骨髓来源免疫抑制细胞参与肿瘤进展的相关信号通路

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[摘　要]　骨髓来源免疫抑制细胞(myeloid derived suppressor cells，MDSCs)是一群异质性的骨髓来源的未成熟前体细胞，它们在肿瘤微环境中大量聚集，阻碍T细胞的抗肿瘤免疫应答反应。MDSCs的产生、聚集和发挥促肿瘤功能依靠STAT3、IL-1β/NF-κB、PI3K/AKT/mTOR、PGE2/Cox2及RAS信号通路的调节，信号通路的调节紊乱导致骨髓造血功能异常，形成具有免疫抑制功能的骨髓来源细胞，在肿瘤间质中聚集形成免疫抑制微环境。了解这些信号通路,特别是STAT3信号通路，能帮助我们理解恶性肿瘤中MDSCs功能的分子机制，找到一些消除肿瘤微环境中MDSCs的方法。

[关键词]　骨髓来源抑制细胞(MDSCs)；信号通路；STAT3；免疫抑制

Signaling pathways involved in myeloid derived suppressor cells promoting tumor growth

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Abstract　Myeloid derived suppressor cells (MDSCs) represent a population of heterogeneous myeloid cells that are at early stages of development. There is an accumulation of MDSCs in tumor microenvironment. The generation of MDSCs can counteract T cell responses. Generation, expansion and playing a role in promoting tumor of the MDSCs rely on signaling pathways such as STAT3, IL-1β/NF-κB, PI3K/AKT/mTOR, PGE2/Cox2 and RAS. Perturbation of signaling pathways involved during normal hematopoietic and myeloid development, leading to the generation and accumulation of suppressive MDSCs and immunosuppressive tumor microenvironment. Targeting these pathways should help in elucidating mechanisms that lead to the expansion of MDSCs in cancer and point to methods for eliminating these cells from the tumor microenvironment, especially the STAT3 signaling pathway.

Key words　myeloid derived suppressor cells (MDSCs); signaling pathways; STAT3; immunosuppression

　　骨髓来源免疫抑制细胞(myeloid derived suppressor cells，MDSCs)被定义为一群骨髓来源的异质性免疫抑制细胞，包括单核/巨噬细胞、粒细胞、树突状细胞等未成熟的前体细胞。多数研究者认为荷瘤小鼠的MDSCs是一群Gr-1+和CD11b+的细胞[1]，但是目前对于人类MDSCs的鉴定还没有统一的标

准。有学者将 MDSCs主要分为两类：CD33+HLA-DRlowLineage- MDSCs(主要存在于宫颈癌，卵巢癌，结直肠癌，肾癌和头颈部鳞状细胞癌中)和CD11b+CD33lowHLA-DRlowLineage- MDSCs(主要存在于乳腺癌中)[2]。正常情况下MDSCs能够迅速分化为成熟的具有免疫功能的细胞；在炎症、肿瘤等病理情况下，受各方面的作用，成熟受阻停留在较幼稚阶段，成为具有免疫抑制功能的一群细胞，主要通过促进肿瘤新生血管、抑制抗肿瘤的T细胞反应达到促进肿瘤生长的目的[3]。MDSCs募集、扩增、功能相关的信号通路直接影响MDSCs对肿瘤的作用，本文对相关信号通路作一综述。

1 STAT3通路与MDSCs

1.1 MDSCs的STAT3通路激活

STAT3持续的磷酸化活化是多数肿瘤的特征，活化的STAT3能上调肿瘤细胞的一系列细胞因子和炎症因子的表达(IL-10、IL-6、VEGF、FGF2、COX2、CXCL12、IL-11、IL-23、IL-21、IL-17)，而这些细胞因子又是MDSCs的STAT3通路激活因子[4]。肿瘤微环境中的各种炎症因子通过旁分泌方式作用于基质中的MDSCs，激活MDSCs的STAT3通路。

1.2 MDSCs的STAT3激活对自身的影响

在恶性黑色素瘤中发现MDSCs的STAT3高表达与其自身的募集有关[5]，舒尼替尼可以通过抑制STAT3信号通路有效的减少肿瘤组织中的MDSCs数量[6]。胰腺癌的干细胞也能激活间质中单核细胞的STAT3通路，促使其向MDSCs方向分化，促进了肿瘤的进展[7]。具体来讲MDSCs通过STAT3通路上调或者下调各种自身蛋白的表达，直接或间接影响自身的募集、凋亡、成熟分化：上调下游基因Bcl-xl、c-myc、cyclinD1、survivin[8]的转录，抑制MDSCs凋亡；上调S100A8/S100A9的表达，促进了MDSCs的聚集，而且S100A8/S100A9二聚体参与了NADPH氧化酶的合成，进一步促进反应性氧产物(reactive oxygen species，ROS)的生成，间接抑制MDSCs的成熟分化[9]；上调CCAAT增强子结合蛋白β，抑制MDSCs的聚集与成熟分化[10-11]；下调蛋白激酶CβII的表达，抑制DCs分化成熟[12]。

1.3 MDSCs的STAT3激活后的促肿瘤作用
1.3.1 促肿瘤新生血管

MDSCs通过活化的STAT3上调一些促血管生成基因的表达，刺激肿瘤的血管生成。有研究[13]证实肿瘤间渗出的B细胞的STAT3是持续激活的，这种B细胞能通过STAT3通路上调S1PR1，MMP9、HIF1α等促肿瘤血管生成基因的表达。在人的肾癌研究中表明舒尼替尼能抑制MDSCs的STAT3信号通路，下调肿瘤血管生成相关基因VEGF、CXCL2的表达[6]。

1.3.2 促进IDO的表达

吲哚胺2,3-双加氧酶(indoleamine 2,3-dioxygenase，IDO)主要由树突细胞、单核细胞和巨噬细胞分泌，以超氧阴离子作为辅助因子降解吡咯环，最适底物是L-色氨酸，消耗肿瘤微环境中的色氨酸。T细胞对色氨酸的降解极其敏感，在缺乏色氨酸的条件下，T细胞不能进入细胞周期，停滞于G1期。MDSCs利用STAT3通路上调IDO的表达[14-15]，消耗肿瘤微环境中的色氨酸并产生免疫抑制性的代谢产物，产生免疫抑制反应[16-17]。

1.3.3 促进ARG-1的表达

精氨酸酶-1(arginase-I，ARG-1)能分解耗竭微环境中的L-精氨酸。而L-精氨酸为T细胞活化所必须的氨基酸，其缺乏可促使T细胞上调细胞周期素D3、细胞周期素依赖激酶4，阻滞T细胞增殖；并下调T细胞受体相关CD3ζ链表达，导致CD8+T细胞活化信号传导障碍[18]。MDSCs的pSTAT3能通过直接与ARG-1的启动子结合[19]上调ARG-1的表达。

1.3.4 促进NADPH氧化酶的表达

NADPH氧化酶由催化亚基gp91phox、p47phox、p22phox、p67phox、p40phox、Rac六个亚基组成，是细胞生成ROS的催化酶。ROS与多分叶核性MDSCs的成熟分化受阻、T细胞免疫功能的抑制有关[20]。在gp91−/−小鼠试验中发现MDSC不能诱导T细胞的免疫耐受。研究发现pSTAT3能与gp91、p47的启动子结合增强ROS表达，诱导抗肿瘤的免疫耐受[21]。

1.3.5 促进iNOS的表达

诱导型一氧氮合成酶(inducible nitric oxide synthase，iNOS)是生成内源性NO合成的重要生物酶，NO可以导致单核细胞性MDSCs的免疫耐受，其具体机制是：抑制T细胞的JAK3/STAT5通路；抑制MHCII类分子的表达；诱导T细胞的凋亡。而且NO能与ROS协同作用产生过氧亚硝基，导致TCR–CD8分子的酪氨酸残基被硝化而构象改变，影响其与MHCI类分子的结合，进一步阻碍CD8+ T细胞的激活[22]。pSTAT3能直接与iNOS启动子结合，刺激iNOS的转录[23]，进一步诱导免疫耐受。

2　IL-1β/NF-κB通路与MDSCs

NF-κB是与炎症、肿瘤相关的转录因子，家族成员包括五种p65/RelA、RelB、c-Rel、NF-κB1/p50和NF-κB2/p52。肿瘤微环境中的IL-1β通过与MDSCs细胞的IL-1R结合，激活MDSCs的NF-κB信号通路，调控下游靶分子IL-6、TNF-α等表达增加[24]。而IL-6作为经典的激动剂激活MDSCs细胞中的STAT3通路，诱导MDSCs的聚集及发挥促肿瘤功能。另外激活的STAT3促进乙酰转移酶p-300的转录加强，引发RelA的乙酰化，诱导NF-κB通路被动持续激活[25]，产生大量的炎症因子，其中包括IL-1β、IL-6。这就形成了NF-κB/STAT3的正反馈机制，促进了肿瘤相关炎症的发展。

3　PI3K/AKT/mTOR通路与MDSCs

IL-2、IL-6、IL-7、GM-CSF等作为激活剂顺次激活磷脂酰肌醇3-激酶(phosphoinositide3-kinase，PI3K)、信号蛋白AKT(也称为蛋白激酶B，protein kinaseB)及mTOR分子。mTOR通路的激活与MDSCs有关：有证据表明mTOR通路与单核细胞转变为肿瘤相关巨噬细胞有关[26]；最近有学者发现溶酶体酸性脂肪酶基因缺陷(lal-/-)的小鼠能自发通过过度激活的mTOR通路，直接诱导MDSCs的聚集与功能[27]。

4　PGE2/Cox2通路与MDSCs

前列腺素E2(prostaglandin E2，PGE2)是花生四烯酸环氧合酶代谢产物，其中最重要的是环氧合酶-2(Cyclooxygenase-2，cox2)。PGE2与MDSCs细胞膜受体EP4结合，能促进精氨酸酶-1的表达，诱导MDSCs的免疫抑制功能，Cox-2抑制剂也能部分纠正MDSCs的免疫抑制能力[28-29]。Cox-2抑制剂还能阻碍MDSCs细胞 CxCr4的表达，导致其对CxCl12的反应性减弱，限制了MDSCs细胞在肿瘤微环境的聚集[30]。

5　RAS信号通路与MDSCs

Ras基因突变现象在各种肿瘤都很常见，不仅肿瘤细胞Ras信号通路能直接刺激肿瘤的进展，而且MDSCs细胞的Ras信号通路能影响抗肿瘤免疫。在持续高表达Kras蛋白的小鼠胰腺癌动物模型中Ras信号通路能刺激细胞因子MIP-2 和MCP-1的表达，促进MDSCs细胞向肿瘤基质聚集并诱导免疫抑制反应[31]。另外在Kras蛋白高表达的肺癌中发现肿瘤基质中抗肿瘤免疫反应明显减弱并且出现较多的MDSCs细胞[32]。

6　结语

很多炎症病变都是癌前病变，能导致癌症的发生。MDSCs是联系炎症和肿瘤的关键节点。MDSCs细胞的信号通路错综复杂，共同组成一个精细的调控网络控制肿瘤微环境中MDSCs的生物学功能。IL-1β/NF-κB通路诱导MDSCs的免疫抑制功能最终依赖IL-6/stat3轴；NF-κB通路的持续激活也需要pSTAT3的持续表达；各种生长因子和细胞因子是MDSCs细胞STAT3持续激活的结果，而且它们又是IL-1β/NF-κB、PI3K/AKT/mTOR、Ras、PGE2 /Cox2信号通路的质膜外信号。这些都确定了STAT3在MDSCs的细胞信号调控网络中的核心地位。骨髓来源的本该发挥"抗癌"作用的免疫细胞因为STAT3的持续激活而发挥了促癌的作用。确定STAT3为研究MDSCs的靶分子有助于认清肿瘤发生、发展的机制。靶向干预STAT3的治疗不仅能直接抑制肿瘤细胞的生长，而且能抑制MDSCs的促肿瘤功能。依此理论为依据建立体外的促癌MDSCs模型，为进一步研究MDSCs奠定基础。

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