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肿瘤坏死因子α在肝细胞癌中的研究进展

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·综　述·

肿瘤坏死因子α在肝细胞癌中的研究进展

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［摘要］ 肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）是一种多功能炎性细胞因子，在肿瘤发生和发展中具有双向调节作用，对肝细胞癌（hepatocellular carcinoma，HCC）的发生、发展调节途径多样，机制尚不完全清楚。血管内皮生长因子（vascular endothelial growth factor，VEGF）分子信号通路和核因子κB（nuclear factor kappa B，NF-κB）信号通路在HCC发生和发展中扮演着重要的角色。外周血TNF-α浓度和肿瘤组织中TNF-α浓度对HCC患者接受一些治疗后的预后表现出了较好的预测价值，但对接受精确放疗的HCC患者预后预测价值，需要被进一步明确。

［关键词］ 肿瘤坏死因子α；肝细胞癌；放射治疗；预后
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Research progress of tumor necrosis factor-α in hepatocellular carcinoma

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［**Abstract**］ Tumor necrosis factor-α (TNF-α) is a multifunctional inflammatory cytokine that has a bidirectional regulatory role in the occurrence and development of tumors. TNF-α participates in various regulatory pathways for the occurrence and development of hepatocellular carcinoma (HCC), but the mechanisms are not fully clear. Vascular endothelial growth factor (VEGF) and nuclear factor kappa B (NF-κB) signal pathways are considered as important roles in the occurrence and development of HCC. Peripheral blood TNF-α concentration and tumor tissue TNF-α concentration have shown good predictive values for the prognosis of HCC patients after receiving some treatments. The prognostic predictive value of TNF-α for HCC patients receiving precise radiotherapy needs to be further clarified.

［**Key Words**］ tumor necrosis factor-α; hepatocellular carcinoma; radiotherapy; prognosis

1975年，Carswell等发现了血清中的肿瘤坏死因子（tumor necrosis factor，TNF），这种细胞因子可以导致肿瘤组织发生出血、坏死[1]。TNF家族2个核心成员分别是TNF-α和TNF-β[2-3]。TNF-α主要由活化的巨噬细胞、T淋巴细胞、B淋巴细胞等分泌产生[4]。TNF-α是一种炎性细胞因子，生物学活性极其广泛，除了具有促炎、抗病毒和免疫调节的功能之外，还能杀灭肿瘤细胞[3,5]。有趣的是，随着研究的深入，TNF-α在肿瘤的发生和发展中表现出了抑瘤和促瘤的双重功能[6-7]。

肝细胞癌（hepatocellular carcinoma，HCC）是目前世界上最常见的恶性肿瘤之一，其发病率和死亡率居高不下，严重威胁着人类的健康[8-9]。在中国，乙型肝炎病毒和丙型肝炎病毒慢性感染是导致HCC发生的主要危险因素，尤其是乙型肝炎病毒的持续感染，导致肝硬化的发生，继而发生HCC[10-12]。根据病期不同，HCC目前的治疗手段主要有手术切除（含肝移植）、消融治疗、经导管动脉化疗栓塞、放射治疗以及靶向和免疫等全身系统治疗[13-15]。

1　TNF-α在HCC发生过程中的机制

HCC是一种慢性炎症相关性疾病，主要是由肝脏长期病毒感染损伤和纤维化导致[16-17]。

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Hammam等[18]揭示在HCC的发生过程中，血清TNF-α的表达明显增加；伴有肝硬化的HCC患者与不伴有肝硬化的HCC患者相比，肝脏组织的TNF-α表达明显增加；肝脏炎症程度较高或纤维化分期较高的患者中，血清TNF-α表达也明显增加。另外，该研究还进一步揭示了TNF-α诱导血管生成在肝炎到肝硬化再发展成为HCC过程中可能扮演着重要角色；在该进程中，血管内皮生长因子（vascular endothelial growth factor，VEGF）分子信号通路可能是一条重要的信号通路[18-19]。

肝前体细胞（hepatic progenitor cells，HPCs）具有多向分化功能，在长期的慢性炎症微环境中，HPCs的扩增和分化可能会发生异常，进而导致HCC的发生[20-21]。有学者[22]利用单细胞转录组测序揭示TNF-α在诱导HPCs向肿瘤细胞转化过程中TNFR2至关重要，TNFR2-hnRNPK-YAP信号轴发挥的作用很关键。也有研究[23]报道，脂多糖（lipopolysaccharide，LPS）可以诱导HPCs向肌成纤维细胞分化，形成肝脏促瘤的炎症微环境、肝脏纤维化，HPCs分化形成的肌成纤维细胞分泌白介素-6和TNF-α，进而导致Ras信号通路的激活和p53信号通路的失活，最终促进HPCs向HCC细胞分化。

TNF-α基因启动子区域存在多态性位点，TNF-α基因变异与HCC之间的关系尚不完全清楚。有研究[24]报道，特定的TNF-α多态性可能与HCC易感性有关。TNF-α-308G/A多态性与HCC易感性增加显著相关，在亚洲人群中，有研究报道TNF-α-238G/A多态性与HCC风险没有显著相关性，但是TNF-α-238 G/A多态性与HCC易感性之间的关系仍然存在争议[25-29]。亚洲人群中，TNF-α-863C/A的多态性也被认为与HCC发生有关，而TNF-α-857C/T和TNF-α-1031T/C的多态性与HCC的发生风险则无关[29]。垂体肿瘤转化基因1（pituitary tumor transforming gene 1，PTTG1）是HCC中潜在的炎症相关癌基因，TNF-α诱导PTTG1表达，PTTG1上调c-myc，参与HCC的发生[30]。

2 TNF-α在HCC进展过程中的机制

TNF-α诱导的信号传导通过激活核因子κB（nuclear factor kappa B，NF-κB）、c-Jun N-末端激酶（c-Jun N-terminal kinase，JNK）途径，促进HCC的进展[31-33]。另外，STAT3炎性转录因子也可以被TNF-α激活，通过下游通路促进HCC的疾病进展[34-35]。TNF-α可以促进HCC的转移，A20蛋白是NF-κB信号通路的负调控因子，A20蛋白对TNF-α诱导的HCC细胞运动具有负调控作用，对于微血管侵犯（microvascular invasions，MVI）细胞的HCC患者，A20的表达下调[36]。肿瘤微环境中的TNF-α还可以通过NF-κB途径诱导HCC细胞中肌腱蛋白C的表达，从而促进HCC细胞的迁移，进而促进HCC的转移[37]。TNF-α通过激活Erk1/2-NF-κB途径，明显增强HepG2细胞中MMP-13/MMP-3的表达并促进细胞迁移；TIPE2能够通过抑制Erk1/2和NF-κB的激活来抑制TNF-α诱导的HCC转移[38]。蛋白激酶D（protein kinase D，PKD）对TNF-α诱导的HCC上皮-间质转移和HCC转移中也被发现具有正向调节作用[39]。

3 TNF-α对HCC治疗预后的影响

手术切除是HCC治疗的主要方式[40-41]。Nakazaki等[42]曾发现HCC复发患者的血清TNF-α浓度要明显高于无复发的患者（$P<0.01$）。Cai等[43]回顾性分析了157例经病理证实的HCC手术切除患者临床资料后发现，HCC患者术前血清TNF-α浓度越高，患者的无复发生存率越低，HCC患者术前血清TNF-α浓度是术后无复发生存的独立预后因素；该研究中，血清TNF-α的最佳截断值是14.9 pg/mL。Li等[44]采用免疫组织化学染色方法检测HCC（BCLC-0-B）患者肿瘤组织中TNF-α和NF-κB的表达，通过分析发现TNF-α和NF-κB均高表达的HCC患者生存时间明显延长（$P<0.05$）；HCC肿瘤组织中，TNF-α和NF-κB的高表达反而是预测HCC患者术后生存率和复发的独立预后因素（$P<0.05$）。

除手术切除外，HCC的另一项根治性治疗手段是射频消融治疗（radiofrequency ablation，RFA）[45-47]。Guo等[48]通过前瞻性研究共纳入22例行RFA治疗的HCC患者，在RFA前（基线水平）、RFA后1周、RFA后4周时分别检测了患

者外周血中的TNF-α浓度，结果发现RFA后第4周时TNF-α浓度低（低于20.4 pg/mL）的患者更容易复发，RFA后第4周时外周血TNF-α的浓度可以预测肿瘤的复发。

放射治疗在HCC治疗中同样扮演着重要的角色。对于小肝癌，立体定向放射治疗（stereotactic body radiation therapy，SBRT）同样可以取得与手术切除或RFA相类似的根治性效果，是不宜手术切除或RFA患者的替代治疗手段[49-51]。Cha等[52]对接受常规放射治疗的51例HCC患者放疗前血清炎性因子进行研究，暂未发现放疗前血清TNF-α浓度对患者的预后具有预测价值。

对于中晚期HCC，系统治疗如靶向治疗在HCC的治疗中发挥重要作用[53-54]。Iida-Ueno等[55]对无法手术切除的100例HCC患者血浆进行了分析，其中27例患者有治疗开始后的血浆TNF-α浓度变化随访，发现血浆TNF-α浓度在索拉非尼治疗的前5～10 d的变化可以预测HCC患者对索拉非尼治疗的反应，血浆TNF-α浓度出现上升的患者，肿瘤更容易进展。

4　抗TNF-α治疗在HCC治疗中的作用

研究[56-57]报道，在较低区间内的高浓度TNF-α在HCC生长中具有促瘤作用。Li等[58]报道，TNF-α在HCC组织以及HCC细胞系HepG2和Hep3B中高表达。在体外研究中，抗TNF-α抗体（英夫利昔单抗和依那西普）通过抗体依赖性细胞介导的细胞毒性和补体依赖性细胞毒性的作用，可以降低HCC细胞活力，英夫利昔单抗治疗可以显著增加HepG2和Hep3B细胞的凋亡；在体内实验[58]中，抗TNF-α治疗延迟了小鼠HCC的进展。

综上所述，TNF-α是一种炎性细胞因子，可以通过多条途径影响HCC的发生和发展。TNF-α的表达水平对HCC患者的治疗预后具有较好的预测价值。但是，对接受传统放疗的HCC患者，TNF-α的表达水平与预后关系不密切；精准放疗时代，特别是SBRT技术治疗HCC时，对机体免疫的影响尚不完全清楚，TNF-α对HCC接受精准放疗患者的复发、转移影响机制以及对患者预后的“指示剂”功能尚待进一步探索。抗TNF-α治疗和TNF-α高浓度灌注治疗也值得进一步研究。

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