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在线全文

多发性骨髓瘤细胞与骨髓微环境互作机制研究进展

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【摘要】 多发性骨髓瘤（multiple myeloma, MM）是浆细胞来源的血液系统恶性肿瘤，其发生发展机制主要包括肿瘤细胞遗传学异常和细胞与骨髓微环境（bone marrow microenvironment, BMME）互作。MM细胞在BMME内恶性增殖，通过细胞与细胞外基质的直接或间接互作，促进MM的发生发展。探讨MM细胞与微环境的互作机制，对阐明MM发生发展机制及早诊和治疗有着重要意义。肿瘤的代谢重编程是肿瘤学研究的重点之一。本文总结出微环境中MM的代谢重编程改变和MM代谢与微生物互作的特征，以便于深入了解MM的发生发展及耐药性机制，最终达到挖掘MM治疗的新策略之目的。

【关键词】 多发性骨髓瘤　克隆演变　骨髓微环境　代谢微环境

Latest Findings on the Mechanism of the Interaction Between Multiple Myeloma Cells and Bone Marrow Microenvironment

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【**Abstract**】 Multiple myeloma (MM) is a hematologic malignancy of terminally differentiated plasma cells. The mechanisms of the pathogenesis and progression of MM include genetic abnormalities of the MM cells and the interaction between MM cells and bone marrow microenvironment (BMME). MM cells start malignant proliferation in BMME and contribute to the pathogenesis and progression of MM through direct or indirect interactions between cells and the extracellular matrix. Exploring the mechanism of interaction between MM cells and the microenvironment is crucial to improving our understanding of the pathogenesis and progression of MM and early diagnosis and treatment. In addition, the metabolic reprogramming of tumors is one of the key issues of oncology research. Herein, we summarized published findings on the the altered metabolic reprogramming of MM and the characteristics of MM metabolic-microbial interactions in order to gain an in-depth understanding of MM pathogenesis and progression and drug resistance mechanisms, and ultimately to explore for new strategies for MM treatment.

【**Key words**】 Multiple myeloma　Clonal evolution　Bone marrow microenvironment　Metabolic microenvironment

多发性骨髓瘤（multiple myeloma, MM）是浆细胞来源的血液系统恶性肿瘤，其肿瘤特征是骨髓中浆细胞恶性增生，血清和尿液中单克隆免疫球蛋白累积。随着我国人口老龄化的增长，MM的发病率呈逐年上升趋势。随着沙利度胺、来那度胺和硼替佐米（bortezomib, BTZ）等新型药物的引入以及自体干细胞移植技术的改进，MM缓解率得以显著提高[1]。然而，由于MM存在发病机制复杂、复发和耐药等问题，MM仍无法治愈。MM细胞中遗传学异常是MM发展的重要驱动因素，同时，骨髓微环境（bone marrow microenvironment, BMME）对于MM细胞恶性增殖和存活起支持作用。因此，探究MM细胞遗传学异常及MM细胞与微环境的相互作用，对于了解MM发生发展机制及未来治疗有着重要意义。

1　MM肿瘤细胞

MM是一种浆细胞恶性增殖的血液系统肿瘤。在生理状态下，B 细胞接触抗原后被活化并迁移到生发中心。在生发中心，免疫球蛋白重链基因座 高变区的 DNA 经历体细胞超突变（somatic hypermutation, SHM）产生高度特异性的抗体。通过类转换重组（class-switch recombination, CSR），B细胞产生不同免疫球蛋白（Ig）。SHM与CSR都需要活化脱氨酶（activation-induced deaminase, AID）的表达，并诱导生成Ig位点断裂双链DNA。AID与基因组中其他位置断裂双链DNA结合，引起染色体易位，这就是MM中常见的分子标志之一。在B细胞分化过程中转录因子如IRF4、BLIMP1、XBP1的上调，分化产生浆细胞。研究表明细胞分裂周期蛋白37（CDC37）表达与XBP1s相关，抑制CDC37或抑制CDC37/Hsp90的结合可诱导浆细胞去分化，并且破坏CDC37会导致浆细胞通过XBP1s成熟逆转，从而导致体外和体内的BTZ抗性[2]。

MM的发生发展是多基因、多阶段、多步骤的。生理状态下浆细胞异常增殖，发展为意义不明的单克隆丙种球蛋白病（monoclonal gammopathy of undetermined significance, MGUS），进而发展为冒烟型MM (smouldering

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multiple myeloma, SMM), 最后演变成MM。

MM细胞中异常的CSR产生染色体易位。例如t(4;14)易位导致成纤维细胞生长因子受体3(FGFR3)基因的过度表达使CCND2上调, 在新诊断的MM患者中约占7% ~ 8%, 并且与MM恶化有关[3]。由CSR驱动的t (6; 14)和t (11; 14) 易位导致致癌基因例如细胞周期蛋白家族成员CCND1和CCND3高表达, 激活下游的MAPK信号通路, 导致肿瘤细胞的恶性增殖[4]。基因改变被认为是MM的驱动事件。MM发展相关的遗传学异常主要包括染色体数目改变、扩增、异位和丢失等。基因组不稳定性(genomic instability, GIN), 指基因组获得改变的趋势增加[5]。而染色体片段或甚至整个染色体的增殖、缺失和重排通常被称为染色体不稳定(chromosomal instability, CIN), 作者研究发现CIN基因*NEK2*通过激活AKT和NF-κB信号通路, 导致癌细胞产生耐药性[6]。同时作者进一步发现NEK2可以增强MM细胞自噬。自噬抑制剂氯喹(CQ)和BTZ联合可显著降低NEK2诱导的MM细胞耐药[7]。大多数的抑瘤基因失活需要两个等位基因同时缺失, 而双打击型MM是指存在任何两个或更多的高风险异常, 作者研究表明, 高表达NEK2的患者常同时伴有TP53缺失, 该类型患者预后较差。TP53和NEK2的双重缺陷者为带有 *p*53 失活、预后最差的MM 患者, NEK2可以作为带有 *p*53 异常的侵袭性 MM 的新治疗靶点[8]。

2 MM微环境

2.1 MM细胞与BMME细胞互作

作者参考文献[9]绘制了图1。MM细胞在骨髓中恶性增殖, 因此 BMME对于支持MM细胞生长和存活起到关键作用。虽然MM的起始事件在遗传学上是克隆性的, 但驱动病变往往发生在BMME中, 通过达尔文选择过程

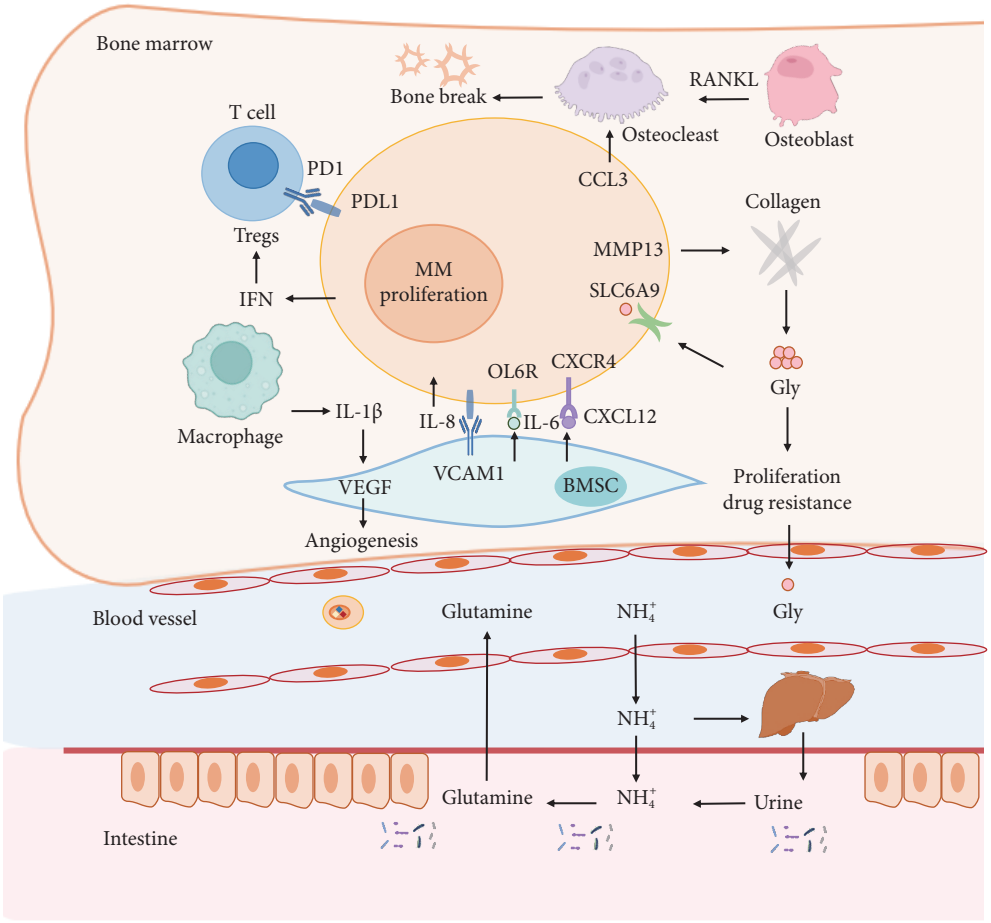

图 1 MM肿瘤细胞与微环境的相互作用

Fig 1 The interaction between MM cells andthe microenvironment

VEGR: vascular endothelial growth factor; IFN: interferon; MMP13: matrix metalloproteinase 13; RANKL: receptor activator of nuclear factor-kappa B ligand; PD1: programmed cell death protein 1; PDL1: programmed death ligand 1; IL: interleukin; IL6R: interleukin 6 receptor; IFN: interferon; CCL3: C-C motif chemokine ligand 3; SLC6A9: solute carrier family 6 member 9; CXCR4: C-X-C motif chemokine receptor 4; CXCL12: C-X-C motif chemokine ligand 12; VCAM1: vascular cell adhesion molecule 1; BMSC: bone marrow stromal cells; Gly: glycine.

促进疾病的进展。研究MM细胞和 BMME之间的相互作用对于理解MM的发展、治疗和进展具有重要意义[9]。

BMME中造血细胞(包括T细胞、B细胞)、巨噬细胞和破骨细胞参与浆细胞的分化发育,并且在肿瘤发展过程中参与免疫检测。MM细胞通过表达细胞程序性死亡1配体1(PDL1),逃避了T细胞的免疫监控。在MM细胞浸润较多的患者的BMME中免疫细胞被抑制,有利于MM逃避免疫监视,并且PD-1、PIM、KLRB1和KLRC1的异常表达也参与了MM患者免疫细胞的缺陷[10]。研究证明MM细胞通过分泌Ⅰ型干扰素(IFN)来驱动Treg细胞的扩增和激活。阻断Tregs上的IFN α和β受体1(IFNAR1)可显著降低MM相关的Treg免疫抑制功能和MM的进展[11]。近期临床研究证实嵌合抗原受体(CAR)T细胞疗法提高了B细胞恶性肿瘤的治疗效果。在MM的临床治疗中,CAR-T疗法在RRMM患者中疗效和安全性进行评估,以B细胞成熟抗原(BCMA)为靶点的CAR-T和含有抗BCMA的治疗方案显示出更好的疗效[12]。MM的BMME中巨噬细胞产生细胞因子如IL-1β,作用于BMSCs并诱导IL-6产生[13]。MM-龛位衍生的IL-18推动了骨髓源性抑制细胞(MDSCs)的产生,促进了MM的疾病进程[14],IL-18驱动免疫抑制,成为BMME中潜在的治疗靶点。MM患者的骨质破坏80%以上是由于破骨细胞的作用产生。破骨细胞被MM细胞以互作方式诱导激活,导致MM的溶骨性骨病。CC-化学因子配体3(CCL3)等因子参与巨噬细胞向成熟破骨细胞的分化,并参与MM的骨破坏。

BMME的核心是骨髓基质细胞(BMSC),它与MM细胞受体配体直接相互作用,为MM细胞生长创造了一个有利的生态环境,促进MM恶性增殖。BMSC细胞表面的血管细胞黏附蛋白1(VCAM1)和MM细胞上的整合素相互作用,促使细胞因子分泌,有助于MM细胞增殖并抑制细胞凋亡[15]。BMSC表达CXCL12与MM上的CXCR4结合,促进MM细胞向骨髓迁移。骨髓基质干细胞衍生的COX2促进了MM细胞的生长并增强了其黏附[16]。MM细胞与成骨细胞相互作用导致RANKL的产生和增加,并使骨保护素水平降低[17]。RANKL与前破骨细胞表达的RANK结合,促进破骨细胞的分化,导致骨质破坏和骨病的发展。由BMSC产生的血管内皮生长因子A(VEGFA)通过增加局部丰富的血管增加氧气供应,造成MM患者不良预后。骨髓脂肪组织(BMAT)随着MM患者的衰老和肥胖而增加。同时MM细胞改变BMAT的基因表达和细胞因子分泌,这与生物能量的变化和诱导衰老表型相关[18]。见表1。

表 1　MM骨髓微环境互作细胞及功能

Table 1　The functions of interacting cells in bone marrow microenvironment in MM

Cell	Cytokines	Functions	Ref.
BMSC	IL-6	Stimulating MM cell growth, survival and drug resistance (DR)	[19]
	Growth factor, TNF-α	MM cell growth, survival, DR, and migration	[20]
	VEGF	Upregulation of IL-6 secretion	[21]
	CD40 & CD40L	Increasing MM cell adhesion	[21]
	IL-8	Enabling MM cells to recruit new blood vessels in the bone marrow	[22]
BMEC	Angiopoietin 1	Up-regulation of angiogenically active factors after MM cell growth promotion by mutual adhesion	[23]
	IL-6 , IGF1	MM cell growth	[24]
	TGFβ, PDGF, IL-1	Pro-angiogenic molecules	[25]
Osteoclast	RANKL	Promotion of osteolytic lesions	[26]
	MIP-1α	Osteoclast formation inducer	[27]
Osteoblast	DKK1, IL-3	Inhibition of osteoblast differentiation	[28]

BMSC: bone marrow stromal cells; IL: interleukin; TNF-α: tumor necrosis factor-alpha; VEGF: vascular endothelial growth factor; CD40: CD40 antigen; CD40L: CD40 antigen ligand; IGF1: insulin like growth factor 1; TGFβ: transforming growth factor beta; PDGF: platelet derived growth factor subunit B; RANKL : receptor activator of nuclear factor-kappa B ligand; MIP-1α: macrophage inflammatory protein-1 alpha; DKK1: Dickkopf WNT signaling pathway inhibitor 1.

2.2　MM骨髓代谢微环境

肿瘤的代谢重编程一直是肿瘤学研究的重点之一,肿瘤微环境中的代谢改变是肿瘤进展的关键因素。对于MM的BMME代谢特征了解较少。在已发表的文献中,对于MM的代谢特征及代谢重编程改变,涉及到肿瘤细胞的糖酵解反应、氨基酸代谢、脂肪酸代谢等三个方面。

2.2.1　*糖酵解*　新诊断的MM(NDMM)患者的浆细胞比MGUS患者的浆细胞有更高的线粒体和糖酵解ATP形成率,证明浆细胞内的能量代谢对MM患者的发病机制和结果有影响[29]。研究证明,转录因子叉头盒M1 (FOXM1)

是骨髓瘤代谢的一个正向调节器,影响细胞的糖酵解和氧化磷酸化。FOXM1增加了MM细胞的葡萄糖摄取、乳酸输出和氧气消耗[30]。而葡萄糖能维持骨髓细胞白血病因子1(MCL-1)的水平,促进细胞耐药[31]。丙酮酸激酶M2(PKM2)可以调节有氧糖酵解和促进MM细胞增殖和生存。NEK2通过调节PKM的剪接和增加骨髓瘤细胞中PKM2/PKM1的比例来促进有氧糖酵解,促进MM细胞恶性增殖[32]。蛋白酪氨酸磷酸酶4A3(PRL-3)在MM中高表达。过表达PRL-3的细胞有氧糖酵解率升高、氧化磷酸化增强和产生ATP增加。PRL-3促进了葡萄糖的摄取和乳酸的排出,提高了细胞糖酵解的丝氨酸/甘氨酸合成水平[33]。

此外MM细胞糖代谢特征的改变与MM耐药性相关,与BTZ敏感细胞U266相比,耐药细胞U266-R中的糖基化尿苷二磷酸葡萄糖(UDP)衍生物累积,证明在耐药细胞中六胺生物合成途径(HBP)的活性更高,线粒体生物生成和线粒体动态的增加,细胞因此具有更强的抗氧化能力以增加耐药性[34]。单细胞scRNA-seq数据分析显示MM患者和MM细胞系依赖于氧化磷酸化(OxPhos)反应,并且在复发时氧化磷酸化被激活。代谢通量分析证实氧化磷酸化是耐药的MM细胞首要能量途径[35]。

2.2.2 氨基酸代谢 氨基酸代谢失衡也是MM的重要代谢特征之一。在体外,MM细胞由谷氨酰胺代谢产生的$NH4^+$过多,因此MM细胞可能对谷氨酰胺有成瘾性。除此之外在MM细胞的谷氨酰胺(Gln)代谢中,缺失Gln后存活的MM细胞,会增强BIM的表达和与BCL-2的结合,使得细胞对维奈妥拉(BCL-2抑制剂)敏感。研究揭示靶向谷氨酰胺代谢以增加MM对药物敏感性。参与谷氨酰胺代谢的代谢物和酶可能成为MM细胞的治疗靶标。

经代谢组学分析发现,MM的BMME中氨基酸含量失衡,甘氨酸浓度升高。甘氨酸浓度升高是由于MM细胞分泌的基质金属肽酶13(MMP13)介导的骨胶原降解,促进骨溶解并降低MM的总体存活率[36]。研究表明,骨溶解与MM患者血清甘氨酸升高呈正相关[37]。BMME中甘氨酸失衡促进MM细胞增殖和耐药[38]。

先前研究表明,MM细胞的BTZ耐药与细胞丝氨酸合成途径(SSP)增加相关。发现 SSP 中的第一个限速酶磷酸甘油酸脱氢酶 (PHGDH) 在来自复发性 MM 患者的$CD138^+$细胞中显著升高。PHGDH 通过增加 MM 细胞中的 GSH 合成以促进MM细胞的增殖和 BTZ 耐药[39]。

2.2.3 脂肪酸代谢 脂肪细胞占据了骨髓内70%的体积,癌症相关的脂肪细胞通过相应机制支持MM细胞,包括癌细胞的代谢重编程。研究发现,MM细胞诱导BM脂肪细胞的分解,同时在MM细胞表面的脂肪酸转运体1和4表达上调,促进MM细胞对分泌游离的脂肪酸(FFAS)的吸收,而阻断MM细胞对FFA的吸收可以作为MM治疗的潜在靶标[40]。对MM细胞系中的脂质进行分析,由于激活转录因子4(ATF4)诱导的胆固醇调节元件结合蛋白(SREBP1/2)表达升高,蛋白酶体抑制剂增强了MM的异常脂质积累[41]。

MM细胞对铁死亡诱导剂(RSL3)表观遗传重编程很敏感。铁质细胞的死亡与表观基因组的压力反应有关,这可能推动铁质化合物的临床治疗的适用性[42]。MM细胞从外环境中吸收乙酸盐,促进细胞的增殖。标记的^{11}C-醋酸酯-PET在体内的骨髓瘤细胞中检测到,代表醋酸酯代谢是MM细胞脂质代谢的关键,同时利用^{11}C-醋酸酯-PET是一种很有前途的MM成像方式[43]。乙酰辅酶2(ACSS2)可能是与肥胖相关的MM的关联因素。研究发现脂肪细胞分泌的血管紧张素Ⅱ直接导致ACSS2表达增加。ACSS2与肿瘤蛋白干扰素调节因子4(IRF4)相互作用,并通过激活乙酰化增强IRF4的稳定性和IRF4介导的基因转录。ACSS2在来自肥胖患者的MM细胞中过量表达,并促进了MM的进展[44]。

2.2.4 MM代谢与微生物 研究者们对MM中肠道微生物组的作用及其代谢功能知之甚少,通过宏基因组分析初诊的MM患者和健康对照的粪便宏发现,氮循环相关的细菌如克雷伯菌和链球菌在MM中显著富集,且富集氮循环细菌与宿主代谢组学显著相关,表明微生物与宿主之间存在强烈的代谢相互作用[45]。氮循环细菌中的肺炎克雷伯杆菌在小鼠体内重新合成谷氨酰胺,促进了MM的进展,结果揭示肠道微生物组的改变促进MM恶变,通过改变MM患者肠道微生物群以达到MM治疗的新策略[45]。肠道-肺轴强调了肠道微生物群与肺炎的相关性,表明肠道微生物群的功能受损可能容易导致肺炎。肠道克雷伯氏肺炎在MM患者中富集,并促进MM的发展。该项研究探讨了肠道微生物群与MM患肺炎之间的关系[46]。

同时也有研究发现,MM患者的细菌丰度或多样性降低与双磷酸盐相关的颌骨坏死相关[47]。在治疗后的MM患者中,通过比较不同CAR-T治疗阶段的肠道微生物组的组成和多样性,发现肠道菌群可能反映患者对复发/难治性MM的治疗反应[48]。同时MM患者经自体干细胞移植(HSCT)后疾病的进展/复发,与MM患者肠道微生物完整性或细菌的丰度有关[49]。通常MM患者肠道微生物的多样性越高,移植效果越好。研究发现,普雷沃氏肝素化促进了Th17细胞的分化,进而促进细胞定植于在

MM癌前期模型VK*MYC小鼠的肠道中, 并进入MM小鼠的骨髓, 促进肿瘤进展[50]。

3　小结

随着我国人口老龄化的增长, MM的发病率呈逐年上升趋势, 在亚洲和中国发病率大约为1/10^6 ~ 2/10^6, 并且在2008–2016年中国癌症登记年报中, MM在中国的发病率上升了5%[1, 9]。近年来, 临床对于MM的治疗方案增加, 包括沙利度胺、来那度胺和BTZ等新型药物的引入、自体干细胞移植、以及BCMA和CAR-T的靶向治疗, MM的缓解率和总生存期显著提高。即使如此, MM复发和耐药仍存在, MM依旧无法治愈。因此进一步了解MM起始的病因, 以及发生发展过程, 对于治疗MM尤其重要。

MM细胞在骨髓中恶性增殖, 因此 BMME对于支持MM细胞生长和存活起到关键作用。研究MM细胞和BMME之间的相互作用对于理解MM的发展、治疗和进展具有重要意义。肿瘤的代谢重编程是肿瘤学研究的重点之一。目前对于MM的BMME代谢特征了解较少。在已发表的文献中, 本文总结出MM的代谢重编程改变及MM的代谢特征, 从糖代谢、氨基酸代谢、脂肪酸代谢等三个方面进行阐述, 以便于深入了解MM的发生发展及耐药性机制。目前对MM中的肠道微生物组的作用及其代谢功能了解甚少, 本文总结出MM代谢与微生物互作的特征, 揭示了改变肠道微生物组在加速MM恶变进展及MM治疗方面的新功能, 并通过改变MM患者肠道微生物群以达到MM治疗的新策略。

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利益冲突　所有作者均声明不存在利益冲突

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