Tumor-Associated Inflammatory Cells in Thyroid Carcinomas

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KEYWORDS

• Thyroid • Cancer • Inflammation • Dendritic cells • Macrophages • Mast cells • Lymphocytes • Chemokine

ABSTRACT

The complex interactions between immune cells and tumor cells in cancer play a major role in tumor development and subsequent patient outcomes. Different types of tumor-associated inflammatory cells (TAICs), such as dendritic cells, macrophages, lymphocytes, and mast cells, have been recognized for many years in several tumors; however, the role of TAICs in cancer is still not completely understood. This review article focuses on the major types of TAICs, including their general role in cancer and, more specifically, their role and distribution in thyrocyte-derived carcinomas.

OVERVIEW

The link between cancer and inflammation was first proposed approximately 250 years ago with the observation by Rudolf Virchow (1821–1902), a German pathologist, that tumors in different organs often arose in sites of chronic inflammation, and that inflammatory cells, including macrophages, were present within and around tumors.[1] Classic examples include *Helicobacter pylori*–associated gastric cancer and inflammatory bowel disease–associated colorectal cancer. In the thyroid gland, an association between chronic lymphocytic thyroiditis (CLT) (Hashimoto or autoimmune thyroiditis) and papillary thyroid carcinoma (PTC) has been reported in several studies since the 1950s.[2–4] Although chronic inflammation is a well-known risk factor for tumor initiation and promotion, once established, cancer cells may also produce proinflammatory chemokines within the tumor bed, supporting cancer progression.[5,6] Simultaneously, cancer cells must also evade destruction by the immune system to persist and thrive, a recognized hallmark of cancers,[7] which frequently arise in a background of immunodeficiency.[8] Conversely, aspirin, the most prolific anti-inflammatory drug worldwide, has been shown to reduce the incidence and mortality of several cancers (eg, colorectal) and is being considered for daily prophylaxis.[9] Therefore, the complex interactions between immune cells and tumor cells play a major role in tumor development, including tumor growth, invasion and metastasis, and subsequent patient outcomes.

Tumor-associated inflammatory cells (TAICs), including dendritic cells (DCs), macrophages, lymphocytes, and mast cells (MCs), have been recognized for many years in several tumors,[6,10–16] where they can play both protumorigenic and antitumorigenic roles (Jekyll and Hyde role), depending on cell number, state of activation, and surrounding microenvironment. It has been suggested that dysfunction of DCs induced by the tumor is a critical mechanism for escaping immune surveillance in cancer.[17,18] The role of TAICs in cancer, however, is not fully understood.

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In the thyroid gland, there are 4 primary types of thyrocyte-derived carcinomas: well-differentiated thyroid carcinomas (WDTCs), including PTC and follicular thyroid carcinoma (FTC), poorly differentiated thyroid carcinomas (PDTCs), and anaplastic thyroid carcinomas (ATCs). PTC is the most common thyroid malignancy (80%–90%), and it is usually associated with an excellent prognosis and therapeutic response, primarily surgical. However, 10% to 30% of PTC patients who have undergone primary thyroidectomy and radioiodine treatment develop recurrences and metastases, largely in regional lymph nodes, that are usually sensitive to further radiodine treatment. In contrast, ATC, the most aggressive form of thyroid carcinoma, has a dismal prognosis because patients with ATC are rarely candidates for surgery, and their tumor is typically resistant to conventional treatments. Therefore, there is a need for new treatment modalities, including targeted therapies and/or immunotherapies, mostly in patients with advanced and/or poorly differentiated cancers, where conventional treatments with surgery and radioiodine therapy are not (or no longer) effective.

On the genetic level, PTC harbors distinct molecular alterations that are mutually exclusive: the point mutations in the *BRAF* or (*H*, *K*, and *N*) *RAS* genes, and *RET*/*PTC* rearrangements. These genetic alterations are present in up to 70% of PTC cases, with *BRAF* mutation the most common (approximately 40% of PTCs),[19] and result in activation of the mitogen-activated protein kinase cascade. The oncoproteins expressed in PTC may trigger a proinflammatory program in tumor cells by release of cytokines/chemokines and/or upregulation of their receptors.[20–26] *BRAF* mutations and *RET*/*PTC* rearrangements are highly specific for PTC,[19] although they may also be present in a subset of ATCs that are probably derived from PTC. In contrast, *RAS* gene mutations can also be found in up to 40% of thyroid follicular adenomas (FAs).

This article focuses on the major types of TAICs, including their general role in cancer and, more specifically, their role and distribution in the major thyrocyte-derived carcinomas. The role of the TAIC-related immunomodulators (cytokines and chemokines) in thyroid cancer is also briefly discussed.

TUMOR-ASSOCIATED INFLAMMATORY CELLS

The cell population in any cancer, including thyroid cancer, is heterogeneous, not solely comprising neoplastic cells but also consisting of various amounts of fibroblasts, endothelial cells, and TAICs, depending on tumor type, size, stage, and prior treatment (**Box 1**).[7] In some cancers, such as lymphoepithelial carcinoma or seminoma, neoplastic cells may be obscured by the reactive TAICs, which are composed mainly of T lymphocytes.[27,28] Tumor-infiltrating macrophages (TAMs) can represent up to 50% of the tumor mass in some cancers, including ATCs.[29,30] On the other hand, some of these TAICs are not apparent on routine microscopic examination and may require immunohistochemistry for detection and phenotypic characterization.[31] In general, pathologists tend to regard TAICs in cancer only as part of the background architecture or reactive milieu, with a main focus on the architectural, histologic, and cytologic features of the tumor proper, for diagnostic and prognostic reporting. Recent studies demonstrate that nonneoplastic elements, such as TAICs, may predict the clinical behavior of a cancer even better than the characteristics of the neoplastic cells themselves.[32]

Box 1
Tumor-associated Inflammatory Cells in Thyroid Cancer

1. Different types of tumor-associated inflammatory cells are present in thyroid cancer.
2. Cancer cells attract inflammatory cells through the release of many chemokines.
3. These cells play a major role in thyroid cancer where they can be both protumorigenic or antitumorigenic.
4. In contrast to other thyroid cancers, papillary carcinoma is characterized by the presence of numerous intratumoral dendritic cells.
5. Anaplastic thyroid carcinoma is characterized by the presence of numerous intratumoral macrophages with peculiar morphology.

DENDRITIC CELLS

DCs originate from hematopoietic precursors in the bone marrow and subsequently migrate to peripheral tissues where they mature. DCs are highly specialized (so-called professional) antigen-presenting cells that play a major role during the primary immune responses against pathogens and tumors.[10,33–35] After cytokine exposure, immature DCs, including Langerhans cells, migrate from peripheral tissues to lymphoid organs, where they participate in antigen-specific immune responses.[36,37] They subsequently lose their ability to capture and process antigens (including tumor antigens) and acquire the ability