

Lymphocytes and thyroid cancer: more to it than meets the eye?

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Abstract

Immune responses by innate and adaptive immune cells are crucial for the suppression of carcinogenesis and tumor spread. Effector T cells such as, cytotoxic CD8⁺ T (CTL), natural killer (NK), and NK T cells (NKT cells) prevent tumor growth by their ability to induce apoptosis in cancer cells. To circumvent anti-tumor immunity, tumors commonly attract regulatory T cells (Treg), which suppress the function of CTL and NKT cells in a contact- and cytokine-dependent manner. Recent findings in patients with thyroid cancer have suggested that an imbalance between immune suppressive and anti-tumor cells occurs during thyroid carcinogenesis. However, the composition and regulation of immune responses in thyroid cancer are still elusive and a comprehensive immune profile of thyroid cancer is missing. In this issue of *Endocrine-Related Cancer*, Imam *et al.* compare immune profiles between patients with papillary thyroid carcinoma and autoimmune thyroiditis. Their data suggest that an imbalance between immunosuppressive Treg cells and effector T cells occurs during papillary thyroid carcinogenesis. Their study identified double-negative T cells as a novel key factor involved in this process. Future research is required to recapitulate these findings, to elucidate the mechanisms by which the immune response is regulated and to evaluate if this process might be used for the therapeutical management of thyroid cancer.

Key Words

- ▶ thyroid carcinoma
- ▶ tumor immunology
- ▶ Treg
- ▶ CD4⁻CD8⁻T cells

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Thyroiditis and thyroid cancer

In the beginning of the 19th century, the Japanese surgeon, Haku Hashimoto, first described a thyroid pathology dominated by fibrosis and diffuse lymphocyte infiltration. Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disorder. Hallmark of HT is the progressive loss of thyroid epithelial cells that are replaced by an infiltration of mononuclear cells (T cells) that eventually leads to thyroid atrophy and hypothyroidism (Caturegli *et al.* 2013, Jankovic *et al.* 2013).

The relationship between thyroiditis, especially HT, and differentiated thyroid cancer (especially papillary thyroid cancer (PTC)) has a long history of debate. The current literature on this topic is inconsistent and there

are conflicting data on the association between PTC and HT. While some studies suggest that these two thyroid conditions are positively correlated, others failed to find an association (Segal *et al.* 1985, Ott *et al.* 1987, Eisenberg & Hensley 1989, Di Pasquale *et al.* 2001, Mechler *et al.* 2001, Pisanu *et al.* 2003). However, it is important to note that the caveat is most pronounced between studies using paraffin-embedded tissue (i.e. thyroidectomy specimens) and those using fine-needle aspiration (FNA) biopsy samples. On the basis of FNA studies including over 18 000 patients, the prevalence of PTC in HT is estimated to about 1.2% with a non-significant risk ratio (RR) of 0.69. In contrast, prevalence of PTC in HT based on about 10 000 archival thyroid specimens is 27% (RR 1.59;

Ott *et al.* 1987, Kashima *et al.* 1998, Loh *et al.* 1999, Kebebew *et al.* 2001, Jankovic *et al.* 2013). Thus, limiting the analysis to archival thyroidectomy specimens might carry a selection bias because the indication for surgery is commonly due to the presence of suspicious nodules. On the other hand, there is a consensus that peritumoral chronic lymphocytic infiltration alters the clinical presentation of differentiated thyroid cancer. Kebebew and others found that chronic lymphocytes infiltration in patients with PTC correlates with an improved outcome or less aggressive disease (Eisenberg & Hensley 1989, Kashima *et al.* 1998, Kebebew *et al.* 2001).

At first notion, this does not match up as on the one hand lymphocyte infiltration might contribute to PTC carcinogenesis (i.e. pro carcinogenic) but on the other hand the presence of these inflammatory cells exert protective effects and is associated with a less aggressive disease (i.e. anti carcinogenic). Explanation is found in the diversity of these mononuclear cell that each not only present with unique cellular features – not seen on standard H&E microscopy – but also distinct functional properties ranging from pro-oncogenic and immunosuppressive to the ability to induce an effective host anti-tumor response (Guarino *et al.* 2010, Gogali *et al.* 2012).

Tumor infiltrating lymphocytes and cancer progression

The field of immunology expands at rapid pace and has been become much more complex than was initially thought when the difference between B- and T-lymphocytes was discovered in the late 1960s (Peterson 2012, Hillhouse & Lesage 2013). Today, there is no aspect in medicine that is not influenced or even controlled by the immune system.

Tissues are constantly challenged by a multitude of exogenous and endogenous stressors endangering their structural and genomic integrity. It is evident that the human immune system is not only responsible to protect the organism from the harmful outside intruders but also from the enemies within. For the latter, a comprehensive system identifies and eliminates mutated and dedifferentiated cells, using the innate and adaptive immune system (Coussens & Werb 2002, Peterson 2012). Homing of lymphocytes into the tumor stroma creates an environment, in which the immune system homeostasis and control of self-tolerance are strongly modified (Balkwill & Mantovani 2001, Coussens & Werb 2002). Cytotoxic CD8⁺ T cells (CTL), natural killer (NK), and NK T cells (NKT cells) are important suppressors of tumor

growth because of their cytotoxic function and ability to destroy cancer cells (Grivennikov & Karin 2010). Other populations such as the interleukin 10 (IL10)-producing CD4⁺ T-helper 1 (Th1) cells, the TGF- β -producing CD4⁺ Th3 cells, CD4⁺ CD25⁺ FoxP3⁺ T cells (regulatory T (Tregs)), CD4⁻ and CD8⁻ (double negative (DN)) T cells share the ability to inhibit immune response, induce tolerance, and help the neoplastic cells to escape the immune attack (Strober *et al.* 1996, Dittel 2008, Shevach 2009, Juvet & Zhang 2012, Peterson 2012, Hillhouse & Lesage 2013, Muranski & Restifo 2013). Interestingly, this fundamental concept that there is a strong link between chronic inflammation and cancer dates back to the 18th century when Virchow proposed that cancer initiates at sites of chronic inflammation (Balkwill & Mantovani 2001).

Over the last years, the various cell types that make up this immunoreactive tumor stroma have been delineated. These cells are characterized by their cell surface markers and the cytokines that they produce. Extensive research allowed to define how distinct T cell populations contribute to cancer progression. The most common ones express CD4 (T-helper cells) and CD8 (cytotoxic lymphocytes) (Peterson 2012).

CD4⁺ T-cells hold a key role in the modulation of immune response. These naïve CD4⁺ cells are capable to expand into functionally distinct subpopulations that express a unique set of cytokines. They are thought to differentiate into diverse forms with unique functional properties such as Th1, Th2, Th17, and Tregs. Tregs (CD4⁺, IL2 receptor α -chain (CD25⁺), and Forkhead box P3 (FoxP3⁺)) as a subset of T-lymphocytes, constituting 5–10% of CD4⁺ T cells, are defined by the presence of the FoxP3 transcription factor that is critical for their functional capacity (Shevach 2009, Sakaguchi *et al.* 2010). They mediate a multiplicity of actions, such as the inhibition of T cell-mediated autoimmune and anti-tumor response (Nishikawa & Sakaguchi 2010, Sakaguchi *et al.* 2010). Furthermore, they are able to induce tolerance by repressing CD4⁺, CD8⁺ cells as well as NK-cells, dendritic cells, mast cells, and monocytes/macrophages (Coutinho *et al.* 2005, Bluestone *et al.* 2008, Dittel 2008, Simpson *et al.* 2008, Akdis & Akdis 2009). Thus, Tregs play an important role in evasion of anti-tumor T cell response in cancer cells.

In addition, there are CD4 negative and CD8 negative (CD4⁻ and CD8⁻), thus DN Tregs that promote the development of tolerance (Strober *et al.* 1996). This cell population has been identified in xenotransplant models (Chen *et al.* 2003, Ma *et al.* 2008). On the basis of animal studies, it has been shown that DN cells show only limited suppressive function in naïve mice, while DN Tregs are

strongly suppressive in xenograft recipients and induce tolerance to such extent that organ rejection is prevented (Strober *et al.* 1996, Chen *et al.* 2003, Ma *et al.* 2008, Juvet & Zhang 2012). Similarly, tumors develop strategies to escape cytotoxic T cells and are able to induce a micro-milieu that inhibits the anti-neoplastic function of effector T cells and memory CD8⁺ T cells.

Tumor infiltrating lymphocytes in thyroid cancer

In this issue of *Endocrine-Related Cancer*, Imam *et al.* (2014) present in their study 'Lymphocytic profiling in thyroid cancer provides clues for failure of tumor immunity' a phenotypic analysis of thyroid tumor-associated lymphocytes and compare those with lymphocytes found in autoimmune thyroiditis. They show an infiltration of tumors with CD4⁺ and CD8⁺ T cells as well as CD3⁺ but CD4⁻ and CD8⁻ DN cells. Patients with PTC harbored a higher frequency of CD4⁺ FOXP3⁺ T cells when compared to patients with HT. Furthermore, the authors identified CD4⁻ and CD8⁻ DN T cells as a dominant cell type associated with thyroid cancer and showed that these cells produce IFN λ and IL17 when stimulated *ex vivo*. The authors claim that DN T cells downregulate proliferation and cytokine production of activated effector T cells and suggest that these DN T cells are responsible for the suppression of tumor immunity. The identification of DN T cells is a novel observation and if it holds true, it would not only add to the growing understanding on the role of tumor infiltrating lymphocytes in thyroid cancer but might open a new approach for thyroid cancer therapy.

However, previous studies have analyzed the T cell populations in thyroid cancer as well, but have failed to find a predominant DN T cell population. In a recent study by French *et al.* the group has identified CD4⁺ T lymphocytes as the predominant tumor-associated T cell population in PTC. An increase in CD4⁺ cells was found in larger tumors. The infiltration of PTC stroma with Tregs correlated with disease stage and metastasis. Interestingly, while Tregs were found in all tumor samples, their frequency was highly variable ranging from 12 to 36% of all CD4⁺ T cells (French *et al.* 2010). Similarly, Gogali *et al.* examined the thyroid gland of 65 patients with PTC, 25 patients with thyroid nodular goiter (TNG), and 50 healthy controls for the presence of lymphocyte infiltration (Treg and NK cells). The authors found that there was a significant increase in Treg infiltration in thyroid tissue of PTC patients compared with TNG samples. Interestingly, the difference was more

pronounced based on flow cytometry than compared with immunohistochemistry (IHC), indicating that limitations and potential lack of comparability between these techniques. Furthermore, Gogali *et al.* (2012) found a significant increase in the NK cell fraction (5.6 vs 2.7%), while CD4(+) (38 vs 32%) and CD8(+) (36 vs 30%) cell fractions remained unchanged. In their study, increased Treg infiltration was positively correlated with advanced disease stage, while NK infiltration was negatively correlated.

Imam *et al.* in his study reported an almost complete absence of Foxp3⁺ CD25⁺ CD4⁺ CD3⁺ T cells (0.332% in HT vs 44% in PTC), which is in conflict with what one would expect as multiple other diseases are associated with increased Treg. However, the data are supported by a study by Marazuela *et al.* who isolated mononuclear cells from 14 patients with autoimmune thyroid and determined CD4⁺ FOXP3⁺ cells to be <0.5% (Marazuela *et al.* 2006).

The study by Imam *et al.* comprises the challenge to rule out a potential contamination by effector T cells (CD25⁺) as there is no specific marker for DN Tregs. DN Tregs have to be distinguished from other CD4⁻/CD8⁻ populations such as mucosa-associated invariant T (MAIT) cells and, importantly, invariant NKT (iNKT) cells that are frequently CD4⁻/CD8⁻ (Treiner & Lantz 2006). Imam *et al.* present experiments show that the DN cells after stimulation with ionomycin/phorbol-12-myristate-13-acetate (PMA) produce high levels of IFN γ that has been shown to act pro tumorigenic. Thus, these DN cells appear to behave like effector cells. Furthermore, the observation that DN cells produce IL17 under stimulation requires further discussion. It is thought that IL17 is a key cytokine also produced predominantly by effector T cells (CD4⁺), whereas CD4⁻ cells only have limited potential to express IL17.

Th17 cells are thought to be the predominant source of IL17 in HT. However, others have shown alternate mechanism to induce HT by using a NOD-H2h4 mice model, which are deficient for IL17. In this model, the depletion of Tregs leads to the development of autoimmune thyroiditis. The authors argued that an increase in Th1 cell as a result of a Treg depletion can induce thyroiditis (Horie *et al.* 2011). Thus these alternate mechanisms of HT genesis might explain the observations made by Imam *et al.* and might set the stage for the expansion of a DN cell population.

In addition, Fountoulakis *et al.* (2007) have elucidated the role of iodine in the progression of thyroid autoimmunity. This group described an inverse relationship between serum IL17 and HT progression that might be explained by a more cytotoxic responses of Th1 compared with Th17. The group developed a mouse model and

showed that moderate iodine intake promotes Th17 while excessive iodine supplementation induce Th1 cells that in turn caused autoimmunity and thyroid cell apoptosis. Therefore, iodine intake might potentially effect and regulate the micro milieu. Thus, CD4⁺ cell polarization likely plays an important role not only in HT but also in PTC and there is a plasticity between protective Th1 or Th17 and evasive Th2 or Treg response. Indeed, the presence of DN T cells might be a novel regulatory factor and not due to effector cell contamination. This notion is also supported by a Crispin *et al.* (2008), who described IL17-secreting DN T cells derived from a CD8⁺ precursor in lupus patients.

Overall, the study by Imam *et al.* provides an interesting new view on the role of tumor-associated DN T cells with potentially immunomodulatory activity in PTC. However, it becomes clear that extensive further research is required to fully understand the whole picture. It is evident that the T cell infiltration is very heterogenous. This is not only true between different thyroid disease (i.e. PTC, TNG, and HT), but also within each defined entity there appears to be a rather heterogenous and maybe observer-dependent admixture and expression of the various T cell fractions. This might be due to technical limitations and also environmental factors.

As the final decision on the role of immune system in differentiated thyroid cancer will take some time, it is important to further characterize the function of these DN T cells found in PTC. Therefore these cells should be sorted and tested for immune-suppressive functions in T cell suppression assays. Future studies will also be necessary to evaluate how the immune cell infiltration influences the clinical outcome of PTC. For that purpose, it would be important to identify the presence of DN T cells in patients with aggressive PTC and those with more indolent stage I disease.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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