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Vav1与浸润T细胞活性 肿瘤局部IDO表达相关性的研究

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Association of Vav1 with Activity of Infiltrating T Cells and Local Expression of IDO in Tumor

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摘要

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摘要 通过对Vav1与肿瘤浸润T淋巴细胞（tumor infiltrating T lymphocytes，TIL-T） 活性关系的研究，提出T细胞失能的可能分子机制；初步探讨TIL-T中Vav1的表达情况及其与肿瘤局部微环境中吲哚胺2，3双加氧酶（indoleamine-2， 3-dioxygenase，IDO）表达的相关性。方法：收集天津医科大学附属肿瘤医院肺外科手术切除的新鲜肺癌标本、癌旁正常肺组织及蜡块40例，通过实时定量RT-PCR检测TIL-T中Vav1 mRNA表达变化；免疫印迹及免疫沉淀技术检测Vav1蛋白表达及磷酸化活性。BrdU法检测T细胞增殖活性。此外，运用Real time-PCR法检测肺癌组织中IDO mRNA表达水平，免疫印迹及免疫组化检测IDO蛋白表达情况。结果：部分肺癌局部浸润的T细胞处于功能抑制状态，这种抑制状态可能与细胞内重要的信号传导蛋白Vav1的表达量及活性相关。IDO表达阳性组肺癌标本局部TIL-T中Vav1 mRNA水平及Vav1蛋白的表达和磷酸化水平明显低于IDO表达阴性组（P<0.05）。结论：Vav1的表达和活化在TIL-T功能中具有重要的作用。肿瘤局部微环境中的IDO蛋白可能是影响TIL-T中Vav1表达和活化的重要因素之一。IDO可能通过抑制Vav1 的表达及磷酸化活化过程，使TIL-T的主动免疫受损，从而降低宿主的抗肿瘤免疫效应。

关键词： Vav1 吲哚胺2 3双加氧酶 肿瘤浸润T淋巴细胞 磷酸化 增殖

Abstract: This study explored the relationship between Vav1 and tumor-infiltrating T lymphocytes (TIL - T), which provide a molecular mechanism inducing a state of T cell anergy. The expression of Vav1 in TIL-T and indoleamine 2,3-dioxygenase (IDO) from the tumor microenvironment was invetigated in order to present a possible molecular mechanism for tumor-induced T cell immune tolerance. Methods: A total of 40 lung cancer patients who had undergone surgery in the Tianjin Medical University Cancer Institute and Hospital were involved. The expression levels of Vav1 mRNA in TIL-T were detected by real-time PCR, while the expression and activation of Vav1 were determined using Western blot and immunoprecipitation. T cell proliferation was detected using the BrdU method. The levels of IDO expression in lung cancer and corresponding normal lung tissues were determined using semi-quantitative RT-PCR, immunohistochemistry, and Western blot. The SPSS17.0 software was used for statistical analysis. Results: TIL-Ts are a part of cancer tissues and are in a state of functional suppression. This suppressive condition may involve the key signal transducer Vav1. Both mRNA and protein levels of Vav1 in T cells were significantly decreased in lung cancer tissues with IDO-positive expression compared with those with IDO-negative expression. In addition, the levels of Vav1 phosphorylation was decreased (P < 0.05). Conclusion: The expression and activation of Vav1 play critical roles in the function of TIL-T. IDO, secreted by the tumor cells themselves or antigen-presenting cells, has an important impact on the expression and activation of Vav1 in TIL-T. IDO may suppress the expression and phosphorylation of Vav1, leading to inhibition of the T cell active immune response, which may consequently reduce the anti-tumor defenses of the host.

Key words: Vav1 Indoleamine 2,3-dioxygenase Tumor infiltrating T lymphocytes Phosphorylation Proliferation

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