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EDITORIAL

TLR-10 polymorphism and papillary thyroid cancer: one more SNP to consider?

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Activated toll-like receptor (TLR) signaling pathway has been reported in several endocrine neoplasms and has been found to be associated with the upregulation of proinflammatory cytokines. These cytokines are widely known as critical mediators of tumorigenesis. The stimulation of antitumor immunity through the activation of the TLR pathway can lead to the inhibition of the carcinogenesis process. However, TLRs have been considered as putative therapeutic target in various human cancers. A chronic inflammation in the absence of infection induces oxidative stress, DNA damage, and tissue damage promoting tumorigenesis. Thus, TLRs can be viewed as having a double-edged sword function.

Accumulating evidences show the association between over-activation of TLR and cancer progression and TLR-signaling molecules are often involved in tumor progression. For example, *TLR4* expression has been described in several human cancer, including intestinal [1], breast, and prostate cancers [2, 3] and *TLR3* in papillary thyroid cancer and cervical carcinoma [4]. Several studies support that TLR activation via TLR-adaptors such as MyD88 induces NFkB translocation to the nucleus. This induces proinflammatory cytokine secretion (IL6 and IL1), antiapoptotic factors (Bcl-XL, cIAP1, ABL), as well as, pro-angiogenic factors expression (VEGF). High expression of *TLR3* has been reported in a papillary thyroid cancer cell line which is consistent with its overexpression in human papillary thyroid cancer in vivo [5]. As one of the main mediator of lipopolysaccharide action, the lack or overexpression of *TLR4* has also been associated with aggressive follicular thyroid cancers [6].

In this issue of *Endocrine*, Kim et al. [7] report that single nucleotide polymorphism (SNP) in *TLR10* is associated with tumor size in patients with papillary thyroid cancer. *TLR-1-TLR6-TLR-10* is located on the same chromosome and forms a cluster, and thus was the rationale for the authors to analyze these three TLR SNPs. They found that only a missense SNP in *TLR10* (rs11466653, Met326Thr) showed a significant association with small tumor size (<1 cm). SNPs in the *TLR-1-TLR6-TLR-10* cluster have been associated with increased risk of prostate cancer [8].

Altered *TLR-10* signaling in papillary thyroid cancer may be involved in the interplay between inflammation and tumorigenesis. For example, it has been shown by several groups that *IL-6*, *IL-1*, and *VEGFA* are important cytokines in thyroid carcinogenesis [9–11]. Most importantly, common somatic mutations in papillary thyroid cancer such us *RET/PTC* rearrangements and *BRAF* are involved in inflammation, where they have been shown to be involved in inflammatory response and in the infiltration of innate suppressive inflammatory cells in papillary thyroid cancer [12]. Thus, a cooperation of dysregulated TLR signaling pathway in the inflammatory response of microcarcinoma seems plausible.

Based on our current knowledge, *TLR-10* expression seems to be restricted to immune cells like B cells or dendritic cells. Lymphocytic and dendritic cell infiltration is higher in patients with papillary thyroid cancer as compared to those with benign thyroid tumors [13]. Thus, the missense *TLR-10* SNP reported by Kim and colleagues may influence the amount of lymphocytic infiltration in patients with small papillary thyroid cancer. Although lymph node metastasis and multifocality are important

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clinical characteristics of papillary thyroid microcarcinoma, the authors did not see any significant difference between patients with papillary thyroid cancer with and without lymph node metastasis. Future investigations including the analysis of *TLR-10* polymorphism in microcarcinoma with and without lymph node metastasis and those with tumor lymphocytic infiltration will be important to better characterize the role of *TLR-10* in papillary thyroid cancer.

There are several limitations to the study by Kim and associates. The authors excluded SNPs with minor allele frequency (MAF) less than 0.1. However, Tabangin et al. [14] have emphasized the importance of including MAF SNPs in analyses to rule out or minimize false-positive results. Therefore, minimizing MAF SNPs may result in loss of data. Another limitation is that the study was done in a homogenous population and thus the data may not be applicable to other populations. Despite these limitations, Kim and colleagues provide us with new data which suggest an association between missense *TLR-10* SNP and papillary thyroid cancer and set the stage for future studies to determine the prevalence of this association and the relevance to papillary thyroid carcinogenesis by performing functional studies looking at the effect of the missense *TLR-10* SNP in tumor cell biology.

References

1. P. Pimentel-Nunes, L. Afonso, P. Lopes, R. Roncon-Albuquerque Jr, N. Goncalves, R. Henrique, L. Moreira-Dias, A.F. Leite-Moreira, M. Dinis-Ribeiro, Increased expression of toll-like receptors (TLR) 2, 4 and 5 in gastric dysplasia. Pathol. Oncol. Res. POR **17**(3), 677–683 (2011). doi:10.1007/s12253-011-9368-9
2. S. Gonzalez-Reyes, L. Marin, L. Gonzalez, L.O. Gonzalez, J.M. del Casar, M.L. Lamelas, J.M. Gonzalez-Quintana, F.J. Vizoso, Study of TLR3, TLR4 and TLR9 in breast carcinomas and their association with metastasis. BMC Cancer **10**, 665 (2010). doi:10.1186/1471-2407-10-665
3. S. Gonzalez-Reyes, J.M. Fernandez, L.O. Gonzalez, A. Aguirre, A. Suarez, J.M. Gonzalez, S. Escaff, F.J. Vizoso, Study of TLR3, TLR4, and TLR9 in prostate carcinomas and their association with biochemical recurrence. Cancer Immunol. Immunother. CII **60**(2), 217–226 (2011). doi:10.1007/s00262-010-0931-0
4. Q. Jiang, H. Wei, Z. Tian, Poly I:C enhances cycloheximide-induced apoptosis of tumor cells through TLR3 pathway. BMC Cancer **8**, 12 (2008). doi:10.1186/1471-2407-8-12
5. K.D. McCall, N. Harii, C.J. Lewis, R. Malgor, W.B. Kim, M. Saji, A.D. Kohn, R.T. Moon, L.D. Kohn, High basal levels of functional toll-like receptor 3 (TLR3) and noncanonical Wnt5a are expressed in papillary thyroid cancer and are coordinately decreased by phenylmethimazole together with cell proliferation and migration. Endocrinology **148**(9), 4226–4237 (2007). doi:10.1210/en.2007-0459
6. J. Hagstrom, A. Heikkila, P. Siironen, J. Louhimo, I. Heiskanen, H. Maenpaa, J. Arola, C. Haglund, TLR-4 expression and decrease in chronic inflammation: indicators of aggressive follicular thyroid carcinoma. J. Clin. Pathol. **65**(4), 333–338 (2012). doi:10.1136/jclinpath-2011-200402
7. K.S Kim, K. Hong II, Y.G. Eun, J. Chung, A missense polymorphism (rs11466653, Met326Thr) of toll-like receptor 10 (TLR10) is associated with tumor size of papillary thyroid carcinoma in the Korean population. Endocrine (2012). doi:10.1007/s12020-012-9783-z
8. V.L. Stevens, A.W. Hsing, J.T. Talbot, S.L. Zheng, J. Sun, J. Chen, M.J. Thun, J. Xu, E.E. Calle, C. Rodriguez, Genetic variation in the toll-like receptor gene cluster (TLR10-TLR1-TLR6) and prostate cancer risk. Int. J. Cancer J. Int. du Cancer **123**(11), 2644–2650 (2008). doi:10.1002/ijc.23826
9. J.P. Russell, S. Shinohara, R.M. Melillo, M.D. Castellone, M. Santoro, J.L. Rothstein, Tyrosine kinase oncoprotein, RET/PTC3, induces the secretion of myeloid growth and chemotactic factors. Oncogene **22**(29), 4569–4577 (2003). doi:10.1038/sj.onc.1206759
10. J.P. Russell, J.B. Engiles, J.L. Rothstein, Proinflammatory mediators and genetic background in oncogene mediated tumor progression. J. Immunol. **172**(7), 4059–4067 (2004)
11. B. Belletti, P. Ferraro, C. Arra, G. Baldassarre, P. Bruni, S. Staibano, G. De Rosa, G. Salvatore, A. Fusco, M.G. Persico, G. Viglietto, Modulation of in vivo growth of thyroid tumor-derived cell lines by sense and antisense vascular endothelial growth factor gene. Oncogene **18**(34), 4860–4869 (1999). doi:10.1038/sj.onc.1202869
12. H. Sumimoto, F. Imabayashi, T. Iwata, Y. Kawakami, The BRAF-MAPK signaling pathway is essential for cancer-immune evasion in human melanoma cells. J. Exp. Med. **203**(7), 1651–1656 (2006). doi:10.1084/jem.20051848
13. I. Okayasu, The relationship of lymphocytic thyroiditis to the development of thyroid carcinoma. Endocr. Pathol. **8**(3), 225–230 (1997)
14. M.E. Tabangin, J.G. Woo, L.J. Martin, The effect of minor allele frequency on the likelihood of obtaining false positives. BMC Proc. **3**(Suppl 7), S41 (2009). doi:10.1186/1753-6561-3-S7-S41