树突状细胞在缺氧微环境中的研究进展

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摘要 胚胎发育, 高原生活, 体育锻炼以及严重创伤、心血管疾病和肿瘤等都可能引起缺氧微环境, 从而导致机体生理和病理特征的改变。缺氧微环境可通过免疫细胞直接影响机体免疫功能。树突状细胞(dendritic cell, DC)是体内最强的抗原递呈细胞(antigen presenting cell, APC), 可有效连接天然免疫和适应性免疫, 但其在不同微环境中的作用并不相同。因此, 该文就DC在缺氧微环境中调控细胞分化、凋亡、迁移, 抗原递呈和相关基因表达等生物学功能作一综述。

关键词 树突状细胞; 缺氧; 微环境

Progress of Dendritic Cell under Hypoxic Microenvironment

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Abstract Hypoxic microenvironment is resulted from many factors, such as embryogenesis, life on the plateau, physical exercise, severe trauma, cardiovascular disease and tumor, and leads to the characteristic changes of physiology and pathology. Moreover, hypoxic microenvironment may influence immunity function via immunocytes directly. DC (dendritic cell) is not only the strongest APC (antigen presenting cell) *in vivo*, but also a “bridge” between innate immunity and adaptive immunity. However, the roles of DC are not coincidental in different microenvironments. Thus, the biological functions of DC in differentiation, apoptosis, migration, antigen presenting and related gene expression under hypoxic microenvironment are reviewed in this paper.

Keywords dendritic cell; hypoxia; microenvironment

近年来, 缺氧微环境下的细胞功能变化及其生物医学意义日益被关注[1]。除胚胎发育、高原生活、体育锻炼状态外, 缺氧微环境也可由许多伤病引起, 如严重创伤、心血管疾病、脑中风、肿瘤及呼吸系统疾病[2]。各种原因引发的组织缺氧会导致细胞微环境改变, 进而使相应细胞的生物学功能发生变化, 各类免疫细胞也不例外。树突状细胞(dendritic cell, DC)在天然免疫和适应性免疫中扮演了重要角色, 但它在缺氧微环境中的作用研究却非常有限。本文对DC在缺氧微环境中调控细胞分化、凋亡、迁移, 抗原递呈和相关基因表达等生物学功能进行综述, 为揭示缺氧微环境下DC介导免疫学功能的作用机理奠定基础。

1 缺氧微环境与疾病

缺氧是指因组织的氧气供应不足或用氧障碍,

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而导致组织的代谢、功能和形态结构发生异常变化的病理过程。环境中的低氧分压可能成为组织缺氧的原因, 但导致组织缺氧的原因还包括一些伤、病。组织缺氧在临床各种疾病中极为常见, 脑、心脏等生命重要器官缺氧也是导致机体死亡的重要原因[3-4]。缺氧微环境是导致疾病发生发展的重要因素, 可引发组织损伤和包括风湿性关节炎、动脉粥样硬化、炎症性皮肤病和原发性实体瘤在内的多种疾病[1,5-6]。研究表明, 缺氧微环境可诱导新生血管形成, 促进肿瘤生长和癌细胞转移[7-8]。

2 缺氧微环境与免疫细胞

缺氧的本质是细胞对缺氧微环境的一种适应性改变, 而免疫细胞对缺氧微环境的适应是其发挥免疫功能清除入侵病原体的重要保证[1]。天然免疫细胞通常最先到达病灶, 从而直接受到缺氧微环境的刺激[5]。中性粒细胞能够从无氧糖酵解中获得大部分能量, 以适应缺氧微环境。巨噬细胞稍晚于中性粒细胞到达病灶, 也能以多种方式适应缺氧微环境, 维持代谢活动[9-11]。研究表明, 缺氧微环境能够降低巨噬细胞的吞噬活性, 严重时可致其死亡, 并导致中性粒细胞增多[12-13]。同时, 缺氧微环境下免疫细胞功能的改变也能保护健康组织, 避免过度免疫反应造成的机体生理功能紊乱或组织细胞损伤。例如, 缺氧微环境下的B细胞仍能产生免疫球蛋白, 但辅助型T细胞(helper T cell, Th)的功能却被抑制[14-15]。研究还表明, 缺氧微环境能够抑制小鼠中性粒细胞的促炎反应, 从而使肺组织免受过度损伤[5]。可见, 缺氧微环境能够通过各类免疫细胞调节机体的天然免疫和适应性免疫。

3 缺氧微环境中DC的生物学功能

3.1 DC与氧环境

DC是体内最强的抗原提呈细胞, 通常被称为免疫系统的“哨兵”, 可根据环境情况及时调整免疫反应, 是天然免疫和适应性免疫之间的“桥梁”[16-17]。DC功能是在复杂发育过程中获得的, 该过程受到局部氧环境中各种信号途径的严格调控, 从而决定DC发生发展的结局[18]。研究显示, 缺氧微环境影响DC的分化和活化, 表现为早熟的DC表型复氧后又可以被逆转[19-21]。可见, 合适的氧环境对DC生物学功能的形成至关重要。

3.2 缺氧微环境促进DC的成熟和凋亡

缺氧微环境下, DC的成熟受白细胞介素-10(interleukin-10, IL-10)和血管内皮生长因子(vascular endothelial growth factor, VEGF)的抑制, 导致其天然免疫功能增强[22-23]。研究表明, 组织缺氧造成的微环境可使DC的促炎功能减弱, 迁移功能增强, 并促进非成熟DC(immature DC, iDC)分化为成熟DC(mature DC, mDC)[21]。缺氧微环境也可诱导iDC中天冬氨酸特异性半胱氨酸蛋白酶-3(cysteinyl aspartate specific proteinase-3, caspase-3)活化, 进而使多聚ADP核糖化酶(poly ADP-ribose polymerase, PARP)发生裂解, 后者可使细胞发生凋亡[23]。另有研究表明, 缺氧诱导因子-1α(hypoxia inducible factor-1α, HIF-1α)也可抑制细胞存活, 在损害iDC功能方面发挥重要作用[24-25]。

3.3 缺氧微环境影响DC的迁移和分泌

DC迁移是其发挥免疫功能的必需环节, 对微环境变化高度敏感, 同时与DC的成熟状态有关[20,26-27]。在迁移过程中, DC将经历不同组织供氧状态的快速变化。研究表明, 缺氧微环境可通过下调基质金属蛋白酶-9(matrix metalloproteinase-9, MMP-9)和上调基质金属蛋白酶组织抑制剂1(tissue inhibitor 1 of matrix metalloproteinase, TIMP1)的表达, 进而抑制体外培养的人单核细胞来源DC通过细胞外基质的迁移, 该过程需要腺苷受体A2b参与激活的环磷酸腺苷(cyclic adenosine monophosphate, cAMP)/蛋白激酶A(protein kinase A, PKA)信号通路的介导[26]。另外, 缺氧微环境可增强DC中p38和p42/44丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)的磷酸化水平[27], 但这种作用在mDC中不明显[28]。也有研究显示, 组织短期缺氧可通过磷脂酰肌醇-3-激酶/蛋白激酶B(phosphoinositide 3-kinase protein kinase B, PI3K/AKT)通路增强DC的迁移能力[29]。可见, 缺氧微环境可以影响DC的迁移能力, 从而干预其适应性免疫功能的发挥。

DC的成熟以及对初始T细胞(Naïve T cell, Th0)分化结局的影响受多种细胞因子和趋化因子的调控, 而这些因子与DC的分泌功能关系密切[30-32]。一方面, 缺氧微环境既可影响DC分泌相关细胞因子, 反馈调控其成熟过程[23], 也能通过分泌不同的细胞因子谱干预Th0的分化结局, 即DC驱动Th0向Th2分化, 抑制分泌干扰素-γ(interferon-γ, IFN-γ), 促进分泌

IL-10和IL-4[24,33]。另一方面, DC细胞分泌对其迁移功能的影响更为显著, 这主要是因为DC分泌的多种趋化因子是调控DC迁移的关键因素[20,31]。体外实验表明, 缺氧微环境可导致不同的DC趋化因子表达谱: 趋化因子受体CCR2、CCR3、CCR5、CX3CR1、C5R1、FPR3、CCL3、CCL5和CCL20的表达在缺氧时上调, 而趋化因子CCL14、CCL24和CCL26的表达在缺氧时受到抑制, 进而影响病灶对白细胞募集和激活能力的调节[7,20,30-31,34]。另外, 缺氧微环境可使mDC中CCR7的表达下调, 可能是导致mDC向淋巴结归巢的重要原因[28,35]。

3.4 缺氧微环境抑制DC的抗原递呈能力

DC捕获抗原后, 离开外周组织, 进入淋巴系统并迁移到淋巴结, 定位于富含T细胞的区域, 然后将抗原呈递给T细胞以启动适应性免疫应答[16-17]。持续的缺氧微环境能够抑制DC抗原提呈相关分子的表达, 降低体外培养DC的抗原摄取能力, 即经缺氧微环境刺激的DC表达较低水平的主要组织相容性复合体II(major histocompatibility complex class II, MHCII)类分子、共刺激分子(CD80、CD86)和促炎细胞因子(IL-1β、IL-6和TNF-α), 从而降低DC启动T细胞免疫反应的能力[23,36-38], 其机制可能与抗原摄取相关分子白细胞分化抗原209(cluster of differentiation 209, CD209)的表达下降有关[36]。另外, 感染或创伤早期导致的缺氧微环境可通过转化生长因子-β(transforming growth factor-β, TGF-β)非依赖性方式促进IL-6分泌, 使Th0分化为Th17[39-40]。

4 缺氧微环境中的DC相关基因

4.1 *HIF-1α*与DC

缺氧微环境主要通过*HIF-1α*调节细胞功能[41]。*HIF-1α*是抗原呈递和成熟的必需因子, 可促进DC依赖性T细胞的增殖[42-43]。例如, 特异性缺失*HIF-1α*的DC可促进硫酸葡聚糖钠(dextran sodium sulfate, DSS)诱导的结肠炎小鼠促炎细胞因子的产生, 加重肠道炎症[42,44]。研究显示, *HIF-1α*可促进缺氧微环境下小鼠骨髓来源的DC迁移[37,45], 并与DC的存活有关[25]。有观点认为, 通过*HIF-1α*对缺氧微环境下DC生物学功能进行调控具有潜在的临床应用价值[27,46]。

4.2 髓样细胞表达的驱动受体-1(triggering receptor expressed on myeloid cells-1, *TREM-1*)与DC

*TREM-1*不但被认为是炎症的“放大器”, 还被鉴定为DC中的缺氧诱导基因[21,47]。研究表明, 在中性粒细胞、单核细胞和巨噬细胞中, *TREM-1*被各种因子(如Toll样受体配体和促炎细胞因子)刺激后显著上调[47-48]。然而, 在单核细胞分化为mDC的过程中, *TREM-1*的表达则完全下调[21]。研究还显示, 缺氧微环境可促进DC中*TREM-1*的表达, 进而增强mDC调节炎症部位白细胞募集的能力, 诱导Th0分化为Th1[47]。同时, 体内mDC中*TREM-1*的表达可能随着局部氧合程度的变化而改变[21,48]。

5 结论与展望

DC的发育和迁移可能经历氧环境的变化, 对各种微环境的适应是DC发挥免疫功能的前提[36-37]。缺氧微环境是调控DC成熟、死亡、迁移、分泌和抗原呈递的重要因素, 涉及多种趋化因子和细胞因子的改变, 影响Th0向各类T细胞亚群分化的结局, 进而调控机体T细胞免疫应答。因此, 缺氧微环境可以调控DC功能, 使其具有与正常DC不同的生物学特征, 而*HIF-1α*和*TREM-1*与该环境下DC功能的发挥密切相关(图1)。

缺氧微环境是调控DC生物学功能的关键因素, 深入研究缺氧微环境对DC反应的调控机理对于干预机体微环境的局部免疫应答具有潜在的应用价值。目前, DC的氧感受机制和缺氧信号已成为炎症性疾病的潜在治疗靶点, 并逐渐推广到急性肺损伤、心肌缺血以及肿瘤的DC治疗领域[49-50], 而且靶向缺氧依赖性信号通路的干预策略有助于减轻大手术患者因缺血导致的器官衰竭, 或减轻实体器官移植后缺氧微环境驱动的炎症反应[1,51]。

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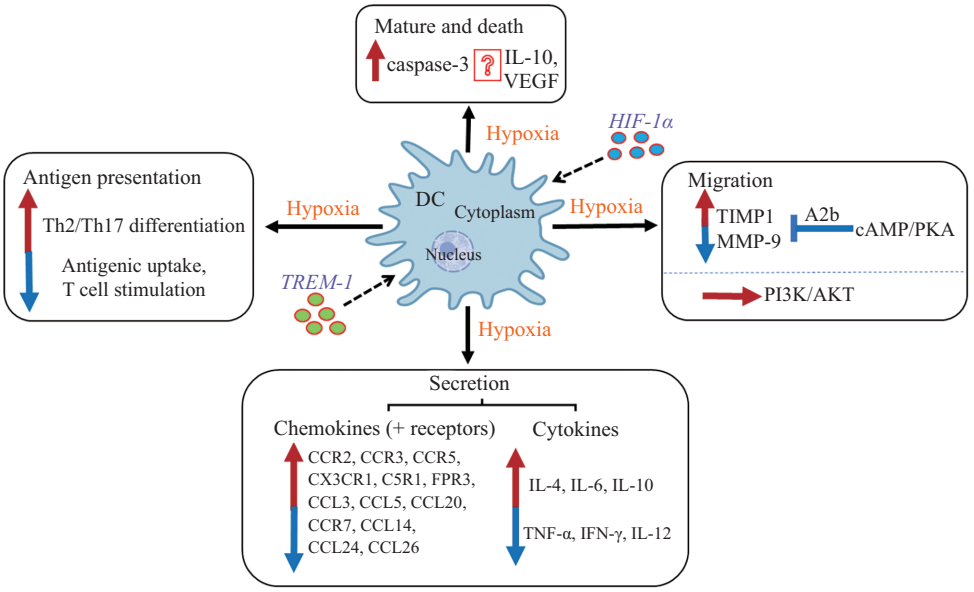

红色箭头代表上调, 蓝色箭头代表下调。

The red arrow represents up-regulation and the blue arrow represents down-regulation.

图1 缺氧微环境调控DC

Fig.1 The regulation of hypoxic microenvironment on DC

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