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Dendritic cells in the thyroid lesions: Viewpoint

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Abstract:

Thyroid cancer accounts for around 2% of all human cancers. Most of the cases will respond very well with current therapy; however, 10–30% of them will present recurrent disease and part of them will stop responding to radioiodine treatment and subsequently metastasize. Thyroid nodular proliferations are extremely common and up to 7% of the general population develops clinically palpable thyroid nodules. The evaluation of clonality in these proliferations has identified a large proportion of monoclonal nodules supporting the notion of hyperplasia-neoplasia sequence. The association between thyroid cancer and thyroid inflammation (immune cells of the tumour ‘s microinviroment) has been repeatedly reported. This association reinforces that the immune system is important for the development and progression of the thyroid cancer. In support, thyroid papillary carcinomas may evolve in a background of Hashimoto’s thyroiditis and chronic lymphocytic thyroiditis. The dendritic cells, professional antigen-presenting leukocytes, represent key players in the immune mechanism of tumours. These immunocytes infiltrate the microenvironment of the follicular-patterned thyroid lesions and the balance of protumor and antitumor activity of these cells may be associated with the evolution and the progression of these lesions.

Keywords: Dendritic cells, thyroid, carcinoma.

1 Background:

Dendritic cells: The dendritic cells (DCs) are professional antigen-presenting leukocytes that are found in nearly every tissue in the human body [1]. They have the ability to present antigen in the context of MHC class II and costimulatory molecules. Accordingly, they are extremely efficient stimulators of immunity and are considered to be key players in initiating the body’s immune response [2]. DCs mature from precursor CD34+ stromal cells (dendritic interstitial cells [DICs]) or monocytes. They have been historically classified either by their presumed origin (myeloid, and plasmacytoid dendritic cells) or by their spatial distribution (circulating blood dendritic cells, draining lymph node dendritic cells, epidermal dendritic cells, and dermal dendritic cells [3-5].

2 Dendritic cells in the follicular lesions of the thyroid gland:

DCs were previously examined in some benign and malignant follicular lesions. Hirokawa et al reported the expression of S100 positive DCs in adenomatous goitre (few cells), follicular adenoma (few cells), and follicular carcinoma (large number of cells) in the subcapsular area and/or the hyalinized stroma [6]. Batistatou et examined the distribution of S-100+ DCs and CD34+ DICs in nodular hyperplasia and neoplastic lesions of the thyroid gland. Dense infiltrates of S-100+ DCs were noted in the neoplastic conditions (majority of papillary carcinomas), specifically at the periphery and within the tumor capsule Sparse infiltrate was noted in the non-neoplastic lesions. These findings suggest a possible role for DCs in the development and progression of these lesions [7]. Pusztaszeri et al. assessed the presence of DCs that were positive for CD1a in cytologic samples of histologically confirmed papillary thyroid carcinomas and in a control group of benign thyroid nodules. CD1a-positive DCs were identified in 97% papillary thyroid carcinomas in thyroid fine-needle aspiration specimens. DCs were largely present in two distinct patterns: either as isolated DCs in the background or as associated with tumor cells. Both thyrocyte-associated DCs and background DCs were more numerous in papillary thyroid carcinomas fine-needle aspirations than in benign thyroid nodule fine-needle aspirations, but only the thyrocyte-associated group of DCs was statistically significant, suggesting that malignant cells are able to recruit DCs during carcinogenesis [8]. Similarly, Yu et al examined the distribution of the DCs in the cytological preparations from patients with papillary thyroid carcinomas and the benign thyroid nodules. CD1a-positive DCs were present in FNA specimens of papillary thyroid carcinomas, typically in close association with tumour cells, whereas they were rare in the benign thyroid nodules. The increased presence of CD1a-positive DCs in papillary thyroid carcinomas may be a useful diagnostic adjuvant [9]. Hilly et examined the S100 positive DCs in thyroid lesions. Sparse DCs were found in normal thyroid tissue. There was increased density of these cells in thyroiditis and inn papillary carcinoma. Dendritic cell density in papillary carcinoma correlated with the thyroiditis grade and dendritic cell density in surrounding areas of thyroiditis [10]. Likewise, Proietti et al. selected 91 consecutive cases of follicular variant of papillary thyroid carcinomas, in which they evaluated the presence of mature and immature DCs. In intratumoral and peritumoral areas, the expression of immature marker of DC was significantly higher in follicular variant of papillary thyroid carcinomas than in adenomas [8].

Dendritic cells (DCs) have a unique capacity to elicit primary and secondary antitumor responses. In thyroid malignancies, DCs are suggested as an important element of both tumour defence and tumour immune evasion mechanisms. Several previous investigations support this notion. Tsuge et al. reported the infiltration of DCs in the differentiated thyroid carcinomas. Thyroid tissues were obtained at thyroidectomy from 85 patients with primary thyroid cancer, most with papillary thyroid carcinomas had a higher frequency of CD1a+ immature DCs than other thyroid tumours [11]. A series of 527 consecutive cases of thyroid carcinoma treated by total thyroidectomy was examined by Ugolini et al. They examined the inflammatory infiltrate in these tumours. Immature DCs were detected in the papillary thyroid carcinomas and markedly reduced in undifferentiated thyroid carcinomas, suggesting the protective role of DC and infiltrating lymphocytes against thyroid tumors [12]. Hilly and his colleagues investigated specimens from 69 cases of papillary thyroid carcinomas, counting S100+ DC. DC density in papillary thyroid carcinomas correlated with the thyroiditis grade and DC density in surrounding areas of thyroiditis [10]. The association between papillary thyroid carcinomas and DCs suggested that the infiltration of DC may be

linked to a complex immunological phenomenon caused by carcinogenesis.

3 Cross-talks between the neuroendocrine and immune system:

DCs represent key players in the immune mechanism of tumours. The immunoregulatory properties of DCs strongly depend on the microenvironment in which DCs have been matured and activated. Thyroid hormones are an important part of this environment and regulate many vital processes including growth and cellular metabolism. The potential for DCs to amplify immune function in an antigen-specific manner makes them ideal candidates for cancer immunotherapy, which attempts to eradicate tumors by manipulating the body's own innate immune mechanisms [2] [13,14].

There is a bidirectional cross-talk between the neuroendocrine and immune systems which orchestrates immune responses in both physiologic and pathologic settings. This proposes that there is an immune-endocrine bridge associated with dendritic cells, and the endocrine cells. This proposition is supported by several experimental leads. In animal model, using a discontinuous trypsinization procedure, a DC population represented 2% to 3% of the thyroid cell suspension in the thyroid glands of pigs [15]. Using highly enriched populations of B cells, T cells, and dendritic cells, Bagriacik and his colleagues reported the presence of trace amounts of Thyroid-stimulating hormone-receptors (TSHr) precipitated from B cells and T cells. In contrast, high levels of TSHr were precipitated from the dendritic cell fraction [16]. Intrathyroidal dendritic cells (DC) isolated at the same time and then cultured with thyrocytes in the presence of thyrotropin (TSH) keep a phenotype of immature DC. In cell culture mode, DCs cultured with TSH, proliferated increasing their population 2- to 3-folds. In the presence of TSH, DCs acquired and maintained a high capacity for internalizing labeled ligands, expressed the mannose receptor, and exposed MHC class II molecules at the cell surface [17]. In contrast, DCs populations cultured without TSH decreased by more than 75% due to a loss of cell-substrate adhesion and subsequent cell death. DCs were devoid of endocytic activity and mannose receptor and, and lost exposure of MHC class II molecules at the cell surface. Therefore, it is conceivable that in response to TSH, the thyrocytes are able to produce soluble factors capable of activating proliferation and endocytic activity of DC. This TSH-regulated signaling process between the thyrocytes and DCs suggest that the thyroid follicular cells can promote and maintain the DCs within the thyroid gland [17].

Thyroid-stimulating hormone (TSH), a central neuroendocrine mediator of the hypothalamus-pituitary-thyroid axis, can affect various aspects of immunological development and function. The thyroid hormone triiodothyronine has several roles in controlling the maturation and antitumor functions of dendritic cells (DC). The roles of TSH and thyroid hormone in the modulation of several roles of DCs is supported by several observations. Using a thyroid hormone receptor (TR) beta mutant mouse, Alamino et al reported that TRbeta signaling endowed DCs with the ability to stimulate antigen-specific cytotoxic T-cell responses during tumour development. T3 binding to TRbeta enhanced DC viability, migration to the lymph nodes, and its antigen-presenting capacity ability of DCs [18].

4 Chronic inflammation, immune response and the development of thyroid neoplasms:

A close relationship between inflammation (immune response) and cancer was first proposed by Virchow in 1863 who proposed that cancer can arise in a background of chronic inflammation. Presence of intratumor or peritumor infiltration of lymphocytes is evidence that the immune system may respond to neoplastic transformation. We previously examined the

immune cells (tumor infiltrating lymphocytes,TILs) in several tumours including melanocytic lesions, hepatocellular carcinomas and breast proliferative and neoplastic conditions. Moreover, we previously presented our view about the complex interactions among DCs and and melanoma cells [3-5]. In the thyroid pathologies, several observations suggest a link between chronic inflammation/immune response and the development of malignancies. Some thyroid malignancies such as papillary thyroid carcinfomas are markedly infiltrated by immune cells. The local immune response [19] and concurrent chronic lymphocytic thyroiditis may be associated with favorable/unfavorable prognostic profile of patients with thyroid carcinomas [20] [19] [21].

Hashimoto's disease, Graves' disease and chronic lymphocytic thyroiditis are common forms of thyroiditis. They are characterized by lymphocytic infiltrate. The rates of malignancy in thyroid nodules in patients having Hashimoto's thyroiditis ranged from 0.5% to 53% [22] [20] [23] [24] [25] . According to Chui et al., the follicular epithelium in chronic lymphocytic thyroiditis is not homogenous throughout the entire thyroid gland and incidental multifocal papillary microcarcinomas are often identified. In addition, some reports from clinical observations suggest that atypical lesions that are not microcarcinomas should be classified as either reactive or premalignant "dysplastic" foci [26].

Similar to the papillary thyroid carcinomas, strong diffuse staining was observed for HBME-1, cytokeratin 19, galectin-3, and cyclin-D1. In contrast, normal thyroid, reactive atypia, and follicular nodular disease were negative or, at most, exhibited focal weak staining for HBME-1, cytokeratin 19, and galectin-3. These findings showed the presence of atypical microscopic lesions in lymphocytic thyroiditis with an immunohistochemical profile similar to papillary thyroid carcinomas, suggesting the idea of a premalignant lesion preceding papillary thyroid carcinomas, arising in the context of severe chronic inflammation.The MAPK pathway plays an important role in the differentiated thyroid carcinomas, and three of its genes (BRAF, RET/ papillary thyroid carcinomas, and RAS) can suffer mutually exclusive genetic alterations which have been implicated in the pathogenesis of papillary thyroid carcinomas [27] [28].

Several authors have found RET/ papillary thyroid carcinomas rearrangements in the chronic lymphocytic thyroiditis. Different mechanisms could also explain the association between chronic lymphocytic thyroiditis and RET/ papillary thyroid carcinomas rearrangement. The first hypothesis is that chronic inflammation might facilitate the rearrangement. It is worth noting that the production of free radicals, cytokine secretion, cell proliferation, and other phenomena correlated with inflammation might predispose to the rearrangement in follicular cells [29].

The molecular mechanism that links inflammation and cancer is not completely understood so far. A link between thyroid cancer, in particular the papillary thyroid carcinoma, and thyroid inflammation/autoimmunity has long been recognized, although the precise relationship between the two diseases remains elusive. In support Toll-like receptor (TLR3) that signal the activation of innate and adaptive immunity [30] [31] [32] had been reported to be restricted primarily to DCs. McCall et al. showed that the papillary thyroid carcinoma cells express TLR3 RNA and that TLR3 signal systems are functional in these cells [33] [34].

5 Expert commentary:

In the thyroid pathologies, several observations suggest a link between chronic inflammation/immune response and the development of malignancies. The association between thyroid cancer and thyroid inflammation (immune cells of the tumour's

microenvironment) has been repeatedly reported [26,35-37].

6 Five-year view:

It is of the opinion of these authors that the dendritic cells possibly paly some roles. This author hypothesizes that "The development of the hyperplastic nodules, well-differentiated thyroid tumors of uncertain malignant potential and papillary thyroid carcinomas in a background of chronic lymphocytic thyroiditis is associated with alterations of the dendritic cells". It is possible that an understanding of the roles of the dendritic cells in the development of papillary carcinoma may help developing novel therapeutic strategies i.e. targeting these cells and their related mediators.

7 Key issues:

- As proposed by Virchow in 1863, there is possible relationship between inflammation (immune response) and cancer.
- There is a bidirectional cross-talk between the neuroendocrine and immune systems in both physiologic and pathologic states[2] [13,14].
- Intratumor or peritumor infiltration of lymphocytes is quite often noted in the papillary thyroid carcinomas.
- Immune/dendritic cells seems to play some roles in the development of papillary thyroid carcinomas.

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