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低氧环境与上皮性卵巢癌侵袭转移的相关临床研究进展

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摘　要

低氧微环境是近几年来肿瘤研究的热点话题，大量研究结果表明，肿瘤的复发转移与肿瘤微环境中的多种因素密切相关，其在肿瘤的生长代谢、转移及耐药过程中发挥着至关重要的作用。此外，在高海拔环境下卵巢癌的发生也同当地的民族特性及生活习俗等存在某些关联。在妇科恶性肿瘤中，由于卵巢癌早期缺乏有效的诊断指标，故早期易复发转移、浸润以及对化疗药物的耐受，这是造成其高死亡率并影响预后的关键因素。本文主要结合相关文献对低氧微环境与卵巢癌侵袭转移的预后相关因素的关联性作一综述。

关键词

低氧微环境，上皮性卵巢癌，侵袭转移

Research Progress on the Relationship between Hypoxia Environment and Invasion, Metastasis and Prognosis of Epithelial Ovarian Cancer

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Abstract

Hypoxic micro-environment is a hot topic in tumor research in recent years. A large number of research results show that tumor recurrence and metastasis are closely related to various factors in tumor micro-environment, which plays a crucial role in tumor growth, metabolism, metastasis and drug resistance. In addition, the incidence of ovarian cancer in high altitude environment is also associated with local ethnic characteristics and living customs. In gynecological malignancies, ovarian cancer is prone to relapse, metastasis, invasion and resistance to chemotherapy drugs in the early stage due to the lack of effective diagnostic indexes, which is the key factor causing high mortality and affecting prognosis. This article reviews the relationship between hypoxic micro-environment and prognostic factors related to invasion and metastasis of ovarian cancer.

Keywords

Low Oxygen Micro-Environment, Epithelial Ovarian Cancer, Invasion and Metastasis

1. 引言

卵巢恶性肿瘤是女性生殖系统中常见的三大恶性肿瘤之一，尤以上皮性卵巢癌最为常见且死亡率居妇科肿瘤首位。卵巢癌因其具有血管生成作用且代谢活跃，高度侵袭性及耐药性并发生远处转移是造成患者预后不良的主要原因。当前，肿瘤转移与微环境中转化生长因子、肿瘤相关巨噬细胞、凝血酶等多种因素密切相关。明晰卵巢癌与肿瘤低氧微环境的关系，进而明确在肿瘤发生发展、侵袭转移过程中发挥重要作用的关键因素，对于积极寻找其相对应的治疗措施，提高卵巢癌的预后具有重要的作用。

2. 低氧微环境下的卵巢癌的现状

肿瘤微环境(Tumor Micro-Environment, TME)是指肿瘤细胞与浸润的免疫细胞、基质细胞、血管、细胞外基质和分泌因子等共同构成的在肿瘤发生发展过程中形成的一种局部内环境。肿瘤的发生和转移与肿瘤细胞所处的内外环境密切相关。缺氧是实体肿瘤微环境的基本特征之一[1] [2]，在促进肿瘤进展、肿瘤细胞侵袭转移中发挥着重要的作用[3] [4]。大量实验研究证明，缺氧能产生和诱导某些蛋白酶，从而降解细胞外基质[5] [6]；临床研究也表明，肿瘤缺氧与肿瘤转移倾向有关[7]。

上皮性卵巢癌(Epithelial ovarian cancer, EOC)是卵巢癌的主要类型，也是女性最致命的恶性肿瘤，在中国的患病率非常高，目前可用的诊断标志物不够有效。EOC 是最致命的妇科癌症，它是女性癌症相关死亡的第五大原因[8]。因其缺乏疾病特异性症状使其早期发现变得困难，大多数女性在晚期被诊断出患有 EOC [9]。在诊断时，大多数女性患有大的原发性卵巢肿瘤、多个转移性继发性肿瘤和腹水[8]。由于诊断处于晚期，很难有效治疗该疾病，从而导致患者在第 3 和第 4 阶段诊断的女性 5 年生存率分别为 42% 和 26% [10]。在妇科恶性肿瘤中，由于卵巢癌(Ovarian Cancer, OC)的特点是发病率高、死亡率高、预后差[11] [12]。肿瘤分化差、疾病分期较高、细胞减灭术后存在残留病灶、年龄较大、吸烟、体重过重和缺乏体力活动与 OC 预后不良有关[13] [14]。虽然大多数患者起初对化疗治疗反应良好，但部分患者会因复

发而逐渐耐药。因此，明晰低氧微环境下卵巢癌侵袭转移的预后相关因素对于改善卵巢癌的治疗提供新的思路和借鉴意义。

3. 低氧微环境下可能促使卵巢肿瘤转移的机制

缺氧是大多数实体瘤中发生的一种生理压力，这会促使实体瘤中产生坏死区域且与患者预后不良相关。这些坏死区域预后不良的原因源于肿瘤缺氧的适应性反应，其中一些癌细胞将通过增加生长因子的自分泌产生、增加侵袭和迁移能力以及诱导自噬而在缺氧细胞死亡中存活[15]，这导致癌细胞对化学疗法具有更强的抵抗力、侵袭和转移能力并且具有更强的增殖性。与正常细胞一样，肿瘤细胞的生长也需要通过新生血管的形成而获取氧气与营养物质。而低氧则是血管生成最主要的影响因素。缺氧诱导因子 HIF (Hypoxia-Inducible Factor, HIF)通过激活一系列促血管生成因子的表达而引发新血管生成，其中以血管内皮生长因子(Vascular Eendothelial Growth Factors, VEGFs)最为重要[16]。血管生成是从预先存在的脉管系统发展出新血管的自然发生的过程。血管生成涉及许多稳态过程，包括伤口愈合中的血管修复[17]。为响应损伤，促血管生成刺激物被激活，包括血管内皮生长因子(VEGF)、成纤维细胞生长因子、血管生成素、缺氧诱导因子等[18] [19] [20] [21] [22]。虽然血管生成在成人中通常是静止的，但在卵巢中，这会发生周期性血管生成，并且是有助于调节卵巢功能的重要过程[23]。

血管生成过程在实体瘤的发生和进展中至关重要，通过启动血管生成，肿瘤可以刺激血管形成以提供氧气和营养，并促进代谢废物的清除[24]。为刺激血管形成，肿瘤经历了“血管生成转换”，其中促血管生成因子过度表达，同时血管生成抑制剂被抑制[25]。血管生成不会在整个实体瘤中均匀地发生，并且大多数肿瘤具有血管镶嵌图案[26]。这种血管分布不均的情况导致肿瘤内的含氧量正常的区域高度血管化，从而使氧气扩散到肿瘤细胞中。通常在血管生成开关之后，促血管生成刺激具有侵略性，导致肿瘤血管的快速形成[27]。由于快速血管化，许多肿瘤血管的形态发生了改变，出现盲端、收缩、分流和其他畸形[28]。由于治疗化合物不能到达肿瘤内部，这种减少的血管灌注代表了癌症治疗成功的显着障碍。低灌注和由此产生的缺氧与化学抗性的发展有关，这是卵巢癌患者的主要问题[29] [30]。出现化疗耐药的 EOC 女性已表现出特定的血管生成基因特征，这可能有助于针对这些患者进行靶向治疗[31]。

4. 高原低氧环境与卵巢肿瘤的相关性

在高原环境中卵巢癌的发生发展与其他恶性肿瘤的发生相似，也是多因素多阶段构成的错综复杂的过程。青海位于我国西北内陆地区，属于高原大陆性气候，其海拔平均在 3000 米以上，依托其独特的地理位置和民族特性，目前卵巢癌生长浸润转移的细胞和相关分子机制还未完全了解，但大量研究表明，缺氧或低氧的微环境在卵巢癌的侵袭、黏附、转移中起着至关重要的作用[32] [33]。在卵巢癌细胞中，低氧状态能促进肿瘤血管生成、抑制肿瘤细胞凋亡、影响细胞周期和增殖、增加放化疗及手术的抵抗性，使肿瘤对放化疗的疗效明显下降，加重卵巢癌患者的不良预后，促进卵巢癌细胞侵袭和远处转移[34] [35]。同时，青海作为多民族聚居的地区，世居的少数民族主要为藏族、回族、土族、撒拉族和蒙古族。有相关研究认为卵巢癌与基因构成、遗传和环境因素、生活方式、饮食习惯、心理压力等之间存在某种直接联系。其中有研究发现，因长期高寒缺氧，可导致机体代谢发生一系列变化，当机体代谢产物攻击细胞时可引起 DNA 损伤，使其 DNA 修复能力低下[36]。DNA 修复基因多态性可能是卵巢癌的遗传易感因素之一。同时，缺氧又加重了机体酸性代谢产物增多并使其清除受限。因此，可考虑高原低氧环境与卵巢癌之间可能存在某种程度上的关联。此外，藏族患者的饮食结构中存在着高脂高蛋白高盐、生活习惯及卫生条件不合理等均与其发病相关，这符合刘霞[37]等当机体免疫功能下降时，这些因素可导致体质过度酸化，引起卵巢异常增生进而导致卵巢囊肿甚至癌变。因高海拔地区低氧、低温等特征，在卵巢组织中

可能引发卵巢早衰、肿瘤发生等不良改变，因此早期诊断与治疗对于维护患者远期生育需求及生存质量有关键意义[38]。高海拔地区存在低氧、低温等气候特征，对于女性生殖系统尤其是卵巢组织的生理功能具有不利影响，可能因卵泡衰竭快、雌激素水平低等原因发生卵巢早衰，增加卵巢肿瘤的发生的可能[39]。目前，卵巢癌仍缺乏特异度的筛查手段，常规的筛查方法包括超声、CA125 等。超声诊断可以较好地描述卵巢肿物的形态学特征，进而可对其良恶性进行预测分析。但超声诊断对于技术、经验等要求较高，若诊断医师经验不足，往往无法迅速、准确对卵巢肿物的性质进行合理判断，从而影响筛查的效率[40]。既往国内研究中关于卵巢肿瘤的定性诊断多集中于东部低海拔地区，而关于高海拔地区的相关研究较少[41]。高海拔地区有多民族混居的特征，地理环境及生活习惯存在差异性，分析原因包括高海拔地区经济和卫生条件较差、医疗条件较为落后外，且少数民族早婚、早育、多产外，而关键因素在于未能做到在筛查基础上对卵巢肿瘤及癌前病变行持续监测。

5. 低氧微环境下卵巢癌的治疗

卵巢癌被描述为全球第七大最常见的女性癌症。根据相关研究显示，卵巢癌患者的 5 年总生存率低于 40% [42]。尽管仅通过手术就可以成功切除早期卵巢癌，但大多数患者被诊断为晚期。由于晚期疾病表现和化疗耐药性，卵巢癌的死亡率居高不下。虽然大多数患者最初对化疗反应良好，但多数患者复发并产生化疗耐药性，这为提高患者生存率带来了难以逾越的障碍[43] [44]。卵巢癌患者最初对手术治疗反应良好，复发和存活率低主要是由于化疗耐药，这通常是由于卵巢癌干细胞引起的耐药性疾病。癌症干细胞有助于卵巢癌的化学抗性和转移并导致肿瘤形成。因此，开发可以靶向肿瘤干细胞的治疗策略有利于提高患者的生存率，尤其是那些临床化疗和转移的患者。

化学抗性的发展与缺氧的多种机制与有关。缺氧诱导化疗耐药的机制之一是通过改变癌细胞代谢。作为对缺氧的反应，卵巢癌细胞会发生代谢转换，糖酵解途径发生变化，从而促进对卡铂的耐药性[45] [46] [47]。随着卵巢肿瘤变得缺氧，糖酵解酶上调以代谢葡萄糖，导致乳酸形成[48]。乳酸过度的积累则导致肿瘤细胞中 pH 值降低并抑制化疗药物的效果。由于上皮性卵巢癌主要在晚期被诊断出来，这给患者带来了巨大的治疗挑战，故其 5 年生存率很低。在卵巢癌中，其存在显着的肿瘤异质性及肿瘤微环境多样。肿瘤异质性导致肿瘤内治疗反应的多样性，这可能导致其耐药或复发。治疗开发和肿瘤分析的进步已经开始从“一刀切”的方法转向以患者为基础的精准治疗。个体患者在年龄、生育能力和避孕药具使用方面存在很大差异，这些因素先天的影响卵巢的内分泌环境。同样，个体肿瘤的免疫特征也存在显著差异，这会影响免疫疗法的疗效。肿瘤大小、恶性腹水的存在和血管密度进一步改变了肿瘤微环境，从而产生显著的缺氧区域。目前，卵巢癌的常见治疗方案包括细胞减灭术和化疗，通常采用卡铂和紫杉醇[49]。尽管卵巢癌患者通常对化疗有初始反应，但大多数女性会出现化疗耐药和疾病复发[50]。尽管恶性细胞在缺氧的情况下茁壮成长，但理想情况下会产生针对肿瘤相关抗原的抗肿瘤反应的免疫细胞，但通常会因这种环境而变得无反应或死亡[51]。这种系统失衡创造了促肿瘤环境并阻碍了患者对免疫疗法的反应。因此，这需要探索新的治疗方法来预防化学抗性和提高治疗成功率。

6. 结论与展望

在临床工作中，卵巢肿瘤越来越常见且患病年龄逐渐趋于年轻化，因其易复发转移且耐药的特性，故在经过规范、有效治疗后，患者生存率仍有待提高。肿瘤低氧微环境参与了肿瘤的血管生成、能量代谢及细胞增殖、侵袭及转移等关键过程。低氧是恶性实体肿瘤进展中的常见现象，并且与肿瘤的生物学行为密切相关。目前有关研究证据表明，低氧微环境可促进临床癌细胞的侵袭和转移并且其机制是多方面的。因此，探讨卵巢肿瘤、缺氧和影响预后的潜在预测因素之间的相互作用，对于寻求改善卵巢癌的

诊断及治疗可能会为潜在的治疗提供新的契机。通过改善肿瘤的低氧微环境而减弱肿瘤发生发展过程中各方面的促进作用，将对妇科恶性肿瘤的治疗具有重要意义。

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