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◇综述◇

肿瘤微环境对前列腺癌进展至去势抵抗阶段的影响

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摘要 前列腺癌是男性泌尿系统中最常见的恶性肿瘤之一。雄激素剥夺疗法(ADT)是晚期前列腺癌的主要治疗方法,但在治疗过程中几乎所有病人都会发展为去势抵抗性前列腺癌(CRPC)。目前关于CRPC的形成机制研究较多,其中包括肿瘤微环境(TME)相关机制,均为今后治疗CRPC提供了重要帮助。现对近年来TME如何促进前列腺癌进展至CRPC相关研究进行综述,总结相关机制,给未来进一步研究提供参考。

关键词 去势抵抗性前列腺癌; 肿瘤微环境; 肿瘤免疫; 神经周围侵犯

Effect of tumor microenvironment on the progression of prostate cancer to castrated resistance stage

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Abstract Prostate cancer is one of the most common malignant tumors in the male urinary system. Androgen deprivation therapy (ADT) is the mainstay treatment for advanced prostate cancer, but nearly all patients will develop castration-resistant prostate cancer (CRPC) during treatment. At present, there are many studies on the formation of CRPC, including the relevant mechanism of the tumor microenvironment (TME), which all provide important help for the future treatment of CRPC. This article reviews how TME has promoted the progress of prostate cancer to CRPC in recent years, summarizes relevant mechanisms, and provides reference for further research in the future.

Keywords Castration-resistant prostate cancer; Tumor microenvironment; Tumor immunity; Perineural invasion

前列腺癌作为泌尿系统中最常见的恶性肿瘤之一,严重影响中老年男性的健康。统计表明,2023年美国预计增加近30万新发前列腺癌病人,占男性新增癌症病例的29%^[1]。目前雄激素剥夺疗法(androgen deprivation therapy, ADT)是转移性和晚期前列腺癌的主要治疗方法。大多数病人尽管雄激素水平很低,但仍可能在24~36个月内进展为去势抵抗性前列腺癌(castration-resistant prostate cancer, CRPC)而进入治疗困境^[2]。近几年研究普遍认为,肿瘤微环境(tumor microenvironment, TME)在CRPC中起着关键作用^[3]。TME是指肿瘤中非癌细胞和成分,包括它们产生和释放的分子所构成的细胞环境^[4]。TME存在多种免疫细胞和非免疫细胞如:成纤维细胞、内皮细胞、神经元、脂肪细胞、适应性和先天性免疫细胞,以及其非细胞成分,包括可溶性物质,如趋化因子、细胞因子、生长因子和胞外囊泡

等。随着单细胞和空间转录组学的发展,目前对于TME的基质细胞特征、治疗靶点以及其与肿瘤细胞之间的通讯认识愈发清楚,并发现这些成分可通过干扰素基因刺激因子等来调节细胞外基质、激活癌症基因,由此支持肿瘤的上皮间质转化(epithelial-mesenchymal transition, EMT)、侵袭、转移和治疗抵抗等^[5-8]。现对TME相关因素如何促进前列腺癌进展至CRPC的研究进行综述,深入探讨将其作为治疗靶点以阻止CRPC发生的潜力。

1 免疫因素

虽然前列腺癌的免疫细胞浸润度较低,但各种免疫细胞仍然是前列腺癌TME的重要组成部分,其浸润与肿瘤进展密切相关^[9]。前列腺癌TME中各种免疫细胞的研究已有诸多进展,针对T细胞相关免疫检查点(CTLA-4, PD-L1和PD-1等)的免疫治疗在转移性和治疗耐药性前列腺癌中的有效性还需

求证^[10]。

1.1 肿瘤相关巨噬细胞 (tumor-associated macrophages, TAMs) 前列腺癌TME中富含髓系细胞,且多数为TAMs^[11]。已有多项研究表明,TAMs会影响前列腺癌内分泌治疗的临床反应:TAMs<22个/高倍镜下(high-power field, HPF)的病人对ADT的反应明显优于TAMs较多的病人($P<0.001$)^[12]。TAMs具有多种表型,与前列腺癌侵袭性和去势抵抗显著相关的是M2型巨噬细胞^[13-14]。在CRPC中表达上调的SEMA3A募集单核细胞并使其极化为M2亚型,SEMA3A则可以与TAMs的NRP1受体结合,促进下游PI3K和AKT磷酸化,从而促进癌细胞对ADT的耐药性^[15]。CSF-1/CSF-1R信号传导可刺激M1型巨噬细胞极化至M2表型^[16]。当缺乏CAVIN1的基质细胞用于共注射时,M2巨噬细胞在原发性前列腺肿瘤中显著富集^[17]。TAMs衍生的外泌体中miR-95可以通过直接结合其下游靶基因JunB来促进前列腺癌细胞侵袭和EMT,进而起到肿瘤启动子和肿瘤耐药的作用^[18]。同时,M2样TAMs产生代偿性生长因子(如作为TGFβ/SMAD6轴和p2/MAPK兴奋剂的IL-38)以促进神经内分泌分化,进而导致晚期前列腺癌的药物抵抗^[19]。

另一方面,来源于CRPC肠道微生物群的短链脂肪酸(short chain fatty acid, SCFAs)通过诱导癌细胞自噬释放出更高水平的趋化因子CCL20,CCL20招募更多的巨噬细胞浸润,并同时将它们极化为M2型来重新编程TME,从而进一步加强前列腺癌细胞的侵袭性^[20]。巨噬细胞还可通过FN1-ITGA5轴诱导细胞外基质受体基因表达伤口愈合样反应,促进恩扎鲁胺耐药^[21]。巨噬细胞在前列腺癌中可分泌Gas6,可能导致RON-Ack1-NF-κB-AR信号级联反应,在没有雄激素的情况下驱动肿瘤生长^[22]。一项小鼠实验表明TAMs的消耗会导致胆固醇转运和(或)代谢的改变,可能会干扰TME中的雄激素生物合成,从而解释在TAMs耗竭后观察到的雄激素受体(androgen receptor, AR)特征降低^[23]。

1.2 肿瘤相关中性粒细胞 (tumor associated neutrophils, TANs) 研究表明,中性粒细胞与淋巴细胞比值是CRPC病人总生存期的独立预后生物标志物^[24-25]。然而TANs作为TME的一部分,在促进肿瘤耐药方面的研究仍在继续。Hanahan、Weinberg^[26]发现TANs能够通过促进肿瘤相关炎症从而促进肿瘤细胞增殖、侵袭和肿瘤的血管生成。此外有研究发现前列腺癌中CD66ce⁺中性粒细胞明显增多,促进前列腺癌细胞进展^[27]。Lu等^[28]通过生物信息学及生物实验发现CXCL1与中性粒细胞来源的LCN2共

表达模式可以显著预测根治性前列腺切除术后生化复发(biochemical recurrence, BCR),机制与激活Src信号转导、触发EMT有关。

1.3 肿瘤相关髓系抑制性细胞 (myeloid-derived suppressor cells, MDSCs) 来源于骨髓的高度异质性免疫细胞群MDSCs在前列腺癌进展、治疗耐药中起着关键作用^[29]。MDSCs分泌的IL-23可激活前列腺癌细胞的雄激素受体途径,促进雄激素缺乏条件下的细胞存活和增殖^[30]进而促进前列腺癌的耐药。在小鼠前列腺癌模型中发现MDSCs的浸润及其在肿瘤中的作用与PI3K/PTEN/AKT通路有关^[31]。最近研究发现MDSCs来源的外泌体在CRPC进展中也发挥关键作用,具体机制是MDSCs衍生的外泌体S100A9使circMID1表达增加到海绵miR-506-3p,导致MID1表达增加和加速肿瘤进展^[32]。Gil等^[33]发现小鼠MDSCs来源的上清液可在体外促进前列腺癌类器官生长,而这一现象可以通过中和抗NRG1抗体和抑制ERBB来逆转。前列腺癌细胞释放的OBP2A可捕获TME中的CXCL15/IL8以吸引MDSCs浸润到肿瘤中,从而进一步增加TME中CXCL15/IL8的来源(如MDSCs分泌和释放CXCL15/IL8),导致前列腺癌细胞雄激素非依赖性增殖和生长,从而发展为CRPC^[34]。

2 非免疫因素

Chen等^[35]通过单细胞测序描述了来自CRPC的转录组,TME显示出多个进展相关转录组程序的激活。除免疫因素以外,非免疫因素如肿瘤相关成纤维细胞、神经细胞、脂肪细胞等TME细胞同样参与了癌症进展的各个阶段^[36]。

2.1 肿瘤相关成纤维细胞 (cancer associated fibroblasts, CAFs) CAFs在恶性肿瘤进展中起关键作用。已有研究表明CAFs中的表观遗传改变可引发前列腺癌中基质-上皮相互作用的级联反应,促进去势抵抗的发展^[37]。CAFs中的HSD17B2调节AR激活和随后的ITGBL1分泌,促进前列腺癌细胞的恶性行为及去势抵抗^[3]。CRPC病人队列中PLIN2的表达水平高于主要前列腺癌样本,表明由CAFs分泌的乳酸调控的PLIN2可能通过某种方式促进CRPC进展^[38]。CAFs上清液中的神经调节蛋白1(neuregulin 1, NRG1)通过激活HER3促进肿瘤细胞的抗性。使用阻断抗体对NRG1/HER3轴进行药理学阻断后,肿瘤在体内和体外对激素剥夺再次敏感^[39]。SPPI⁺肌纤维母细胞CAFs起源于激素敏感性前列腺癌中的炎性CAFs,SPPI⁺肌纤维母细胞CAFs依次通过SPPI-ERK旁分泌机制使前列腺癌对ADT抵抗^[40]。由CD105信号驱动的CAFs衍生的SFRP1

还可通过旁分泌方式诱导前列腺癌神经内分泌分化,从而导致激素抵抗^[41]。

2.2 肿瘤相关脂肪细胞(cancer associated adipocytes, CAAs) 前列腺周围脂肪组织可通过趋化因子促进前列腺癌的包膜侵犯,即肥胖可能与高级别肿瘤存在关联^[42],产生调节包括前列腺癌在内的肿瘤细胞代谢、增加药物抗性的 CAAs^[43]。其机制包括,IL-6或ADT可通过过氧化物酶体增殖物激活受体 γ 和脂肪细胞分化相关蛋白诱导前列腺癌细胞中的神经内分泌分化^[44]。IL-6/leptin-JAK/Stat3信号轴相关的脂肪细胞效应可削弱NK细胞介导的对CRPC细胞的抵抗力^[45]。Su等^[46]通过细胞共培养模型证明,脂肪基质细胞可诱导前列腺癌细胞的EMT发生以促进肿瘤侵袭。此外,还有生信分析显示,肥胖相关基因MSMB作为肿瘤抑制基因可影响前列腺癌的发生、预后和CRPC的发生^[47]。

2.3 神经细胞 神经细胞作为TME的重要组成部分,在包括胰腺癌、甲状腺癌、肺癌、乳腺癌等恶性肿瘤的发生发展中均发挥重要作用^[48-49],但神经细胞在前列腺癌中的作用还研究甚少。神经周围侵犯(perineural invasion, PNI)是神经细胞与肿瘤细胞相互作用而产生影响的关键行为。曾报道在一例伴有神经内分泌转化和广泛PNI的前列腺癌病例中观察到E-Cadherin降低、Vimentin和N-CAM表达升高,表明前列腺癌的神经内分泌分化、EMT和PNI之间存在潜在的联系^[50]。在生存分析中,较高密度的PD-L1⁺肿瘤相关神经与BCR有显著关系,且PD-L1⁺肿瘤相关神经的密度可独立预测BCR的预后^[51]。MUC1作为神经跟踪中的重要信号,可在肿瘤细胞的神经侵犯中发挥作用,并且,雄激素依赖性前列腺癌细胞中MUC1-C的上调可导致AR轴信号传导的抑制,并激活与神经内分泌前列腺癌相关的MYC-BRN2途径^[52]。

3 总结与展望

目前,随着前列腺癌病人日益增多,CRPC作为一种治疗困难的肿瘤状态越来越受到研究者重视。近年研究发现,除应激、AR激活、肿瘤干细胞形成外,TME也是CRPC发生发展过程中极为重要的一部分,但其促进CRPC发生的机制仍未完全阐明。如何探索巨噬细胞、成纤维细胞、脂肪细胞等TME成分与肿瘤细胞之间的相互作用,并将其作为抑制CRPC发生的治疗靶点已成为后续研究的关键。

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◇ 综述 ◇

IgG4相关自身免疫性胰腺炎的发病机制及治疗进展

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摘要 自身免疫性胰腺炎(AIP)是一种罕见疾病,以对皮质类固醇的迅速临床反应为特征,根据组织病理学镜下特征将AIP分为两种不同的类型,1型自身免疫性胰腺炎(AIP-1)和2型自身免疫性胰腺炎(AIP-2),前者是IgG4相关疾病(IgG4-rd)的胰腺表现,血清IgG4浓度升高,组织学特征为淋巴细胞和浆细胞的大量浸润和簇状纤维化,后者以粒细胞性上皮病变(GEL)为特征,不伴有IgG4升高。据调查,在我国,AIP-1较AIP-2发生率高,尽管基于现有的科学研究对AIP有了初步的认识,但两者的发病机制仍尚不明确。该综述概述近年来AIP-1发病机制的相关研究成果,同时也对AIP-1的现有治疗手段进行分类论述。

关键词 自身免疫性胰腺炎; IgG4相关性疾病; 皮质类固醇; 粒细胞性上皮病变; T淋巴细胞

Research advances in the pathogenesis and treatment of type 1 autoimmune pancreatitis

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Abstract Autoimmune pancreatitis (AIP) is a rare disease, which is characterized by rapid clinical response to corticosteroids. AIP is divided into two different types based on histopathological characteristics: autoimmune pancreatitis type 1 (AIP-1) and autoimmune pancreatitis type 2 (AIP-2). AIP-1 is a pancreatic manifestation of IgG4-related disease (IgG4-rd) with high serum IgG4 concentrations. Its histological features are extensive infiltration of lymphocytes and plasma cells and clustered fibrosis. AIP-2 is characterized by granulocyte epithelial lesion (GEL) and its serum IgG4 level is low. According to the investigation, in China, the incidence of AIP-1 is higher than AIP-2. Although based on the existing scientific research, we have a preliminary understanding of AIP, but the pathogenesis of both is still unclear. This article mainly summarizes the relevant research results of the pathogenesis of AIP-1 in recent years, and also classifies the existing treatment methods of AIP-1.

Keywords Autoimmune pancreatitis; IgG4-related disease; Corticosteroid; Granulocyte epithelial lesion; T lymphocyte;