



Papillary thyroid carcinoma and inflammation

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The relationship between cancer and inflammation is well known since 1863 when Rudolf Virchow, following the observation of leukocytes in neoplastic tissues, hypothesized that chronic inflammation could contribute to the tumorigenic process. In the following decades, several lines of evidence suggested a strong association between chronic inflammation and increased susceptibility to neoplastic transformation and cancer development. It was estimated that up to 20% of all tumors arise from conditions of persistent inflammation such as chronic infections or autoimmune diseases. Indeed, the associations are well known between cervical cancer and papilloma virus, gastric cancer and *Helicobacter pylori* induced gastritis, esophageal adenocarcinoma and Barrett's metaplasia, hepatocellular carcinoma, hepatitis B and C viral infections, and many others. Some of the mechanisms forming the basis of the relationship between inflammation and tumor have been recently elucidated. The inflammatory microenvironment of neoplastic tissues is characterized by the presence of host leukocytes both in the supporting stroma and among the tumor cells, with macrophages, dendritic cells, mast cells, and T cells being differentially distributed (Balkwill and Mantovani, 2001). Several cytokines (TNF, IL-1, IL-6) and chemokines that are produced by the tumor cells and by leukocytes and platelets associated with the tumor have been found to be able to maintain the invasive phenotype (Coussens and Werb, 2002). Tumor-associated macrophages (TAMs) are a major component of the leukocyte infiltrate, initially recruited by inflammatory chemokines (e.g., CCL2) and then sustained by cytokines present in the tumor microenvironment (e.g., CSFs, VEGF-A). In response to cytokines such as TGF- β , IL-10, and M-CSF, TAMs promote tumor proliferation and progression and stroma deposition and, indeed, the density of TAMs is increased in advanced thyroid cancers (Ryder et al., 2008). As far as papillary thyroid cancer (PTC) is concerned,

this tumor is frequently associated with autoimmune thyroid diseases, Graves' disease, and Hashimoto's thyroiditis. The frequency of association is extremely variable in the series from different countries, 0–9% for Graves' and 9–58% for Hashimoto's (Figure 1). It is still debated whether association with an autoimmune disorder could influence the prognosis of PTC. Indeed a worse prognosis was reported in few series (Ozaki et al., 1990; Pellegriti et al., 1998), while the majority of the studies showed either a protective effect of thyroid autoimmunity (Matsubasyashi et al., 1995; Loh et al., 1999; Gupta et al., 2001) or a similar behavior between cancer with and without associated thyroiditis (Yano et al., 2007). These discrepancies can be due to either the low number of patients examined in those studies, the lack of a control group, the existence of different genetic and epidemiological backgrounds, or the use of inappropriate criteria to define remission or persistence/relapse. We recently produced data extending the knowledge about the tight relationships among thyroiditis and thyroid cancer. In particular, the clinical and molecular features, and the expression of inflammation-related genes, were investigated in a large series of PTCs divided in two groups according to the association or not of the tumor with thyroiditis (Muzza et al., 2010). Interestingly, no significant differences between the two groups were found, as far as age at diagnosis, gender distribution, TNM staging, histological variants, and outcome are concerned, suggesting that the association with an autoimmune thyroid process does not modify either the presentation or the clinical behavior of PTC. A crucial finding of the last few years concerns the genetic background of PTCs, since the concept has emerged that the inflammatory protumorigenic microenvironment of this cancer is elicited by the oncogenes responsible for thyroid neoplastic transformation (such as *RET/PTC*, *BRAFV600E*, and *RASG12V*; Borrello et al., 2005, 2008; Melillo et al.,

2005; Mantovani et al., 2008). In particular, we recently demonstrated that the *RET/PTC1* oncogene activates a transcriptional proinflammatory program in normal human primary thyrocytes (Borrello et al., 2005). Moreover, gene expression studies in cellular systems showed that not only *RET/PTC* but also *RAS* and *BRAF* proteins, all belonging to the *RET-PTC/RAS/BRAF/ERK* pathway, are able to induce the up-regulation of chemokines, which in turn could contribute to neoplastic proliferation, survival, and migration (Melillo et al., 2005). Consistently, other Authors demonstrated that *RET/PTC3*-thyrocytes express high levels of proinflammatory cytokines (Russel et al., 2003) and proteins involved in the immune response (Puxeddu et al., 2005). These data are well in agreement with our recent study which firstly showed that PTCs harbor a different genetic background according to the association or not with thyroiditis (Muzza et al., 2010). In particular, *RET/PTC* was more represented in patients with PTC and autoimmunity, while *BRAF^{V600E}* was significantly more frequent in patients with PTC alone. Moreover, we showed that the expression of genes encoding three inflammation-related genes (CCL20, CXCL8, and L-selectin) was enhanced either in *BRAF^{V600E}* or in *RET/PTC* tumors, compared with normal samples. Interestingly, non-neoplastic tissues with thyroiditis displayed the same levels of expression of CCL20 and CXCL8 compared to normal samples, suggesting that these inflammatory molecules could be associated with tumor-related inflammation, and not with the autoimmune process.

In conclusion, recent studies opened a new and extremely attractive scenario on the "connection" between thyroid autoimmunity, inflammation, and cancer. The interest is linked not only to the possibility of better understanding the communication between abnormally growing cells and their microenvironment, but also to the chance to pharmacologically interfere with such pro-tumor interactions.

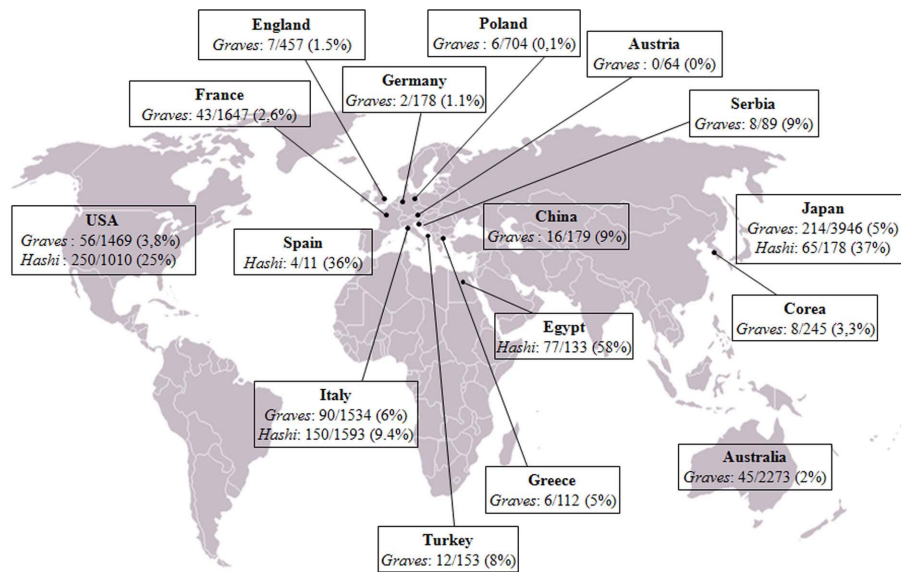


FIGURE 1 | Worldwide prevalence of papillary thyroid cancer in patients with Graves' disease (Graves) and Hashimoto's thyroiditis (Hashi), corresponding to the sum of the data reported to date in the literature.

References: Australia (Graves: Hales et al., 1992; Barakate et al., 2002); Austria (Graves: Rieger et al., 1989); China (Graves: Chou et al., 1993; Lin et al., 2003); Korea (Graves: Kim et al., 2004); Egypt (Hashimoto: Tamimi, 2002); France (Graves: Melliere et al., 1988; Ozoux et al., 1988; Kraimps et al., 1998; Kraimps, 2000; Mssrouri et al., 2008); Germany (Graves: Vahl et al., 1982); Great Britain (Graves: Hancock et al., 1977); Greece (Graves: Linos et al., 1997); Italy (Graves: Pacini et al., 1988; Belfiore et al., 1990; Miccoli et al., 1996; Pellegriti et al., 1998;

Cantalamesa et al., 1999; Zanella et al., 2001; Gabriele et al., 2003; Cappelli et al., 2006; Hashimoto: Fiore et al., 2011); Turkey (Graves: Terzioglu et al., 1993); Japan (Graves: Kasuga et al., 1990; Ozaki et al., 1990; Yano et al., 2007; Hashimoto: Matsubayashi et al., 1995; Ohmori et al., 2007); Poland (Graves: Pomorski et al., 1996); Serbia (Graves: Zivaljević et al., 2008); Spain (Hashimoto: Pino Rivero et al., 2004); USA (Graves: Shapiro et al., 1970; Dobyms et al., 1974; Bradley and Liechty, 1983; Farbota et al., 1985; Behar et al., 1986; Razack et al., 1997; Carnell and Valente, 1998; Weber et al., 2006; Boostrom et al., 2007; Phitayakorn and McHenry, 2008; Hashimoto: Loh et al., 1999; Gupta et al., 2001; Kebebew et al., 2001; Larson et al., 2007).

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