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Thyroid cancer phenotypes in relation to inflammation and autoimmunity

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1. ABSTRACT

Thyroid cancer represents the most frequent endocrine neoplasm and is epidemiologically linked to a growing incidence worldwide, which is only in part explained by the increased detection of small cancers in a preclinical stage. Understanding the molecular pathogenesis of well-differentiated thyroid cancers and poorly-differentiated thyroid cancers has prompted interest into the identification of crucial signaling pathways and molecular derangements related to genetic and epigenetic alterations. Increasing attention has been recently focused on inflammation and immunity as major culprit mechanisms involved in thyroid tumourigenesis, through the detection of activated immune cells, pro-inflammatory cytokines, as well as signal integrations between inflammatory and proliferative pathways within the thyroid tumour micro-environment. In addition to playing important roles in tumour surveillance and rejection, the presence of tumour-associated macrophages and the activation of NF-κB signaling pathway are now reckoned as hallmarks and crucial mediator of inflammation-induced growth and progression of thyroid cancer. Thorough understanding of this immunological link and identification of novel molecular targets could provide unprecedented opportunities for research and development of diagnostic, prognostic and treatment strategies for thyroid cancer.

2. INTRODUCTION

Thyroid cancer is the most frequent endocrine neoplasia and its incidence rates are on the rise (1). Thyroid cancers are usually follicular or para-follicular in their origin, and lesions developing from follicular cells include well differentiated thyroid cancers (DTC), poorly differentiated (PDTC) and anaplastic (ATC) thyroid carcinomas (2). DTCs, which encompass papillary cancers (PTC) and follicular cancers (FTC), usually show a good prognosis after surgery and radioiodine therapy, yet 5–10% of cases progress to radioiodine refractory-disease. On the other hand, PDTCs and ATCs are therapy-resistant and prognosis is unfavorable (3). Medullary thyroid carcinoma (MTC), which originates from the para-follicular C-cells, is either sporadic or familial and, by the time of diagnosis, shows high rate of lymph node metastases, which can elude detection pre-operatively or even intra-operatively (4).

The role of inflammation in DTCs has been the focus of several studies published in the last 10 years, which have demonstrated positive associations between chronic inflammation and increased risk of developing DTC, suggesting that the inflammatory microenvironment is an essential component of cellular transformation and tumour progression (5-8). In support of this inference, there has been demonstration that local activities engaged in thyroid tumourigenesis and thyroid cancer progression are positively influenced by two major inflammatory components: inflammatory cells along with their humoral mediators presenting within the cancer site, and activation of oncoprotein-mediated signalling present in epithelial cancer cells. Inflammatory cells and mediators enrich the tumour stroma and partake in several processes such as tissue remodelling, tissue repair and neo-angiogenesis (9). Cancer stroma englobes both inflammatory cells engaged in antitumour effects and activated immune cells capable of pro-tumour immune responses, and the balance of antitumour/protumour immune responses culminates in the regulation of cancer suppression vs cancer progression (7,10). Cancer stroma thus plays a dominant role in the development and progression of DTCs (11-13), as well as it shows a potential role in MTC and PDTCs (5,14). The aim of this article is to provide an overview on the relationship between inflammation and thyroid cancer in relation to the immune mechanisms regulating thyroid cancer progression. To this purpose, our at-a-glance description will mainly focus on DTCs, where essential evidences related to different histotypes and relative clinical aspects will be collectively described, whereas information resumed in MTC and ATC will be presented separately.

3. INFLAMMATION AND DTCs

In general, two pathways have been proposed to explain the link between inflammation and DTCs (15): the extrinsic (microenvironment-driven) and the intrinsic (oncogene-driven) pathways.

3.1. Extrinsic pathway

3.1.1. Tumour-infiltrating inflammation

The extrinsic pathway is triggered by tumour-infiltrating inflammation that includes leukocyte infiltration, tumour-associated macrophages (TAM), cytokines, chemokines and vascular endothelial growth factor (VEGF) (16). In PTC, TAM and immature dendritic cells accumulate both in tumour stroma and at the invasive front of the tumor, and the strength of their infiltrate positively correlates with capsular invasion, extra-thyroidal extension and aggressive behaviour of the tumour (17).

According to a classical view, tumours are encircled by extracellular matrix (ECM) with its structural and specialized proteins, as well as by stromal cells, which comprises cancer-associated fibroblasts (CAFs), innate and adaptive immune cells, specialized mesenchymal cells, endothelial cells and pericytes. CAFs impact cancer progression by a number of mechanisms, such as remodelling of the ECM, induction of angiogenesis, recruitment of inflammatory cells, and by redirecting cancer cell proliferation via secretion of growth factors, immune suppressive cytokines, and mesenchymal-epithelial cell interactions (18). Cancer stroma contributes to create the so-called tumour microenvironment (TME), which enfolds a significant inflammatory cell infiltrate capable of acting pleiotropically (19). While some cells are engaged in antitumour effects (i.e., dendritic cells, tumour infiltrating lymphocytes, M1 macrophages), others instigate a pro-tumour immune response (i.e., neutrophils, mast cells, NK cells, tumour infiltrating lymphocytes, M2 macrophages), such that the (un) balance of antitumour/protumour immune responses intervenes to regulate cancer suppression vs cancer progression (7,10). Per se, TME acts as a reservoir of protumourigenic and proangiogenic cytokines, which are either produced by tumour cells, CAFs, innate or adaptive immune cells. The resulting inflammatory microenvironment is associated with the production of reactive oxygen species and oxidative stress initiated by the transcription of NF-kB, and perpetuated by activation of the MAPK pathway (19). Several lines of evidence state that TAMs promote cancer cell survival, proliferation, metastases, angiogenesis and immune suppression (20). Likely, the impact of TAMs on tumour progression depends on their specific reprogramming within the tumour. This process is influenced by factors related to local microenvironment such as hypoxia, locally released mediators (i.e. cytokines, growth factors), as well as metabolic products either released by cancer cells or other immune and stroma-related cells (21). Although pathways and mechanisms involved in TAMs reprogramming are not completely understood, activation of the AKT/mTOR pathway has been hypothesized to influence the inflammatory phenotype of DTC-associated macrophages (22).

Furthermore, Melillo et al (6) demonstrated the existence of a complex relationship between mast cells and thyroid cancer cells. In PTC, an increased density of mast cells was observed with respect to normal tissues, and this process is seemingly associated with a worse prognosis (6). *In vitro*, PTC cells recruited mast cells through tumour-derived VEGF-A; in turn, mast cells acted via histamine and chemokines (ex. CXCL-1, CXCL10) to induce cancer cell proliferation, survival and migration, by means of autocrine and a paracrine loops (6). Also TAMs and

mast cells have been experimentally and clinically shown to promote the progression of PTC (23).

3.1.2. Obesity-dependent inflammation

Obesity enhances the risk of at least 13 different cancers, and is a risk factor for tumour recurrence after curative surgery, poor survival, non-cancer-related as well as cancer-related mortality (24,25). Epidemiological linkage between excess body weight and thyroid cancers has been highlighted in cross-sectional studies (26,27) and confirmed in meta-analyses of cross-sectional (28) and prospective studies (26,27,29). In a pooled scrutiny of five U.S prospective studies, BMI was associated with thyroid cancer risk in both men and women, independent of tumour histology (30). Several lines of evidence suggest a potential role for adipose tissue (AT) accumulation in regulating TME pathophysiology, supported by associations found between obesity-dependent inflammation and cancer (31). As such, there is demonstration that hypoxia, chronic inflammation and oxidative stress, which are typical of obese subjects, could favour the development of a subgroup of DTCs characterized by resistance to both ^{131}I treatment and chemotherapy (31-33). The relevance of AT biology in thyroid tumourigenesis is mainly related to its ability to intervene both as a reservoir and regulator of key elements of the immune system, which involve production of immunomodulatory molecules and expression of their receptors within the AT (34,35).

It is known that AT englobes different cell populations, e.g. preadipocytes, mature adipocytes as well as immune and stromal cells. Pre-adipocytes have functional characteristics and transcriptional patterns of multipotent cells that are similar to immune cells, and can transdifferentiate into macrophages both *in vitro* and *in vivo* (36,37). Mature adipocytes share the ability to secrete cytokines acting as pro- or anti-inflammatory factors related to AT accumulation. Immune cells englobed in AT include pro-inflammatory T lymphocytes (predominantly CD8+), which contribute to local inflammatory cell activation by attracting macrophages, which perpetuate the inflammatory response within the AT (38,39). Both M1 and M2 macrophages can be found in AT (40). While resident M2 macrophages play dominant roles in AT physiology and are able to produce anti-inflammatory cytokines, M1-like macrophages are recruited and clustered within the AT as crown-like structures (CLSs) and, upon stimulation by IFNγ or lipopolysaccharide, they are able to produce pro-inflammatory cytokines, thus contributing to inflammatory pathways relating to insulin resistance (41-44). This suggests that M1 and M2 play opposed roles in AT pathophysiology as compared to that seen in DTCs. AT hypoxia may promote the M2 to M1 switching (45), and these macrophages are responsible for AT expression of TNFα, as well as production of discrete amounts of iNOS and IL6 (43). TNFα is a cytokine capable of anti-proliferative actions in a human PTC line, through a receptor-mediated mechanism (46). Nevertheless, the high TNFα exposure related to obesity seems to induce a state of TNFα resistance, which ultimately facilitates thyroid tumour progression (31,46) and metastatic diffusion (47). IL-6 is a cytokine involved in tumourigenesis (48), but its role in thyroid cancer is still confusing. Although results linking directly thyroid cancer to IL-6 are scant (49,50), IL-6 could be important for the inflammation microenvironment in thyroid carcinogenesis, influencing DTC development and progression (7,48). Recently, Kobawala et al (51) demonstrated that IL-6 mRNA expression is higher in the primary tumour tissues of PTC patients as compared to the corresponding adjacent normal tissues, and that serum IL-6 correlates with larger tumour size, presence of distant metastasis, extra-thyroidal extension and poor overall survival.

The obesity-related adipocytokine network could also play a role in relation to the development of thyroid cancer (7,31,33,52). Mature adipocytes produce leptin, which is involved in activation of monocytes and macrophages, stimulation of VEGF and angiogenesis, and suppression of anti-inflammatory cytokines. Leptin promotes cell migration of PTC, while inhibiting the migration of follicular cells (53). Studies *in vitro* demonstrated that leptin is able to stimulate a more aggressive PTC phenotype by activating the PI3K/AKT pathway (54). Moreover, leptin promotes the de-differentiation of thyroid cancer cells via the JAK2/STAT3 signalling pathway (55). Recently, Fan *et al* (56) demonstrated that leptin had negative prognostic significance in PTC, whereas it may play a protective role in FTC.

On the contrary, adiponectin, an adipocytokine capable of exerting strong anti-inflammatory, proapoptotic and antiproliferative effects, appears to be inversely correlated with occurrence and proliferation of DTCs, hence suggesting its protective effect against thyroid tumourigenesis (57). Accordingly, Cheng *et al* (58) found that, when tissues were negative for adiponectin receptors, tumours were significantly associated with extrathyroidal invasion, multicentricity, and higher TNM stage, demonstrating that the expression of adiponectin receptors could associate with a better prognosis. Further potential links between obesity-related inflammation and DTC are represented by ghrelin and obestatin. In particular, a recent review reported that lower levels of ghrelin would favour thyroid cell proliferation, whereas supra-physiological levels would have an inhibitory effect (33).

Obesity-induced inflammation involves other inflammatory components that could contribute to tumourigenesis. These components include matrix metalloproteinases (MMPs), which are associated with cancer-cell invasion and metastasis (59-62).

Finally, the possible association between obesity and autoimmune thyroid diseases might also play a role because of the link between chronic autoimmune thyroiditis and thyroid cancer (63).

4. INTRINSIC PATHWAY

4.1. Genetic alterations

The intrinsic pathway is driven by genetic alterations most frequently found in association with DTC, such as RET/PTC rearrangement and BRAF point mutation. Up to 70% of PTCs express non-overlapping mutations of RET, TRKA, RAS and BRAF genes, which encode the transcription of components of the mitogen-activated protein kinase (MAPK) cascade (5). Both point-mutations and genetic rearrangements can promote the constitutive activation of the tyrosine kinase activity of RET in the absence of ligands. Activation of RET by physiological ligands or by oncogenic conversion results in the phosphorylation of intracellular tyrosine residues, which serve as docking sites for the recruitment of signalling adapters (64-66).

Local activities engaged in thyroid tumourigenesis and thyroid cancer progression are positively influenced by the activation of oncoprotein-mediated signalling present in epithelial cancer cells. Studies investigating the role of the RET/PTC3 oncoprotein in the recruitment of immune cell populations into the tumour site (67-70) showed that the transplantation of RET/PTC3-expressing thyrocytes activates an inflammatory transcriptional program both *in vitro* and *in vivo*, and PTC-like lesions in mice were characterized by a leukocytic infiltrate mainly constituted by macrophages, with parallel increase in cytokine production within the tumour (71). Main humoral components of this program include mediators responsible for different pro-tumour effects, such as growth factors implicated in leucocyte recruitment and survival (G-CSF; GM-CSF, M-CSF), chemokines (CCL2, CXCL12), chemokines receptors (i.e. CXCR4) implicated in monocyte recruitment, angiogenesis and tumour-cell homing to lymph nodes, IL-8, L-selectin and proteases responsible for tumour invasion and dissemination. RET/PTC3-positive thyroid cancers were also found to induce recruitment of CD11b+, Gr1+ cells capable of mediating tumour escape from the immune surveillance (72). Oppositely, the expression of the RET/PTC3 isoform in a rat thyroid cell line (PC Cl3) was demonstrated to increase NF-kB DNA-binding activity with consequent increase in the pro-inflammatory cytokine secretion (73).

NF-kB is a transcription factors laying at the intersection between the intrinsic and extrinsic proinflammatory pathways related to tumourigenesis (15). High constitutive expression of NF-κB is a primary feature of cancer cells but not normal cells, indicating a crucial role for NF-κB in regulating tumourigenesis (74). NF-κB comprises a family of transcription factors involved in transcription of different genes controlling apoptosis, immune response and inflammation, as well as cancer development and progression. Activation of NF-κB results from different signalling pathways triggered by cytokines, growth factors, and tyrosine kinases (75,76). NF-κB is also recognized to play a major role in the initiation and progression of thyroid carcinoma (77,78). In thyroid cancer cells, oncogenic proteins RET/PTC, RAS and BRAF can induce NF-κB activation in PTC, FTC, and MTC, while constitutively de-regulated NF-κB activity has been found in ATC (75). In a subset of PTCs associated with unfavourable outcome, it has been shown that NF-κB-mediated anti-apoptotic effects are enhanced by over-activation of Ras-related C3 botulinum toxin substrate 1 (RAC-1b), a hyperactive variant of the RAS superfamily of small GTP-binding proteins (79).

4.2. The immune network

Conflicting reports deal with the association between the prognosis of PTC and the degree of lymphocytic infiltration surrounding and/or inside the tumour (80-83). Several studies suggest that the immune response might be important in preventing metastases and recurrence of thyroid cancer, improving disease-free survival (63,84,85). On the contrary, other studies showed that patients with tumour-associated lymphocytes exhibited higher disease stage and increased incidence of invasion and lymph node metastases compared to patients without lymphocytes, or with background thyroiditis (13,86,87).

Moreover, recent studies (88,89) showed important clinical implication of autoimmunity on tumour behaviour; in particular, Stassi et al (89) demonstrated that IL-4 and IL-10 activation induce thyroid cancer cells resistance to chemoterapeutic agents.

Autoimmunity stimulates the production of higher levels of proinflammatory cytokines with growth factor activity (IL-17, IFN-γ and TNF-α) and the angiogenesis enhanced by TNF-α and VEGF (84,90-94). Moreover, high-mobility group box 1 protein (HMGB1), a late inflammatory cytokine that signals danger to the immune system, and nitric oxide can be detected both in thyroiditis and PTC patients, and have been found to promote matrix remodelling, inhibit immune response and suppress cell cycle regulators, thus increasing the risk of PTC proliferation (95). Reactive oxygen species (ROS) also contribute to DNA damage and promote the epithelial-to-mesenchymal transition (62). Two hypotheses may explain the association between autoimmune thyroiditis and differentiated thyroid cancer. In both cases, RET/PTC rearrangement can contribute to modulate the autoimmune response (84,94,95). In fact, RET/

PTC rearrangement is considered specific for PTC but can also occur in non-neoplastic conditions like Hashimoto's thyroiditis (97). *In vivo* studies showed that RET/PTC rearrangement is more represented in PTC when it is associated with thyroiditis, whereas $BRAF^{V600E}$ are more often observed in PTC alone (67,88). According to this hypothesis, free radicals production, cytokine secretion, cellular proliferation as well as other phenomena related to local inflammation could predispose to RET/PTC rearrangement in follicular cells and favour tumorigenesis (98). The second hypothesis is supported by the observation that RET/PTC3 rearrangement expresses high levels of proinflammatory cytokines and proteins involved in the immune response (6,70,73,99). Likewise, there is evidence that RET/PTC1 rearrangement is able to induce the expression of genes involved in inflammation and tumour invasion, including chemokines, chemokine receptors, cytokines, adhesion molecules and matrix-degrading enzymes (69). Other gene alterations have been proposed to explain the association between thyroid cancer and autoimmune thyroiditis. For example, p63 protein is commonly expressed in both PTC and Hashimoto's thyroiditis (100), suggesting p63 expression as a potential link between these conditions (101). Moreover, the increased expression of p-Akt, Akt1, and Akt2 in thyroid cancer and autoimmune thyroiditis suggests PI3K/Akt pathway to be involved in both disorders (102).

Other molecules involved in the immune network relating to DTCs include chemokines, which contribute to the development and progression of cancer (103,104) and tumour metastasis (105,106). Chemokines are a family of about 50 chemotactic proteins (8–10 kDa) classified into four highly conserved groups—CXC, CC, C, and CX3C—based on the position of their first two cysteines adjacent to the amino-terminal region (107,108). These molecules can stimulate cell migration during inflammation, as well as the homeostatic transport of hematopoietic stem cells, lymphocytes, and dendritic cells (109,110). The activity of chemokines is mediated by receptors, which promote the signaling leading to the transcription of genes required for cell motility, invasion, interaction with the extracellular matrix, and cell survival (107,111,112). The main chemokine receptors expressed in thyroid cancer include CXCR4 and CCR7 (113,114). CXCR4 has been studied due to its association with the presence of extranodal extension and thus a more aggressive behavior and negative prognosis (115). CCR7 is also expressed in thyroid carcinoma cell lines (TPC-1) and thyroid cancer tissues (113,114), and is thought to contribute to tissue invasion and cellular proliferation (113). CCR3 is another receptor associated with development, progression, and aggressiveness of several types of cancer, included DTC (116,117).

Finally, recent analysis has focused on immune checkpoints as a prognostic and therapeutic tool for DTCs. In a study assessing immunostaining and mRNA levels of programmed death-ligand 1 (PD-L1), a macrophage-related cell surface glycoprotein regulating local inflammatory responses, more intense expression was observed in samples from DTCs than those from benign tumours, and increasing PD-L1 mRNA expression was demonstrated in more advanced tumour stages (118). Similarly, an increased expression of PD-L1 has been observed in advanced DTCs and ATCs, both at the cellular level and on tumour-associated lymphocytes (119). While these findings await confirmation in Tregs, TAMs, and immature dendritic cells, it appears feasible that studies focusing on immune checkpoint inhibitors in DTCs could lead the way to test new therapeutic strategies (120).

Immunotherapies show promise for providing oncologists with a novel array of therapeutic tools in the near future (121). Cancer immunotherapies have been approved in recent years, including preventive and therapeutic cancer vaccines (122), the first immune checkpoint inhibitors (123,124), a bi-specific T-cell engager, and an oncolytic virus (125). Experience with ipilimumab (CTLA-4 antagonist), nivolumab and pembrolizumab (PD-1 antagonists), and atezolizumab (PD-L1 antagonist) has shown a marked impact on overall survival in cancer patients. Immune checkpoint inhibitors that target the PD-1 pathway generated the greatest interest, with response rates across tumour types that averaged 20-30% (126). Intuitively, the effectiveness of the combination of CTLA-4 and PD-1/PD-L1 blockade on overall survival (OS) will be proved to be higher than single therapy (such as in other cancers) (127). However, the use of immune checkpoint inhibitors in aggressive thyroid cancer has not been extensively investigated yet, and further studies in a large number of patients are warranted.

5. INFLAMMATION AND MTC

Data regarding the potential link between MTC and cancer-related inflammation (CRI) originate from few *in vitro* studies. In MTC, the intrinsic pathway, which is driven by genetic alterations associated with thyroid carcinogenesis, seems to play a major role in this link. Germline point mutations of proto-oncogene RET are known to be responsible for almost all familial MTC in multiple endocrine neoplasia (MEN) type 2A and 2B, and familial medullary thyroid carcinoma (FMTC), while somatic point mutations are found in up to 50% of patients with sporadic MTC (128).

RET encodes for the tyrosine kinase receptor of growth factors belonging to the Glial cell-Derived Neurotrophic Factor (GDNF) family, the stimulation

of which activates a variety of signalling pathways, such as the RAS/ERK, the PI3-K/AKT and the MAPK pathways, which are involved in cell survival and differentiation. Gain-of-function mutations of RET cause a constitutive activation of the tyrosine kinase activity of the receptor in the absence of ligands, leading to tumour development and progression (129).

In vitro studies (129) demonstrated that GDNF stimulation induced high level of interleukin-8 (IL-8) production in the TT medullary thyroid carcinoma cell lines. IL-8 is a pro-inflammatory, mitogenic and proangiogenic chemokine that is known to be involved directly in tumour growth, cell migration, and angiogenesis in an autocrine or paracrine way, or indirectly by attracting infiltration cells, including neutrophils and macrophages; therefore, its expression in tumour cells may affect their biological properties such as invasion and metastatic ability (16,129). Transcription of IL-8 is known to depend on activation of Nuclear factor interleukin-6 (NF-IL-6) and NF-kB (129,130).

Two reports have associated RET-mediated carcinogenesis with NF-κB activation, so far (76,130). Ludwig *et al.* (131) found that NF-κB was strongly expressed in tissue specimens from parafollicular C-cell carcinomas, and *in vitro* data suggested that NF-κB-dependent transcription plays an essential role in the development of MTC induced by both oncogenic RET isoforms, i.e. those harboring the mutations C634R or M918T, responsible for MEN 2A and MEN 2B, respectively. Gallel *et al.* (76) also demonstrated that the expression of mutated RET induces an increase in NF-κB DNA-binding activity and a consequent increase in pro-inflammatory cytokine secretion.

RET-mediated transformation would be dependent on NF-κB delivered anti-apoptotic and mitogenic signals. Since most part of pro-inflammatory molecules are under NF-κB transcriptional control, it has been hypothesized that NF-κB could be involved in the regulation of pro-inflammatory program of thyroid cells, and this event would contribute to the onset of thyroid cancer (75).

6. INFLAMMATION AND ATC

There are studies suggesting that inflammation could also be a key factor involved in the development of ATC, one of the most lethal human malignancies. Many characteristics of the inflammatory status leading to enhanced tumour growth, invasion, angiogenesis, and metastasis, are similar between ATC and PDTC, that is the bridge between DTC and ATC.

Compared to DTC and normal thyroid, ATC and PDTC show an increased amount of TAMs accounting for about more than 50% of immune cells infiltrating ATC. Infiltrate of TAMs is higher in PDTCs and ATCs than in PTCs and FTCs, and positively correlated with the poor prognosis of PDTCs (17). TAMs usually form a “microglia-like” structure that is in close contact with cancer cells, and their inter-connection and density correlate with invasive features and worse prognosis of the tumour (21,132,133), as confirmed by the evidence that TAMs infiltrate promoted the invasiveness of ATC cell lines *in vitro* through production of CXCL8/IL-8 (21). In contrast to TAMs, infiltration of lymphocytes and dendritic cells, which are involved in antitumour response (7,10), is reduced or absent in ATC (134). In ATC cell lines, CXCL8/IL-8 plays a central role in cell proliferation both during unstimulated conditions and under the effect of pro-inflammatory stimuli, such as IL-1 and TNF-α (21,134). Recruitment of neutrophils within the thyroid gland, a crucial metastasis-promoting factor, is dependent on the amount of CXCL8 produced by the tumour cells when exposed to TNF-α (135,136). Moreover, there is evidence that reduced expression of CXCL8/IL-8 and MCP-1/CCL2 pathways by the oncolytic adenovirus dl922-947 is able to impair angiogenesis and macrophage infiltration, and to promote ATC cell death *in vitro* as well as tumour regression *in vivo* (137). In a recent study on a xenograft mouse model, it has been shown that several cytokines expressed in ATC cell lines and tumour tissues, such as IL-8, TGF-α, and TNF-α, can be down-regulated by suppressing the ubiquitin-like containing PHD and RING finger domains 1 (UHRF1) (138). The protein binds to specific DNA sequences, and recruits a histone deacetylase to regulate gene expression. This UHRF1-mediated effect was found to be associated with inhibited proliferation of ATC, both *in vitro* and *in vivo* (138).

Moreover, inflammatory conditions relating to production of INF-γ and TNF-α can promote the autocrine production of IL4, IL10, CXCL1/GRO-α, CXCL10/IP-10 in primary human ATC cells (as well as in DTCs), and potentially contribute to up-regulate anti-apoptotic pathways and chemo-resistance (89,139). Also mast cells are present in ATC, and their infiltrate is directly correlated with tumour invasiveness through production of soluble factors involved in epithelial-to-mesenchymal transition, with CXCL8/IL-8 acting, again, as main effector of this mechanism (133). Furthermore, mast cell-derived CXCL1/GRO-α and CXCL10/IP10 production increased ATC proliferation through the engagement of CXCR2 and CXCR3 expressed on thyroid cells (6). Interestingly, the activation of the CXCL10-CXCR3 axis was also induced by NK cell migration in ATC cell lines. Prostaglandin-E2 was identified as the main responsible for the ATC-mediated NK cell suppression (140).

At odds with results obtained in DTCs, there is no evidence of a connection between the oncogenetic

background of ATCs and inflammation. Likewise, no associations have been found between Hashimoto's thyroiditis or thyroid lymphoma and ATC incidence.

Finally, it is worth mentioning that observational studies in humans have investigated different inflammatory biomarkers as a tool to assess aggressiveness of different thyroid cancers subtypes. The neutrophil-to-lymphocyte ratio, a simple surrogate index of the systemic inflammatory response, was shown to be a prognostic factor in some types of cancers. In a cohort of 3,870 patients affected by benign or malignant thyroid diseases, the neutrophil-to-lymphocyte ratio differed between tumour cancer subtypes and was 3.8.-fold higher in ATC than in PDTC or PTC patients (141). Moreover, also eosinophilia refractory to steroids has been recently reported in an ATC patient (142). Finally, serum levels of IL10 and C-reactive protein in ATC patients were directly correlated with higher peripheral blood myeloid cells (MDSSCs), which are known to be immunosuppressive and cancer promoting (143).

7. CONCLUSIONS

The link between inflammation and thyroid cancer involves multiple components of the immune system, ECM, stroma, and AT (5), with pro-tumoural activity of inflammation being is opposed to anti-inflammatory effects favoring protection against cancer progression (7,10).

Within the tumour microenvironment, inflammatory cells, belonging both to innate (macrophages) and adaptive (lymphocytes) immune responses, are interconnected with fibroblasts, endothelial cells, adipocytes, and ECM through cytokines, chemokines and adipocytokines (16). Under the influence of transcriptional regulators, such as NF-kB, PI3K-AKT and MAPK, oncogenes connected to the different subtypes of thyroid carcinomas promote their furthermost proliferative effect on the tumor microenvironment.

As recently reviewed by Antonelly and coworkers, cancer-related inflammation could represent an important target for innovative diagnostic and therapeutic strategies in thyroid cancer (127). The molecular patterns of cytokines and chemokines are key orchestrators and could explain the involvement of the immune system in tumour progression. In fact, anticancer immunotherapy, in particular the immune checkpoint inhibitors, act by promoting lymphocyte activation in order to destroy cancer cells and counteract immune-suppressive signals produced by cancer cells (118). By doing so, they also activate immune memory, leading to a sustained anti-tumour response (118).

Further information on the inflammatory microenvironment may help to explain tumour aggressive behaviour and identify potential new targets of therapy.

8. ACKNOWLEDGEMENT

The authors declare that they have no competing interest.

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