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自身免疫性疾病与恶性肿瘤共病机制的研究进展*

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[摘要]　自身免疫性疾病(AIDs)与恶性肿瘤均属于临床难治疾病,二者之间存在交织关系,两种疾病共病促使患者死亡率大大增加,当务之急是了解两者疾病发展的根本原因和具体的分子机制。一方面,AIDs 中自身特异性抗体、炎性因子释放、免疫失调及治疗 AIDs 应用的药物均可能导致恶性肿瘤的发生。另一方面,恶性肿瘤的免疫检查点抑制剂也是导致两种疾病共病的机制之一。因此,对于两种疾病共病的情况,需要风湿科和肿瘤科医师在诊断时保持谨慎,并保持密切的跨学科合作,剖析共病患者的主要病机,权衡两种疾病共病轻重,择取最佳治疗方式尤为关键。该文就自身免疫性疾病与恶性肿瘤共病机制的研究进展做一综述。

[关键词]　自身免疫性疾病;恶性肿瘤;特异性抗体;炎性机制;免疫失调;综述
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Research progress on comorbidity mechanism of autoimmune diseases and malignant tumors*

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[**Abstract**]　Autoimmune diseases (AIDs) and malignant tumors are both clinically refractory diseases, and there is an interwoven relationship between the two. The comorbidity of the two diseases greatly increases the mortality rate of patients. It is urgent to understand the root causes and specific molecular mechanisms of the development of the two diseases. On the one hand, in AIDs, the release of autospecific antibodies, inflammatory factors, immune imbalance and drugs in treating AIDs may lead to the occurrence of malignant tumors. On the other hand, the immune checkpoint inhibitors of malignant tumors are also one of the mechanisms leading to the comorbidity of the two diseases. Therefore, for the comorbidity of two diseases, it is necessary for rheumatologists and oncologists to be cautious in diagnosis and maintain close interdisciplinary cooperation, analyze the main pathogenesis of the patients with comorbidity, weigh the severity of comorbidity of the two diseases, and choose the best treatment mode. This article reviews the research progress on the comorbidity mechanism of autoimmune diseases and malignant tumors.

[**Key words**]　autoimmune disease; malignant tumor; specific antibody; inflammatory mechanism; immune disorder; review

自身免疫性疾病(autoimmune disease,AIDs)是一类自身免疫系统紊乱、自身抗原发生免疫应答,从而引起损害组织器官或系统的慢性炎症性疾病。AIDs 的发病率和患病率都呈逐年上升趋势,目前已确定 81 种可能的 AIDs[1]。近年来,恶性肿瘤的发病率大幅上升,其治疗已成为世界公共卫生的关注热点。研究发现,AIDs 与恶性肿瘤之间存在交织关系,其中特发性炎症性肌病(idiopathic inflammatory myopathies,IIM)、类风湿关节炎(rheumatoid arthritis,RA)、系统性红斑狼疮(systemic lupus erythematosus,SLE)、系统性硬化症(systemicscleroderma,SSc)等 AIDs 合并恶性肿瘤均呈高风险趋势[2-3]。国内外研究表明,IIM 中皮肌炎和炎性肌病合并恶性肿瘤的比例相对较高(10.19%～18.40%)[4-5]。RA 合并恶性肿瘤的发生率与普通人相近,为 5%～10%,但合并淋巴瘤的发生率较普通人高出很多[6]。一项系统评估显示,SLE 与癌症的发生风险逐年增长,尤其是甲状腺癌、宫颈癌、非霍奇金淋巴瘤、肾癌和血液系统癌

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症的发生风险明显增加[7-10]。SSc 患者并发恶性肿瘤的风险在国内外的研究结果相近，约 20%，最常见的癌症是乳腺癌、肺癌及血液系统恶性肿瘤[11-13]。AIDs 合并恶性肿瘤的患者往往病情严重，对治疗效果不佳，若医生未及早发现和干预，可能会增加患者的痛苦及家庭的压力。AIDs 与恶性肿瘤共病的机制值得深入探讨，对于两种疾病共病相关性的研究国内相对较少，因此，本文就 AIDs 合并恶性肿瘤发病机制进行综述。

1 特异性抗体

目前认为，IIM 患者易患肿瘤的风险较高[14]，与肿瘤发生相关的特异性阳性抗体有抗转录中介因子 1-γ 抗体、抗核基质蛋白 2 抗体和抗小泛素样修饰激活酶抗体[15-17]。此外，ALLENBACH 等[18]研究发现，抗 3-羟基-3-甲基戊二酰辅酶 A 还原酶抗体和抗信号识别抗体阳性也是 IIM 合并恶性肿瘤的关键点。

在 SSc 中，该类病种患者合并恶性肿瘤的现象也屡见不鲜[12-13]，除了以上所涉及的抗转录中介因子 1-γ 抗体与恶性肿瘤相关外[19]，还有研究发现 SSc 患者中抗 RNA 多聚酶Ⅲ抗体阳性与肿瘤相关。EULAR 研究纳入 4 986 例 SSc 患者，证实抗 RNA 多聚酶Ⅲ抗体阳性患者合并恶性肿瘤的风险相对较高（OR = 7.38，95%CI：1.61～33.80），且多年龄偏大，皮肤改变明显[20]。还有一个值得关注的现象，当抗着丝粒抗体、抗拓扑异构酶Ⅰ抗体和抗 RNA 多聚酶Ⅲ抗体同时阴性时，患癌风险却较普通 SSc 患者增加[21]。

肺癌是 RA 患者最多合并的恶性肿瘤。研究表明，抗环瓜氨酸肽抗体是 RA 具有代表性的特异性抗体，该抗体阳性则患有肺癌风险明显增高[22]。SLE 患者合并淋巴瘤及肺癌的可能性较为明显[23-25]，其阳性的特异性抗体为抗核抗体和双链脱氧核糖核酸抗体[26-27]。因此，具有风湿免疫性疾病表现的患者需特别关注其具有典型表现的特异性抗体是否呈阳性，并警惕患者是否存在具有与恶性肿瘤共病的情况。

2 炎性机制

AIDs 是一类慢性炎症性疾病，体内炎性介质长期处于应激状态，炎性因子和免疫系统失控损伤 DNA，导致抑癌基因失活，并刺激肿瘤细胞增殖，导致 AIDs 合并恶性肿瘤的风险增加[28-30]。慢性炎症中主要致炎因子环加氧酶（cyclooxygenase，COX）-2 及下游酶产物前列腺素 E2（prostaglandin E2，PGE2）上调，加速了肿瘤细胞的增殖、血管生成、侵袭和转移[31]，且 PGE2 具有塑造肿瘤细胞的功能，在肿瘤免疫逃逸中起到主导作用[32]。此外，还有研究表明 JAK/STAT 信号通路失调影响 AIDs 和恶性肿瘤的发生、发展[33]。

3 免疫失调

人体免疫系统稳态主要通过调节性 T 细胞和调节性 B 细胞来维持，当调节性 T 细胞失调时，自身免疫和广泛的炎症就会被触发，慢性炎症和组织损伤可能会产生细胞因子和趋化因子，这些细胞因子和趋化因子结合如肿瘤坏死因子-α、白细胞介素（interleukin，IL）-1 和 IL-6 等促炎细胞，通过刺激上皮细胞活化和上皮间充质转化，从而发生细胞癌变[3,34-36]。最近研究发现，在 SLE 患者中，调节性 T 细胞通过 IL-23/IL-17 轴致病，产生炎症因子 IL-17 和抗双链脱氧核糖核酸抗体，导致恶性肿瘤的发生[37-38]。

调节性 B 细胞也同样参与肿瘤免疫逃逸，其中 B 细胞活化因子（B-cell activating factor of the TNF family，BAFF）和增殖诱导配体（a proliferation inducing ligand，APRIL）通过核因子激活的 B 细胞的 κ-轻链增强（nuclear factor-κ-gene binding，NF-κB）信号通路，过度刺激细胞的增殖和存活。一项关于 66 000 例患者的临床研究发现，调节性 B 细胞可导致淋巴瘤的发生[39]。另有关于胃癌的研究发现，调节性 B 细胞通过免疫抑制细胞因子 IL-10 破坏了对癌细胞的免疫力[40]。免疫系统不仅对体外环境防御作用明显，对于体内保持正常环境更有影响力，免疫体系紊乱造成肿瘤细胞免疫逃逸，这是发生恶性肿瘤的关键点，对于恶性肿瘤免疫治疗方面也更加值得关注及研究。

4 AIDs 的治疗

治疗 AIDs 的药物可能增加患癌风险。糖皮质激素广泛用于炎症性疾病，韩国一项回顾性研究发现，长期接触糖皮质激素导致整体癌症风险增加，尤其易导致肺癌及肝癌的发生[41]。糖皮质激素受体激活 PI3K 信号通路，使糖皮质激素诱导激酶 1、结缔组织生长因子过度表达，从而刺激肿瘤细胞进一步发展[42]。除传统的抗风湿药物外，生物和靶向合成的治疗 AIDs 的药物也会导致恶性肿瘤的发生风险增加。其中 JAK 抑制剂和肿瘤坏死因子抑制剂导致恶性肿瘤发生风险的研究较多[43]，如吗替麦考酚酯的使用可能增加患非黑素瘤皮肤癌和中枢神经系统淋巴瘤的风险[44]。一项治疗 RA 的随机对照临床研究也证实了此类药物可能会增加患恶性肿瘤的风险[45]。还有研究发现，在 AIDs 治疗中环磷酰胺与膀胱癌、白血病相关，而硫唑嘌呤、甲氨蝶呤、肿瘤坏死因子抑制剂也显示皮肤癌患病的风险增加[46-47]。

5 免疫检查点抑制剂（immune checkpoint inhibitors，ICIs）不良反应

目前临床应用的 ICIs 有细胞毒性 T 淋巴细胞相关蛋白 4（cytotoxic T-lymphocyte-associated protein 4，CTLA-4）、程序性死亡受体 1（programmed cell death protein 1，PD-1）和程序性死亡受体-配体 1（programmed cell death-ligand 1，PD-L1）这 3 种[48]。ICIs 在恶性肿瘤免疫治疗领域大大改善了恶性肿瘤患者整体预后水平，但其所带来的不良反应也是不可避免的。既往临床试验数据显示，接受 ICIs 治疗的 25%～75% 患者出现不同程度的免疫相关不良反

应[49]，发生风湿性免疫不良反应也被广泛报道，一项纳入 5 560 例临床试验患者的 meta 分析结果显示，使用 ICIs 治疗的患者中，18.4%出现风湿性免疫相关不良反应，较未使用 ICIs 治疗患者风险升高 1.3 倍[50]。风湿性免疫相关不良反应以炎性关节炎、肌炎和风湿性多肌痛最常见[51]。

炎性关节炎多见于多关节炎、脊柱关节炎、反应性关节炎[52]。有综述性研究表明，经 ICIs 治疗的肿瘤患者中，1%～7%发生为关节痛的风湿性免疫相关不良反应，这些患者在急性期的炎性反应物水平升高，而 RA 等特殊的血清学抗体为阴性，部分患者抗核抗体呈阳性[53-54]。但也有研究显示，372 例患者接受 ICIs 治疗后，约 32%的患者风湿因子或抗环瓜氨酸肽抗体检测呈阳性[55]。

肌炎的特征是通过神经生理学和组织病理学检测观察到的四肢近端肌肉无力和肌肉炎症，有的患者伴有肌痛[56]。据报道，肌炎的发生具有滞后性，多发生在接受 ICIs 治疗后的 3 周至 5 个月。与传统肌炎比较，ICIs 诱发的肌炎很少累及皮肤和肺等肌肉外器官[57]。大多数肌炎患者的自身抗体血清学呈阴性，但一小部分患者的对抗横纹肌抗体、抗转录中介因子 1-γ 抗体、抗核抗体、抗 Ro52 抗体和抗 PM/Scl 抗体呈阳性[58]。此外，ICIs 诱导的肌炎与心肌炎和肌无力密切相关，会增加其死亡风险[59]。

风湿性多肌痛则是以肩、髋等大关节的疼痛及晨起僵硬为主要临床表现，关于 ICIs 文献研究报道称，肌痛是第二常见的风湿性免疫相关不良反应，患病率为 2%～21%[60-61]。通常发生在开始接受 ICIs 治疗后的 3 个月，并伴有其他风湿性免疫相关不良反应[62]。

还有 ICIs 导致的其他风湿性免疫相关不良反应，如血管炎、干燥综合征、SSc 等也有相应报道。ICIs 诱导的血管炎很少见，而最常见的恶性肿瘤伴有血管炎的是黑色素瘤[63]。一项国际性肿瘤免疫治疗研究显示，26 例使用细胞程序性死亡-配体 1（programmed cell death 1 ligand 1，PD-L1）的肿瘤患者均发生干燥综合这一风湿性免疫不良反应[64]。国外有报道显示，应用 ICIs 后可诱发皮肤硬化症的发生，不过病例数据过少，有待更多数据支持[65]。

总的来说，与 AIDs 比较，风湿性免疫相关不良反应似乎有一些共同的病理机制，但又不完全吻合。只有更深入了解肿瘤与自身免疫之间的关系，才能有效平衡控制两者。

6 其他因素

因 AIDs 自身免疫功能紊乱，使其感染病毒的风险增加。研究表明，AIDs 患者更加容易感染 EB 病毒、人乳头瘤病毒等，不仅增加了合并淋巴瘤的发生风险，还使合并肝胆、外阴、阴道和宫颈肿瘤风险增加[66-67]。

AIDs 合并癌症的另一共同因素是吸烟。吸烟既是肺癌患病的因素之一，也是患 AIDs 的因素之一。早期呼吸道炎症会触发致病性抗环瓜氨酸肽抗体的产生，随着时间积累，成纤维细胞进而生成。研究表明，成纤维细胞可促进肿瘤微环境的发生，最终导致肺癌的发生[66,68]。

7 总结和展望

自身免疫与癌症之间的联系是动态的、双向的，风湿性疾病引起的慢性炎症可能促进癌症的发生。相反，抗肿瘤免疫反应可能与自身组织发生交叉反应，导致 AIDs 的发生。通过对二者共病机制的研究既可以明白二者疾病的相关性，也可以对该类患者的治疗提供多方面切入点。此外，肿瘤免疫治疗值得纵向研究，通过了解不同免疫细胞亚群和调节通路，临床上合理应用 ICIs，平衡两种疾病，达到消除癌细胞又不造成过度自身免疫反应。总之，由于 AIDs 合并恶性肿瘤临床上具有风湿性的表现，但肿瘤的高风险性不可忽视，在临床工作中，临床医生应警惕 AIDs 患者合并恶性肿瘤的可能性，治疗前需进行肿瘤标志物及影像学等肿瘤相关检查，以便为临床提供更灵敏的诊断依据。此外，两种疾病存在自身特异性抗体、炎性机制、免疫系统等方面联系，治疗时需跨学科多方面考虑，挑选适合的治疗方法，为肿瘤及自身免疫疾病领域的进一步诊断及治疗拓展新思路。

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