

树突细胞及其功能和疫苗的研究现状

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[摘要] 树突细胞(DC)可引发初次免疫应答,在机体免疫抗瘤中起着重要的作用。头颈鳞状细胞癌(HNSCC)局部不同表型的 DC 浸润与肿瘤预后密切相关。本文就 DC 的亚型,DC 浸润的程度及其与肿瘤预后的相关性,HNSCC 患者肿瘤组织、淋巴结和外周血中 DC 的数目、成熟度和功能异常,DC 功能受损的原因,DC 疫苗等研究现状作一综述。

[关键词] 树突细胞; 头颈鳞状细胞癌; 疫苗

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[Abstract] Dendritic cell(DC) play a key role in systemic immune response against tumor for their ability to initiate primary immune response. The infiltration of DC with different phenotype in head and neck squamous cell carcinoma(HNSCC) patients correlates to tumor prognosis closely. This review will discuss the correlation of tumor prognosis with different subtypes of DC and their infiltration in tumor tissue. Followed by the decreased amount, abnormal maturity and dysfunction of DC in HNSCC patients, including DC in tumor tissue, lymph node and peripheral blood. And then discuss reasons for DC dysfunction and the present research on dendritic cell vaccine.

[Key words] dendritic cell; head and neck squamous cell carcinoma; vaccine

近 30 年来,外科手术为主的综合治疗在头颈鳞状细胞癌(head and neck squamous cell carcinoma, HNSCC)治疗中取得了一定疗效,但患者的预后仍未得到根本改善,特别是手术常造成其头颈功能障碍和颌面部畸形,严重影响患者的生活质量。因此,人们希冀通过生物治疗根治肿瘤的愿望备加强烈。树突细胞(dendritic cell, DC)是最有效的骨髓来源抗原呈递细胞,可诱导机体的初次免疫应答,在激活 T 细胞、B 细胞、自然杀伤细胞(natural killer cell, NK cell)和自然杀伤性 T 细胞的免疫反应中起着关键作用,甚至在某些情况下可直接杀瘤。理论上,机体产生的有效的抗肿瘤免疫效应依赖于 DC 功能的正常发挥^[1]。然而在肿瘤患者的体内,DC 的数量和质量异常,严重阻碍了机体的抗瘤反应。

1 树突细胞的亚型

DC 在吞噬抗原、遇到不同刺激因素或迁移

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时,其表型和功能都会改变,故其表型非常复杂,是一个具有高度活性的异质群体。DC 有诸多亚群,其形态和功能各不相同,与其来源、成熟状态和组织定位等有关^[2]。DC 按来源可分为髓系 DC 和浆系 DC;按成熟状态可分为未成熟树突细胞(imatured dendritic cell, imDC)和成熟树突细胞(matured dendritic cell, mDC);按组织定位则分为淋巴组织固有 DC、外周组织 DC 和循环系统 DC,其中,外周组织 DC 主要分布于皮肤和黏膜组织。皮内 DC 包括朗格汉斯细胞(Langerhans cell, LC)和真皮内 DC。LC 是一种 imDC,分布于表皮内,表达 CD1a、朗格汉蛋白(Langerin,即 CD207)和上皮钙黏着蛋白,因此常用 CD1a 和朗格汉蛋白来标志,其主要功能是摄取抗原。真皮内 DC 又称间质 DC,为相对成熟的 DC,与抗原特异性的 T 细胞增殖和白细胞介素(interleukin, IL)-2 的分泌有关,表达树突细胞特异性细胞间黏附分子-3 结合非整联蛋白(dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin, DC-SIGN/CD209)、CD11b 和 CD14,常用 DC-SIGN 标志。

2 树突细胞浸润与肿瘤的预后

肿瘤浸润性DC(tumor infiltrating dendritic cell, TIDC)的多寡与机体免疫抗瘤的功能状态存在着某种联系^[3-8]。DC表型复杂,尚无简单的鉴别方法。TIDC的常用标志物有S-100、CD1a、CD209、CD207、P55、人白细胞DR抗原(human leucocyte antigen DR, HLA-DR)、CD83和树突细胞溶酶体相关膜蛋白(DC-lysosomal-associated membrane protein, DC-LAMP/LAMP3/CD208)等,但每个标志物仅能识别部分亚型而非所有DC,其中后三者用于识别mDC。

S-100是一种酸性蛋白,主要在LC、指突状DC中表达。Kerrebijn等^[9-10]对HNSCC和鼻咽癌组织行免疫组化研究发现,S-100⁺DC可浸润于癌巢和肿瘤间质,且以间质为主。Reichert等^[11]发现,S-100⁺DC可作为口腔鳞状细胞癌的独立预后指标,低S-100⁺DC浸润预示着低生存率,危险系数达7.95,较淋巴结转移(危险系数3.36)和肿瘤T分期(危险系数2.92)等有更好的预后提示作用。但Goldman等^[3]则发现无论是在癌巢还是癌旁间质中,S-100⁺DC都与预后无关。

CD1a可作为imDC,CD1a⁺DC浸润与HN-SCC预后的关系也在一些研究中得到证实。Goldman等^[3]认为在癌旁间质中,CD1a⁺DC高浸润预示着高生存率和较低的肿瘤复发率,而癌巢内CD1a⁺DC与肿瘤预后无关。此结果提示肿瘤的预后不仅与DC浸润程度有关,还与其浸润部位密切相关。即使表型相似的DC(如均表达CD1a),在不同部位也可发挥不同的作用,从而导致肿瘤预后的差异。CD83和DC-LAMP(即LAMP₃或CD208)是mDC的标志物,mDC几乎只存在于癌旁间质中^[12]。成熟状态的TIDC在肿瘤进展过程中对机体有保护性作用。在多数肿瘤中,CD83⁺DC越多,肿瘤的预后越好^[4-5];但在HNSCC中,尚无研究显示此相关性。王志勇等^[13]对34例口腔鳞状细胞癌组织进行了详细的研究,所有病例均未见明显的CD83⁺DC浸润。同样,尽管在黑色素瘤中,DC-LAMP⁺DC浸润与肿瘤预后有着相关性^[6-7],但在口腔鳞状细胞癌,其浸润与临床分期和预后无关^[12],与乳腺癌类似^[8]。

3 荷瘤宿主中树突细胞的异常改变

肿瘤对其宿主有强大的免疫抑制作用,致其

DC在功能和表型上受到损害。1)TIDC的数目减少:王志勇等^[13]在以正常口腔黏膜作对照,分析口腔鳞状细胞癌DC浸润程度时发现,CD1a⁺DC在口腔鳞状细胞癌的浸润明显少于正常黏膜组($P<0.05$)。2)淋巴结内DC的数目减少、成熟受阻:Laguens等^[14]在47例上皮源性肿瘤和11例无瘤患者淋巴结对照研究中发现,肿瘤患者淋巴结内的S-100⁺DC和CD1a⁺DC显著少于对照组;Sakakura等^[15]发现,对无淋巴结转移患者,淋巴结转移者的CD83⁺DC明显减少($P<0.01$);即临床分期越晚,患者DC成熟受阻情况越严重。3)肿瘤患者外周血中DC数目减少、成熟受阻和功能受抑:肿瘤患者(包括HNSCC)外周血中乏成熟细胞标志的淋巴细胞或髓系细胞增多,从而使DC数目相对减少;这些细胞在反式维甲酸的作用下还可分化为成熟DC,是一些分化受阻的前体细胞;对自体DC的功能还有抑制作用,去除该细胞可纠正DC的功能障碍^[16-17]。此外,HNSCC患者外周血中DC的HLA-DR表达水平低于健康对照组,DC的成熟度相对健康组下降,因为HLA-DR在DC成熟过程中的表达会上调^[18]。Tas等^[19-20]先后在HNSCC中发现,DC的趋化和聚集功能受损,会影响细胞介导的免疫反应发生。

O'Donnell等^[12]通过对63例口腔鳞状细胞癌患者肿瘤组织和淋巴结免疫组化分析发现,肿瘤患者的DC功能在以下方面受到了损害。1)imDC捕获抗原的能力受损:因为大部分的CD209⁺imDC亚群不能浸润肿瘤实质,必然导致其抗原捕获能力受损。2)DC的成熟和迁移受损:CD207⁺imDC虽然能浸润肿瘤实质,但肿瘤中DC-LAMP⁺mDC的数目极少,即CD207⁺imDC并没有在肿瘤实质中成熟;即使在与肿瘤最近的淋巴结中,也未见到CD207⁺imDC的积累,即CD207⁺imDC也没有迁移到淋巴结中去。3)激发机体免疫抗瘤反应的能力受损:肿瘤组织中虽有少量的DC-LAMP⁺mDC存在,却无mDC的有效呈递抗原、诱导免疫反应后导致的肿瘤退化,而且DC-LAMP⁺mDC与患者的预后无关;也就是即使存在局限性的免疫反应,也不足使肿瘤消退。

4 树突细胞功能受损的原因

DC分化和功能受损的原因尚不清楚,诸多细胞因子,例如血管内皮生长因子(vascular endothelial growth factor, VEGF)、转化生长因子(tra-

nsforming growth factor, TGF)- β 、粒细胞-巨噬细胞集落刺激因子、前列腺素和神经节苷酯以及 IL-6、10、23 等都可能参与其中^[21]。VEGF 是一种大部分肿瘤都能产生的细胞因子,具有促进肿瘤血管生成的作用。大多数的研究皆证实,VEGF 与肿瘤的预后有关^[22-23]。Gabrilovich 等^[24-25]发现: VEGF 抑制 DC 的成熟和功能;在活体内持续注射 VEGF,可导致 DC 减少。Almand 等^[16]将肿瘤患者血浆中的 VEGF 水平分为异常升高和正常 2 组,结果试验组外周血中不成熟细胞明显增多。IL-10 可阻止单核细胞向 DC 分化^[26],抑制表皮中 LC 的功能^[27],抑制单核细胞或 CD34⁺祖细胞来源的 DC 的功能^[28-29]。值得注意的是,这种 DC 受抑的现象并非某个细胞因子单独作用的结果,而是诸多细胞因子共同作用造成的^[30]。

此外,肿瘤细胞可通过与 DC 的直接接触诱导 DC 程序性死亡^[31],或将 DC 转化为分泌 TGF- β 的致耐受性细胞,进而诱导调节性 T 细胞(regulatory T cell, Treg)生成^[32]。同时在肿瘤微环境中,Treg 的存在也可抑制 DC 的功能。

5 树突细胞疫苗

由于 DC 在机体免疫反应中起着重要的作用,而肿瘤患者体内 DC 的功能又往往受到了抑制,因此人们试图通过体外分离培养获得足量的 DC,经抗原冲击致敏后将其制备成肿瘤特异性的 DC 疫苗回输入患者体内,以克服体内环境对 DC 的抑制作用,让其激活细胞毒性 T 淋巴细胞(cytotoxic T lymphocyte, CTL),克服免疫逃逸,从而清除肿瘤细胞。

DC 疫苗在 HNSCC 的临床研究起步较晚,但其体外和动物研究却取得了一些进展,特别是在寻找肿瘤相关抗原方面。Dasgupta 等^[33]发现,双调蛋白、钙黏蛋白-3、激肽释放酶-10、神经调节肽和分泌性白细胞蛋白酶抑制因子在 HNSCC 中高表达,其表达蛋白有望作为 HNSCC 免疫治疗的靶点。头颈肿瘤多伴有 p53 基因的突变,用野生型 p53 多肽冲击致敏,可产生抗原特异性 DC。Nikifina 等^[34]用此法致敏的 DC 激活 CTL,在体外试验中产生了针对头颈鳞状细胞癌 P53 蛋白的免疫反应。如今,这种 DC 已经用于临床试验^[35-36]。

Wang 等^[37]用冻融裂解后的舌鳞状细胞癌细胞株 Tea8113 致敏 DC,再用致敏的 DC 在体外激活患者自身 T 细胞,结果这种 T 细胞不仅在体外能

杀伤 Tea8113 细胞,还能延缓肿瘤种植裸鼠的肿瘤倍增时间,抑制肿瘤的生长。用此法致敏 DC,无需特异性抗原,也不用考虑主要组织相容性复合体分子的限制性问题,使 DC 疫苗在 HNSCC 中的应用成为可能。此外,Weise 等^[38]将喉癌细胞系(UTSCC-19A)与 mDC 电融合杂交,获得了一种 DC 疫苗;Kacani 等^[39]则采用了一种由 DC 和 HN-SCC 肿瘤坏死细胞组成的疫苗,肿瘤坏死细胞不仅能诱导 DC 生成和成熟,还能使其分泌 IL-12。IL-12 是一重要的辅助性 T 细胞-1 型细胞因子,能直接激活 NK 细胞,诱导 T 细胞分化为 CTL。

自 1995 年 Hsu 等尝试把 DC 疫苗用于临床治疗 B 细胞淋巴瘤后,国内外 DC 疫苗的临床试验亦逐渐开展起来,几乎涵盖了所有的恶性肿瘤,但主要集中于黑色素瘤和前列腺癌^[40]。DC 疫苗治疗是一种安全的、能诱导 T 细胞反应的免疫治疗方法,诸多临床试验也取得了一些疗效^[41-44],但总体疗效还不尽如人意。诸多 DC 疫苗在黑色素瘤的临床应用中,存在客观应答的病例数不足 5%~10%,而更多的是一些混合反应或仅使病情稳定^[45]。Schadendorf 等^[46]在一项 DC 疫苗治疗一期黑色素瘤的临床试验中发现,DC 疫苗治疗相对于标准达卡巴嗪化疗并无优势。一些学者认为,这种疗效的不确定性与 DC 疫苗应用技术尚不成熟有关,如病例的选择(DC 疫苗敏感患者的确定),DC 来源(患者自身或健康供体),DC 的诱导、培养和促使 DC 成熟的方法,疫苗的应用途径、剂量、疗程,免疫佐剂的使用以及与化疗、放疗、热疗等联合应用的时机等。总之,提高 DC 疫苗的临床疗效还有待于进一步的研究。

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