-catenin 信号通路的失调导致了 EMT，其特征是 β-catenin 的核移位和 E-cadherin 的抑制。越来越多的证据表明，EMT 诱导剂也能促进非上皮性肿瘤的间充质特性。众所周知，MM 以多个溶骨性病变为特征，提示骨髓内多个区域的骨髓瘤细胞持续扩散，MM 细胞间充质功能增强，并导致骨髓瘤的进展。因此，上皮间质转化是引起多发性骨髓瘤不良预后的一个重要原因，抑制 Wnt/β-catenin 信号通路有望成为调控骨髓瘤上皮间质转化的关键靶点。

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