MEDWIN PUBLISHERS
Committed to Create Value for researchers

Open Access Journal of Endocrinology
ISSN: 2578-4641

Immunological Oncogenic Factors in Differentiated Thyroid Cancer

Gyan Chand[1]* and Arshi Rizwan[2]

[1]Department of Endocrine Surgery, SGPGIMS, India
[2]Department of Nephrology, AIIMS, India

***Corresponding author:** Gyan Chand, Professor, Endocrine Surgery Department, SGPGIMS, Lucknow, India, Tel: 09451546353; Email: drgyanchandpgi@gmail.com

Mini Review
Volume 4 Issue 1
Received Date: April 24, 2020
Published Date: June 02, 2020
DOI: 10.23880/oaje-16000150

Abstract

Genetic variations or altered Immune system has cogently effect on progression and development of thyroid cancer. A significant number of immune-reactive cells generating during thyroid cancer showing its pronounced function and inflammation. However differential thyroid cancer has distinct immunological properties due to their cause of origin. Frequently finding of tumor-associated lymphocytes as well as differential immunological markers from tumor specimen after surgery of thyroid cancer are explicit evident of immunological sensitivity to this. The nature of this lymphocytic reaction is not well understood and underlying genetics cause of thyroid cancer varies based on its histology. Various confliction has been associated between thyroid cancer and thyroid inflammation are highly debated in the literature. It has been evoked by various study that, both molecular and epidemiological data showing types of diseases are closely related and this association reinforces that the thyroid cancer progression are paramountly affect by immune system.

The innate immune system provides an early first line of defense response that protects the host in a nonspecific manner. The cells involved are neutrophils, monocytes, macrophages and dendritic cells, which all interact with the adaptive immune system and play a prominent role in antitumor immune response by producing immune cells during prognosis of thyroid cancer. However, clinical and experimental research has shown that thyroid tumor escape from immune recognition and tumor-mediated suppression of antitumor immunity can pose a significant obstacle to successful thyroid cancer therapy. Here we are endeavoring immense knowledge of immunological aspects in differentiated thyroid cancer. We are including some evidential fact that immune response may be involved in thyroid cancer and may help to find more aggressive tumors. In this chapter, we discuss how significance of recent discovery of tumor markers to differentiated thyroid cancer, and how genetic variation and dysfunction of immune system to contribute thyroid cancer development and progression.

Keywords: Type 1 Diabetes Mellitus; Insulin; Immunotherapies; DCCT; High Risk Subjects

Abbreviations: DTC: Differentiated Thyroid Cancer; DTCs: Differentiated Thyroid Carcinomas; TLRs: Toll-Like Receptors; SNPs: Single Nucleotide Polymorphisms; NK: Natural Killer; DC: Dendritic Cells; CCR-6: Chemokine Receptor 6; TAM: Tumor Associated Macrophages; TIL: Tumor Infiltrating Lymphocytes; CTLs: Cytotoxic T Lymphocytes; TH cells: T helper cells; APCs: Antigen-Presenting Cells; TCR: T cell Receptors; DN: Double Negative; PBMCs: Peripheral Blood Mononuclear Cells; MNG: Multinodular Goiter.

Introduction

Differentiated thyroid cancer (DTC) is the most rapidly increasing cancer worldwide [1]. The association

between chronic inflammation and DTC has long been recognized. However, a mixture of immune cells and mediators infiltrate in tumor micro environment, associated with tumor progression and patient clinical outcome [2]. Genetic variations or altered Immune system has cogently effect on progression and development of thyroid cancer. A significant number of immune-reactive cells generating during thyroid cancer showing its pronounced function and inflammation. However differential thyroid cancer has distinct immunological properties due to their cause of origin. It is obvious that local immune response [3,4] and concurrent chronic lymphocytic thyroiditis [3,5] would be associated with insightful prognostic of patients with DTC expedite to clinician for immunotherapy.

Immunological Factors

The different immunological factors against differentiated thyroid carcinomas (DTCs) have long been demonstrated. Variation in the two major branches of the immune system, innate and adaptive immunity are deliberating immunological factors in DTC. The innate immunity system includes, recognition, phagocytosis and digestion of pathogens, induction of inflammation and presentation of antigens, whereas the adaptive immunity system produce antibodies, that is associated with a memory of immune responses induced by the innate immunity system [6].

Innate Immunological Factors

The importance of the innate immune factors, in limiting the cancer progression has been highlighted recently. These factors have direct molecular interactions with cancers cells and probably tumors are able to sense the innate immune factors. Innate immunity is thought to produce factors that drive antigen presentation toward induction of adaptive immune response. The Toll-like receptors (TLRs) is one of them, it belong to a family of receptors that take part in innate and adaptive immunity by activating both T-and B-cell-mediated immune responses [7]. A minimum of 11 human TLRs are activated by various bacterial and viral components and also by endogenous factors [8,9]. The activation of TLR-2 and TLR-4, the principal receptors for bacterial antigens (bacterial lipopolysaccharides), leads to secretion of cytokines, chemokines, and other proinflammatory mediators [7]. TLR-2 expression revealed no correlation with any clinical or histological parameters in follicular thyroid carcinoma and follicular thyroid adenoma [7]. TLR-2 and TLR-4 mRNA and protein expression have been reported in thyroid cells in vitro [10,11]. TLRs promote tumor progression in cancer by activating cell proliferation and taking part in tumor invasion [8,12]. Lack of expression, however, may imply immune cell recruitment failure and may lead to invasion of unattended tumor cells [7]. Thus, TLR4 play a prominent role in tumor progression in thyroid follicular cells by triggering signal pathway to dendritic cells for its effective response against antigenic tumors.

Earlier study was demonstrated that Hashimoto's thyroiditis was associated with an increased risk of developing PTC [13]. Also, genetic factors seem to be involved as a risk factor for PTC [14-18]. Indeed, several single nucleotide polymorphisms (SNPs) are thought to contribute to susceptibility to PTC [19-21]. TLR3 protein is overexpressed in human thyrocytes surrounded by immune cells in all patients diagnosed with Hashimoto's thyroiditis, suggesting that TLR3 overexpression can induce an innate immune response in thyrocytes, which may be important in the pathogenesis of HT and in immune cell infiltrates [22]. Other factors of innate immunity include Natural killer cells, Mast cells, Dendratic Cells, & Macrophages. The Natural Killer (NK) cells are more frequently present in the PTC as compare to the follicular thyroid cancer. The exhaustion of NK infiltration in advance stage of thyroid cancer imparts the weakness of the innate immunity [23]. The NK cell have cytotoxic property for the tumors therefore, the NK cell infiltration negatively correlates with the disease stage in PTC. In advance stage of PTC the frequency of cytotoxic NK cell tissue infiltration is directly proportion to progression of tumor. The Dendritic Cells (DC) positive for Chemokine Receptor 6 (CCR-6) are densely accumulated in PTC [24]. The detection of this immature DCs in inflammatory infiltrate of PTCs suggesting the protective role of DCs and infiltrating lymphocytes against thyroid tumors [25]. The expression of immature marker of DC was significantly higher in follicular variant of PTC than in adenomas, however PTC displayed a higher CD1aC DC infiltration compared to FTC and adenomas [26].

The mast cells are highly concentrated around the thyroid cancer cells, it has been found in one study as high as 96% of PTCs than in control, it induce invasive ability, survival, and DNA synthesis of thyroid cancer cell [27]. The activated mast cells in thyroid cancers release cytokines (IL-6, TNF-a, GM-CSF) and chemokines (CXCL10/ IP10 and CXCL1/ Gro-a) which promote the TC cell proliferation. The mast cell expression is high in PTC and follicular variant of PTC than the follicular tumors and also correlate with the infiltrative pattern of the tumors & microangiogenasis [28,29]. The Tumor Associated Macrophages (TAM) represent the M2 type and promote tumor progression. The tumor cells express antigens that are specific for macrophages like CD14, CD68, MAC387, CD163 and DAP12. The TAMs are increased in the TC and positively correlate with de-differentiation, lymph node metastasis, and large tumor size and reduce survival in PTC [30,31]. The extensive infiltration of TAMs is also correlates with capsular invasion and extrathyroidal

extention and decrease cancer related servivial in the PDTC [32].

Adaptive Immunity and Thyroid Cancer

The Adaptive immunity use to counteract the pathogens that evade or overcome the innate immune defense. Normally the components of the adaptive immune system are silent; however, when activated, the defence factors proliferating, and creating potent mechanisms to neutralize or eliminate the microbes. However the adaptive immune system work by specialized mechanism of T cell, B cell and cytokines regulation in a context of DTC development and progression. The T cells in tumors the so-called tumor infiltrating lymphocytes (TIL) have been studied intensively over the past years divided in following types- CD8C cytotoxic T cells CD8C cytotoxic T lymphocytes (CTLs). The TC cells, (CTLs, T-killer cells, killer T cells) are also known as CD8+ T cells, recognize and attack on tumor by binding to antigen associated with MHC1 molecules [33]. A high infiltration of CD8C T lymphocyte affiliated with outstanding survival of DTC patients indicates the cytotoxicity of these cells on tumor [34,35]. A low intratumoral CD8C/Foxp3C ratio was found in human BRAF V600E PTC, associated with increased expression of the immunosuppressive, suggests a BRAF-driven tumor-promoting microenvironment in DTC [36]. The T helper cells (TH cells) also known as CD4+ T cells assist, maturation of B cells, activation of cytotoxic T cells and macrophages. It recognizes and attacks on the tumor by binding with MHCII, which are expressed on the surface of antigen-presenting cells (APCs). Activated helper cells divide rapidly into Th1 and Th2 and secrete cytokines to assist in the active immune response.

Th1-mediated immunity is generally considered as antitumoral as it able to produce pro-inflammatory cytokines during inflammation [37]. In TC, the extent of tumor-infiltrating CD4C cells does not appear to predict patient outcome. And there is no differences in CD4C cell frequencies of tissue or peripheral blood between PTC and other TC patients [38]. Recently, reduced expression or a double negative CD4¡ CD8¡ lymphocyte population has been identified in TC. Frequency of these double negative lymphocyte was more abundant in PTC than in other TC [39]. The Regulatory T cell (Treg) Act as immunosuppressive to effector T cell (CTLs and Th), their major role is to shut down T cell-mediated immunity toward the end of an immune reaction and to suppress autoreactive T cells.

Tregs shut down antitumor immune response via the production of IL-10 or by expressing immunosuppressive molecules, including CTLA4, GITR, PD-1 and stimulate angiogenesis through the production of VEGF-A [40]. Moreover, increased PD-1C T cells in metastatic lymph nodes correlated with a more aggressive TC [41]. A higher Treg density was also observed in PTC samples compared with nodular goiter, and positively correlated to the stage of the disease [42]. Accordingly, in a study performed on 124 tissue samples from PTC micro carcinomas, high infiltration of Foxp3C Treg cells was associated with aggressive features of PTC micro carcinoma.

T cell Receptors

T cells are endowed with specialized receptors (the T cell receptor; TCR), to recognize and to eliminate cancer cells. The T cells are subdivided into two major populations distinguished by their surface expression of αβ and γδ T cell receptors (TCR). Both αβ and γδ T cells arise from common multipotent double negative (DN) precursors in the thymus, which can be further separated into four DN subsets based on CD44 and CD25 expression [43,44]. The T cells undergo extensive DNA rearrangements at the β, γ and δ TCR loci aiming to express functional TCR chains .The αβ TCR generally express CD4 or CD8 lineage markers and mostly fall into helper or cytotoxic/effector subsets, whereas, cells with the γδ TCR in humans usually do not express the lineage markers. They do not require conventional antigen presentation in the context of MHC [45]. IFN-γ, a major cytokine secreted by activated γδ T cells, has multiple anti-tumor effects including direct inhibition of tumor growth, blocking angiogenesis, or stimulation of macrophages. Therefore IFN-γ is a crucial cytokine in the γδ T cell–mediated anti-tumor responses. The role of tumor-infiltrating γδ T cell receptors in TC is still unknown.

In contrast to Tregs, regulatory B cells (Bregs) mainly suppress immune response via the production of interleukin 10 (IL-10) [46,47]. However, there are no specific transcriptions or surface molecular makers identified as Bregs. The most well-established concept of Bregs is the subtype of B cells producing IL-10, which are regulatory B10 cells. Furthermore, lots of studies demonstrated that the surface membrane marker CD5 was expressed on B cells. Meantime, CD19 is the well-established marker to identify B cells from peripheral blood mononuclear cells (PBMCs). Thus, it seems that the expression of CD5+CD19+ is a common feature or hallmark of regulatory B cells [46,48]. Cytokines are the major factors of immune defense regulating crosstalk between the diverse players of the immune system. Cytokines are also secreted by thyroid follicular cells and play a key role in the pathogenesis of autoimmune thyroid disease and contribute to TC initiation and growth.

IFNγ is a cytokine that mediates pleiotropic effects on the innate and adaptive responses to infection, and its deficiency or deficiency of its receptor has been reported to be related to the development of more tumors in mice exposed to

chemical carcinogens [49,50].

All three classes of IFNs, type I (IFN-a/b), type II (IFNg), and type three (IFN-λ/s), can induce apoptosis of tumor cells and control the circuits underlying cancer immunosurveillance [51]. In TC, type I and type II IFNs in vitro induced the expression of MHC-I molecules on human TC cell lines, thus impeding TC immunoevasion and potentiating TC susceptibility to immune destruction [52]. IL-1 promotes tumor growth through the induction of prometastatic genes (e.g., matrix metalloproteinases), angiogenic molecules (VEGF, CXCL8/IL-8, etc.) and cytokines (IL-6, TNF-a, and TGF-b).8 IL-1 stimulated thyroid cell proliferation and the in vitro production of IL-8 [53]. Alterations in serum concentrations of IL1β have been suggested to differentiate PTCs from atrophic thyroiditis [54]. The inheritance of the polymorphism rs2192752 in IL1 receptor (IL1R1) increases the risk of PTC, indicating an association of this IL with DTC [55]. IL10 is an anti-inflammatory factor and an important regulator of several aspects of immune responses [56]. Circulating concentrations of IL10 were investigated in different cancer types and were found to be associated with adverse disease stage or with negative prognosis in bone sarcoma, diffuse large B-cell lymphoma, gastric cancer, colon cancer, Hodgkin's lymphoma, hepatocellular cancer, melanoma, renal cell cancer, NSCLC, and pancreatic cancer [57-59]. In addition, [60] demonstrated that the concentration of IL10 was significantly higher in patients with PTCs associated with multinodular goiter (MNG) than in patients with MNG alone, suggesting that cancer patients would have a specific type of Treg that affects antitumor responses and may facilitate disease progression and worse prognosis.

IL4 is produced by Th2 cells, basophils, mast cells, and eosinophils and, similar to most of the cytokines, is able to regulate other immune molecules [61]. IL4 is one of the most important cytokines for the differentiation of CD4+ cells into Th1 and Th2 cells, essential effectors of immune responses [62]. Besides Th1 and Th2 cell production, IL4 also affects the phenotypes of B and T cells, leading to prolonged cell lifespans, which will affect tissue adhesion and inflammation [63]. On the contrary, IL4 and IL10 have been reported to exert a stimulatory effect on the growth of thyroid cancer cells. The production of IL4 and IL10 has been shown to be related to the promotion of thyroid tumor cell progression through the downregulation of BCL2 and BCL-XL (BCL2L1), leading to the death of a considerable number of cells. Although through different mechanisms, [64] suggested that concomitant Graves' disease and PTC that exhibited IL4 and IL10 expression were more likely to display apoptosis resistance, probably potentiating antiapoptotic factors, such as insulin-like growth factors.

IL6 is involved in both innate and acquired immunity and its production is affected by stimuli from other cytokines (IL1, IL17, and TNFα; (119). In innate immunity, IL6 is considered a regulator of acute-phase responses, through the activation of leukocytes and also the stimuli for the expression of acute-phase proteins [65]. IL6 also participates in acquired immunity, promoting B-cell differentiation and survival and plasma-cell production of antibodies [66]. There are strong positive associations between serum IL6 concentrations and tumor size, tumor stage, and disease progression in patients with gastric cancer, colorectal cancer, bone sarcoma, breast cancer, hepatocellular cancer, nasopharyngeal cancer, renal cell cancer, lung cancer, and melanoma [67-71].

Adipokines or adipocytokines are cytokines produced by the adipose tissue. They have different functions, such as regulation of appetite and energy balance, immunity, insulin sensitivity, angiogenesis, inflammation and acute-phase response, blood pressure, and lipid metabolism [72]. Recently Mitsiades, et al. [73] have demonstrated that serum adiponectin concentrations have protective effect against the development of this cancer. The induction of inflammatory responses by leptin involves its receptor b (LepRb), JAK2, and STAT3 signaling pathway [73], and all these molecules ultimately have an effect on the PI3K/AKT and MAPK signaling pathways. Thus, leptin interacts with several factors that participate in the main signaling pathways of DTCs and could represent one of the links between obesity and DTC. The expression of leptin and its receptor, OBR (LEPR), has already been reported to be associated with a high risk of lymph node metastases, worsening the prognosis of patients, suggesting that the participation of this adipokine in DTCs might be important for their progression [74].

Chemokines are chemotactic cytokines that cause the directed migration of leukocytes, and are induced by inflammatory cytokines, growth factors and pathogenic stimuli. Chemokines can be produced by TC cells, following the activation of the MAPK pathways by the RET/PTC, RAS and BRAF oncogenic drivers [75,76]. Thyroid cells produce several CXC chemokines, including CXCL1, CXCL8/IL-8, CXCL9, CXCL10 and CXCL11, in basal conditions and/or under the influence of specific stimuli [77,78].

Conclusion

The critical role of tumor microenvironment is part of debate in tumor initiation and progression. However a normal tissue microenvironment can suppress malignancy, but different mechanism of certain pathogenic tissues features are critical for tumor development [79,80]. The immunological factors in patients with DTC suggest the same immunological mechanisms are causal follicular and papillary thyroid cancer, although this hypothesis remains

to be confirmed. Different mechanism may account for a specific cancer in patients with DTC. Moreover, it can be difficult to compare the immunological abnormalities in these patients. Studies of tumor in patients DTC for whom there is a clear causal relationship between the immune genotype and infectious phenotypes provide plausible hypothesis concerning the underlying mechanism that can be tested in DTC patients.

Last, but not least, the variation in genetic susceptibility allels including some proteins involved in pathway identify as affected in DTC patients [46] may contribute to the reduced expression of CD4+ and CD8+ T cells. Beyond this genetic variation of T cell receptors the study of different protumorigenic and proangiogenic cytokines/ chemokines [81]. Is of more general value for improving our understanding of progression of tumor. Moreover, targeting these mediators could be exploited to block TC growth, since this strategy has been already developed for other tumors [82]. In conclusion molecular and cellular analysis of the tumor progression through the genetic and immunological study of different immune cells networks as well as angiogenesis/ lymphangiogenesis in different types of TC will result considerable implication in the discovery of diagnostic and prognostic markers and novel targets in this common endocrine malignancy.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global cancer statistics. CA Cancer J Clin 61(4): 69-90.

2. Cunha LL, Marcello MA, Ward LS (2014) The role of the inflammatory microenvironment in thyroid carcinogenesis. Endocrine-related cancer 21(3): 85-103.

3. Matsubayashi S, Kawai K, Matsumoto Y (1995) The correlation between papillary thyroid carcinoma and lymphocytic infiltration in the thyroid gland. Journal of Clinical Endocrinology and Metabolism 80(12): 3421-3424.

4. Gupta S, Patel A, Folstad A, Fenton C, Dinauer CA, et al. (2001) Infiltration of differentiated thyroid carcinoma by proliferating lymphocytes is associated with improved disease-free survival for children and young adults. J Clin Endocrinol Metab 86(3): 1346-1354.

5. Cunhaand LL, Ward LS (2012) Concurrent lymphocytic thyroiditis is associated to less aggressive papillary thyroid carcinomas. European Archives of Oto-Rhino-Laryngology 269(2): 699-700.

6. Janeway CA Jr, Medzhitov R (2002) Innate immune recognition. Annu Rev Immunol 20: 197-216.

7. Hagstrom J, Heikkila A, Siironen P, Louhimo J, Heiskanen I, et al. (2012) TLR-4 expression and decrease in chronic inflammation: indicators of aggressive follicular thyroid carcinoma. J Clin Pathol 65(4): 333-338.

8. Chen K, Huang J, Gong W, Iribarren P, Dunlop NM, et al. (2007) Toll-like receptors in inflammation, infection and cancer. Int Immunopharmacol 7(10): 1271-1285.

9. Kluwe J, Mencin A, Schwabe RF (2009) Toll-like receptors, wound healing, and carcinogenesis. Journal of Molecular Medicine 87(2): 125-138.

10. Rakoff-Nahoum S, Medzhitov R (2009) Toll-like receptors and cancer. Nature Reviews Cancer 9(1): 57-63.

11. Nishimuraand M, Naito S (2005) Tissue-specificm RNA expression profiles of human toll-like receptors and related genes. Biol Pharm Bull 28(5): 886-892.

12. Nicola JP, V´elez ML, Lucero AM, Fozzatti L, Pellizas CG, et al. (2009) Functional Toll-like receptor 4 conferring lipopolysaccharide responsiveness is expressed in thyroid cells. Endocrinology 150(1): 500-508.

13. Voulgarelis M, Ioannou S (2010) Toll-like receptors, tissue injury, and tumourigenesis. Mediators Inflamm 2010.

14. Repplinger D, Bargren A, Zhang YW, Adler JT, Haymart M, et al. (2008) Is Hashimoto's thyroiditis a risk factor for papillary thyroid cancer?. J Surg Res 150(1): 49-52.

15. Malchoff CD, Malchoff DM (2006) Familial nonmedullary thyroid carcinoma. Cancer Control 13(2): 106-110.

16. Sturgis EM, Li G (2009) Molecular epidemiology of papillary thyroid cancer: in search of common genetic associations. Thyroid 19(10): 1031-1034.

17. Elisei R, Romei C, Vorontsova T, Cosci B, Veremeychik V, et al. (2001) RET/PTC rearrangements in thyroid nodules: studies in irradiated and not irradiated, malignant and benign thyroid lesions in children and adults. J Clin Endocrinol Metab 86(7): 3211-3216.

18. Ciampi R, Knauf JA, Kerler R, Gandhi M, Zhu Z, et al. (2005) Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer. J Clin Invest 115(1): 94-101.

19. Lizis-Kolus K, Kowalska A, Kozak-Klonowska B, Siolek M, Sluszniak J, et al. (2010) Case report of a woman with monoclonal gammapathy and papillary thyroid carcinoma, diagnosed because of detection of CHEK2 (I157T) mutation in genetic examinations. Endokrynol Pol 61(5): 502-506.

20. Shifrin AL, Ogilvie JB, Stang MT, Fay AM, Kuo YH, et al. (2010) Single nucleotide polymorphisms act as modifiers and correlate with the development of medullary and simultaneous medullary/papillary thyroid carcinomas in 2 large, non-related families with the RET V804M proto-oncogene mutation. Surgery 148(6): 1274-1280.

21. Siraj AK, Al-Rasheed M, Ibrahim M, Siddiqui K, Al-Dayel F, et al. (2008) RAD52 polymorphisms contribute to the development of papillary thyroid cancer susceptibility in Middle Eastern population. J Endocrinol Invest 31(10): 893-899.

22. Salajegheh A, Smith RA, Kasem K, Gopalan V, Nassiri MR, et al. (2011) Single nucleotide polymorphisms and mRNA expression of VEGF-A in papillary thyroid carcinoma: potential markers for aggressive phenotypes. Eur J Surg Oncol 37(1): 93-99.

23. Harii N, Lewis CJ, Vasko V, et al. (2005) Thyrocytes express a functional Toll-like receptor 3: overexpression can be induced by viral infection and reversed by phenylmethimazole and is associated with Hashimoto's autoimmune thyroiditis. Molecular Endocrinology 19(5): 1231-1250.

24. Gogali F, Paterakis G, Rassidakis GZ, et al. (2012) Phenotypical analysis of lymphocytes with suppressive and regulatory properties (Tregs) and NK cells in the papillary carcinoma of thyroid. J Clin Endocrinol Metab 97(5): 1474-1482.

25. Tsuge K, Takeda H, Kawada S, Maeda K, Yamakawa M (2005) Characterization of dendritic cells in differentiated thyroid cancer. J Pathol 205(5): 565-576.

26. Ugolini C, Basolo F, Proietti A, Vitti P, Elisei R, et al. (2007) Lymphocyte and immature dendritic cell infiltrates in differentiated, poorly differentiated, and undifferentiated thyroid carcinoma. Thyroid 17(5): 389-393.

27. Tsuge K, Takeda H, Kawada S, Maeda K, Yamakawa M (2005) Characterization of dendritic cells in differentiated thyroid cancer. J Pathol 205(5): 565-576.

28. Melillo RM, Guarino V, Avilla E, Galdiero MR, Liotti F, et al. (2010) Mast cells have a protumorigenic role in human thyroid cancer. Oncogene 29(47): 6203-6215.

29. Proietti A, Ugolini C, Melillo RM, Crisman G, Elisei R, et al. (2011) Higher intratumoral expression of CD1a, tryptase, and CD68 in a follicular variant of papillary thyroid carcinoma compared to adenomas: correlation with clinical and pathological parameters. Thyroid 21(11): 1209-1215.

30. Acikalin MF, Oner U, Topcu I, Yasar B, Kiper H, et al. (2005) Tumour angiogenesis and mast cell density in the prognostic assessment of colorectal carcinomas. Dig Liver Dis 37(3): 162-169.

31. Kim S, Cho SW, Min HS, Kim KM, Yeom GJ, et al. (2013) The expression of tumor-associated macrophages in papillary thyroid carcinoma. Endocrinol Metab 28(3): 192-198.

32. Jung KY, Cho SW, Kim YA, Kim D, Oh BC, et al. (2015) Cancers with Higher Density of Tumor-Associated Macrophages Were Associated with Poor Survival Rates. J Pathol Transl Med 49: 318-324.

33. Ryder M, Ghossein RA, Ricarte-Filho JCM, Knauf JA, Fagin JA (2008) Increased density of tumor-associated macrophagesis associated with decreased survival in advanced thyroid cancer. Endocrine-Related Cancer 15(4): 1069-1074.

34. Russell JH, Ley TJ (2002) Lymphocyte-mediated cytotoxicity. Annu Rev Immunol 20: 323-370.

35. Cunha LL, Morari EC, Guihen AC, Razolli D, Gerhard R, et al. (2012) Infiltration of a mixture of immune cells may be related to good prognosis in patients with differentiated thyroid carcinoma. Clin Endocrinol 77(6): 918-925.

36. Cunha LL, Marcello MA, Nonogaki S, Morari EC, Soares FA, et al. (2015) CD8+ tumour-infiltrating lymphocytes and COX2 expression may predict relapse in differentiated thyroid cancer. Clin Endocrinol 83(2): 246-253.

37. Angell TE, Lechner MG, Jang JK, Correa AJ, LoPresti JS, et al. (2014) BRAF V600E in papillary thyroid carcinoma is associated with increased programmed death ligand 1 expression and suppressive immune cell infiltration. Thyroid 24(9): 1385-1393.

38. Ruffell B, DeNardo DG, Affara NI, Coussens LM (2010) Lymphocytes in cancer development: polarization towards pro-tumor immunity. Cytokine Growth Factor Rev 21(1): 3-10.

39. Yu H, Huang X, Liu X, Jin H, Zhang G, et al. (2013) Regulatory T cells and plasmacytoid dendritic cells contribute to the immune escape of papillary thyroid cancer coexisting with multinodular nontoxic goiter. Endocrine 44(1): 172-181.

40. Imam S, Paparodis R, Sharma D, Jaume JC (2014) Lymphocytic profiling in thyroid cancer provides clues for failure of tumor immunity. Endocr Relat Cancer 21(3): 505-516.

41. Wolf D, Sopper S, Pircher A, Gastl G, Wolf AM (2015)

Treg(s) in Cancer: Friends or Foe?. J Cell Physiol 230(11): 2598-2605.

42. French JD, Kotnis GR, Said S, Raeburn CD, McIntyre RC, et al. (2012) Programmed death-1+ T cells and regulatory T cells are enriched in tumor-involved lymph nodes and associated with aggressive features in papillary thyroid cancer. J Clin Endocrinol Metab 97(6): 934-943.

43. Ryu HS, Park YS, Park HJ, Chung YR, Yom CK, et al. (2014) Expression of indoleamine 2,3-dioxygenase and infiltration of FOXP3C regulatory T cells are associated with aggressive features of papillary thyroid microcarcinoma. Thyroid 24: 123240.

44. Porritt HE, Rumfelt LL, Tabrizifard S, Schmitt TM, Zúñiga-Pflücker JC, et al. (2004) Heterogeneity among DN1 prothymocytes reveals multiple progenitors with different capacities to generate T cell and non-T cell lineages. Immunity 20(6): 735-745.

45. Allman D, Sambandam A, Kim S, Miller JP, Pagan A, et al. (2003) Thymopoiesis independent of common lymphoid progenitors. Nat Immunol 4(2): 168-174.

46. Morita CT, Lee HK, Leslie DS, Tanaka Y, Bukowski JF, et al. (1999) Recognition of non-peptide prenyl pyrophosphate antigens by human gamma delta T cells. Microbes Infect 1(3): 175-186.

47. Dilillo DJ, Matsushita T, Tedder TF (2010) B10 cells and regulatory Bcells balance immune responses during inflammation, autoimmunity, and cancer. Ann N Y Acad Sci 1183: 38-57.

48. Blair PA, Norena LY, Flores-Borja F, Rawlings DJ, Isenberg DA, et al. (2010) CD19(+)CD24(hi)CD38(hi) B cells exhibit regulatory capacity in healthy individuals but are functionally impaired in systemic lupus erythematosus patients. Immunity 32(1): 129-140.

49. Hua F, Ji L, Zhan Y, Li F, Zou S, et al. (2012) Pulsed high-dose dexamethasone improves interleukin 10 secretion by CD5+ B cells in patients with primary immune thrombocytopenia. J Clin Immunol 32(6): 1233-1242.

50. Bach EA, Aguet M, Schreiber RD (1997) The IFNγ receptor: a paradigm for cytokine receptor signaling. Annu Review Immunol 15: 563-591.

51. Smyth MJ, Thia KY, Street SE, Cretney E, Trapani JA, et al. (2000) Differential tumor surveillance by natural killer (NK) and NKT cells. Journal of Experimental Medicine 191(4): 661-668.

52. Zitvogel L, Galluzzi L, Kepp O, Smyth MJ, Kroemer G (2015) Type I interferons in anticancer immunity. Nat Rev Immunol 15(7): 405-414.

53. Angell TE, Lechner MG, Jang JK, LoPresti JS, Epstein AL (2014) MHC class I loss is a frequent mechanism of immune escape in papillary thyroid cancer that is reversed by interferon and selumetinib treatment in vitro. Clin Cancer Res 20(23): 6034-6044.

54. Weetman AP, Bennett GL, Wong WL (1992) Thyroid follicular cells produce interleukin-8. J Clin Endocrinol Metab 75(1): 328-330.

55. Kammoun-Krichen M, Bougacha-Elleuch N, Mnif M, Bougacha F, Charffedine I, et al. (2012) IL-1β a potential factor for discriminating between thyroid carcinoma and atrophic thyroiditis. Eur Cytokine Netw 23(3): 101-106.

56. Park SW, Kim MK, Kwon KH, Kim J (2012) Association between a promoter polymorphism (rs2192752, -1028A/C) of interleukin 1 receptor, type I (IL1R1) and location of papillary thyroid carcinoma in a Korean population. International Journal of Immunogenetics 39(6): 501-507.

57. Akdis M, Burgler S, Crameri R, Eiwegger T, Fujita H, et al. (2011) Interleukins, from 1 to 37, and interferon-γ: receptors, functions, and roles in diseases. J Allergy Clin Immunol 127(3): 701-721.

58. Sato T, McCue P, Masuoka K, Salwen S, Lattime EC, et al. (1996) Interleukin 10 production by human melanoma. Clinical Cancer Research 2(8): 1383-1390.

59. Onishi T, Ohishi Y, Imagawa K, Ohmoto Y, Murata K (1999) An assessment of the immunological environment based on intratumoral cytokine production in renal cell carcinoma. BJU Int 83(4): 488-492.

60. Chen CJ, Sung WW, Su TC, Chen MK, Wu PR, et al. (2013) High expression of interleukin 10 might predict poor prognosis in early stage oral squamous cell carcinoma patients. Clin Chim Acta 415: 25-30.

61. Yu H, Huang X, Liu X, Jin H, Zhang G, et al. (2013) Regulatory T cells and plasmacytoid dendritic cells contribute to the immune escape of papillary thyroid cancer coexisting with multinodular non-toxic goiter. Endocrine 44(1): 172-181.

62. Howard M, Farrar J, Hilfiker M, Johnson B, Takatsu K, et al. (1982) Identification of a T cell-derived b cell growth factor distinct from interleukin 2. J Exp Med 155(3): 914-923.

63. Stassi G, Todaro M, Zerilli M, Ricci-Vitiani L, Di Liberto D, et al. (2003) Thyroid cancer resistance to chemotherapeutic drugs via autocrine production of

interleukin-4 and interleukin-10. Cancer Res 63(20): 6784-6790.

64. Vella V, Mineo R, Frasca F, Mazzon E, Pandini G, et al. (2004) Interleukin-4 stimulates papillary thyroid cancer cell survival: implications in patients with thyroid cancer and concomitant Graves' disease. J Clin Endocrinol Metab 89(6): 2880-2889.

65. Hurst SM, Wilkinson TS, McLoughlin RM, Jones S, Horiuchi S, et al. (2001) IL-6 and its soluble receptor orchestrate a temporal switch in the pattern of leukocyte recruitment seen during acute inflammation. Immunity 14(6): 705-714.

66. Hirano T, Taga T, Nakano N, Yasukawa K, Kashiwamura S, et al. (1985) Purification to homogeneity and characterization of human B-cell differentiation factor (BCDF or BSFp-2). Proc Natl Acad Sci 82(16): 5490-5494.

67. Niitsu N, Okamoto M, Nakamine H, Yoshino T, Tamaru J, et al. (2002) Simultaneous elevation of the serum concentrations of vascular endothelial growth factor and interleukin-6 as independent predictors of prognosis in aggressive non-Hodgkin's lymphoma. Eur J Haematol 68(2): 91-100.

68. Chow KC, Chiou SH, Ho SP, Tsai MH, Chen CL, et al. (2003) The elevated serum interleukin-6 correlates with the increased serum butyrate level in patients with nasopharyngeal carcinoma. Oncology Reports 10(4): 813-819.

69. Nikiteas NI, Tzanakis N, Gazouli M, Rallis G, Daniilidis K, et al. (2005) Serum IL-6, TNFα and CRP levels in Greek colorectal cancer patients: prognostic implications. World J Gastroenterol 11(11): 1639-1643.

70. Tas F, Oguz H, Argon A, Duranyildiz D, Camlica H, et al. (2005) The value of serum levels of IL-6, TNF-α, and erythropoietin in metastatic malignant melanoma: serum IL-6 level is a valuable prognostic factor at least as serum LDH in advanced melanoma. Med Oncol 22(3): 241-246.

71. Ahmed OI, Adel AM, Diab DR & Gobran NS (2006) Prognostic value of serum level of interleukin-6 and interleukin-8 in metastatic breast cancer patients. Egypt J Immunol 13(2): 61-68.

72. Kwon H, Pessin JE (2013) Adipokines mediate inflammation and insulin resistance. Front Endocrinol 4: 71.

73. Mitsiades N, Pazaitou-Panayiotou K, Aronis KN, Moon HS, Chamberland JP, et al. (2011) Circulating adiponectin is inversely associated with risk of thyroid cancer: in vivo and in vitro studies. J Clin Endocrinol Metab 96(12): 2023-2028.

74. Cheng SP, Chi CW, Tzen CY, Yang TL, Lee JJ, et al. (2010) Clinicopathologic significance of leptin and leptin receptor expressions in papillary thyroid carcinoma. Surgery 147(6): 847-853.

75. Melillo RM, Castellone MD, Guarino V, De Falco V, Cirafici AM, Salvatore G, Caiazzo F, Basolo F, Giannini R, Kruhoffer M et al. (2005) The RET/PTC-RAS-BRAF linear signaling cascade mediates the motile and mitogenic phenotype of thyroid cancer cells. J Clin Invest 115(4): 1068-1081.

76. Borrello MG, Alberti L, Fischer A, Degl'innocenti D, Ferrario C, et al. (2005) Induction of a proin flammatory program in normal human thyrocytes by the RET/ PTC1 oncogene. Proc Natl Acad Sci U S A 102(41): 14825-14830.

77. Rotondi M, Coperchini F, Chiovato L (2013) CXCL8 in thyroid disease: from basic notions to potential applications in clinical practice. Cytokine Growth Factor Rev 24(6): 539-546.

78. Antonelli A, Ferrari SM, Fallahi P, Piaggi S, Di Domenicantonio A, et al. (2012) Variable modulation by cytokines and thiazolidinediones of the prototype Th1 chemokine CXCL10 in anaplastic thyroid cancer. Cytokine 59(2): 218-222.

79. Bissell MJ, Hines WC (2011) Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. Nat Med 17(3): 320-329.

80. Granata F, Frattini A, Loffredo S, Staiano RI, Petraroli A, et al. (2010) Production of vascular endothelial growth factors from human lung macrophages induced by group IIA and group X secreted phospholipases A2. J Immunol 184(9): 5232-5241.

81. Detoraki A, Staiano RI, Granata F, Giannattasio G, Prevete N, et al. (2009) Vascular endothelial growth factors synthesized by human lung mast cells exert angiogenic effects. J Allergy Clin Immunol 123(5): 1142-1149.

82. Wright KT, Giardina C, Vella AT (2014) Therapeutic targeting of the inflammome. Biochem Pharmacol 92(2): 184-191.