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The Expression of Tumor-Associated Macrophages in Papillary Thyroid Carcinoma

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Solid tumors contain not only malignant cells, but also extracellular matrix and many other nonmalignant cells including fibroblasts, endothelial cells, and inflammatory cells such as macrophages, neutrophils, and lymphocytes. The presence of inflammatory cells within solid tumors suggests that the inflammatory microenvironment could play a major role in promoting tumorigenesis and progression. Macrophage infiltrates in the context of or surrounding a variety of malignancies represent the host's immune response to the tumor [1,2].

It was recently reported that tumor-associated macrophages (TAMs) had important roles in the tumor progression and metastasis of various cancers, including advanced thyroid cancer [3-9]. However, the role of TAMs in papillary thyroid carcinoma (PTC) has not been fully elucidated. Fiumara et al. [10] studied the tissue distribution and prognostic significance of TAMs in a retrospective series of 121 PTCs. They found tumor-infiltrating macrophages in approximately 70% of cases. Phagocytosis of neoplastic cells by macrophages was observed in approximately 15% of tumors, and none of these tumors developed distant metastases. These data suggest that neoplastic cell phagocytosis by macrophages and lymphocytic infiltration play a protective role in the development of distant metastases in patients with PTC.

Conversely, emerging data suggest that TAMs promote tumor progression and metastasis in PTC. Ryder et al. [8] reported that an increased density of TAMs was associated with tumor progression in advanced thyroid cancers and that there was a significant correlation between increased TAMs and histological grade, tumor invasiveness, and decreased cancer-related survival in PTC. Very recently, they also reported that TAMs promoted PTC progression in *BRAF*-induced PTC mouse models, and that targeting CCR2-expressing cells during *BRAF* induction reduced TAM density and impaired PTC development [11]. These results suggested that therapeutic strategies targeting TAMs may be beneficial in the treatment of advanced PTC.

Qing et al. [9] investigated TAMs density in both benign thyroid lesions and PTC tumors by CD68 immunostaining. They found that the overall density of TAMs was significantly higher in PTC tumors compared with thyroid goiter and follicular adenoma. In addition, the density of TAMs was positively associated with lymph node (LN) metastasis in TNM stages III/VI compared with stages I/II. However, no association was observed with other common tumor features, including *BRAF* mutation.

In this issue, Kim et al. [12] investigated the expression of TAMs in 36 PTC patients with LN metastasis using immunohistochemical staining with anti-CD68 antibody. They reported that a higher density of TAMs was correlated with larger tumor size, suggesting a protumorigenic role of TAMs in PTCs. Comparing clinicopathologic characteristics among low (<25%) and high (25% to 70%) TAM density groups, primary tumor

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size was larger in the high density group compared to the low density group (2.0±0.1 vs. 1.5±0.1; P=0.009). However, there was no significant association between high TAM density and poorer clinicopathologic characteristics including multifocality, LN metastasis, and extrathyroidal extension. These data were not in agreement with those of previous studies, which reported that high TAM density was correlated with tumor invasiveness and poor clinicopathologic characteristics, excepting tumor size [8,9,11].

Kim et al. [12] also analyzed the morphological characteristics of TAMs in PTC. They found that TAMs had thin, elongated cytoplasmic extensions, forming a canopy structure over tumor cells, and that the morphological characteristics of thyroid cancer tissue were well maintained irrespective of the presence of TAMs. In view of this, they inferred that TAMs do not play key role in tumor development in PTC. However, Caillou et al. [13] reported that anaplastic thyroid cancer displayed a very dense network of interconnected ramified TAMs in direct contact with intermingled cancer cells, and that this TAM network was directly related to the aggressiveness of thyroid cancer.

Unfortunately, Kim et al. [12] conducted this study using anti-CD68 antibody on only a small sample of PTCs with LN metastasis. A major limitation of this study was the lack of follow-up data with which to evaluate long-term outcomes. Therefore, further studies using a more specific antibody and larger sample sizes of various stages of PTC are warranted to investigate the role of TAMs in tumor development, tumor invasiveness, and metastasis of PTC. Finally, TAM-targeted pharmacologic therapy in patients with advanced thyroid cancer should also be investigated.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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