ImmunoTools IT-Box-139 Award 2012

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HOMEOBOX NKX2-3 PROTEIN INDUCES ONCOGENIC TRANSFORMATION IN B-CELL LYMPHOMA

Molecular cloning of chromosomal translocation t(10;14)(q24;q32) in B-cell lymphoma cells identified *NKX2.3*, a gene encoding a homeobox transcription factor, fused to *IGH,* which resulted in an increase of gene expression with respect normal lymphocytes. In addition, NKX2-3 over-expression was detected in 49 of 170 (29%) patients with splenic and extranodal marginal-zone (MZ) lymphomas and diffuse large B-cell lymphoma (DLBCL) but not in other mature B-cell malignancies. To determine the potential oncogenic role of NKX2-3, transgenic mice with restricted expression of human *NKX2-3* to lymphocytes were generated. Young mice developed partial bone marrow (BM) blockade in the pre-B1-to-pre-B2 transition accompanied by a decrease in the number of circulating B lymphocytes. From ~12 months of age, mice started to develop clinical signs of disease and were euthanized, showing massive splenomegaly (5-10 times larger than normal controls) in all cases (n=46). Immunohistochemical studies showed that the infiltrating cells were mature B lymphocytes, with reactive $CD3^+$ T lymphocytes. In 55% of the mice, additional extranodal tumors involving the lungs, liver and kidneys were detected, showing infiltrates of small mature B lymphocytes. Gene expression profiling analysis reveal overlap between transcriptional signatures of the mouse NKX2-3 splenic lymphomas and human SMZLs, including genes known to be involved in human SMZL pathogenesis, as well as other genes implicated in mature B-cell lymphoma development. Taken together, these data indicate that the murine tumors closely resembled human splenic and extranodal marginal-zone (MALT) lymphomas. Furthermore, analysis of splenic and extranodal lymphomas from mice older than 18 months revealed areas of high-grade transformation to DLBCL, further highlighting the parallelism between splenic and human lymphomas. In conclusion, NKX2-3 protein is over-expressed in a subset of patients with SMZL, MALT lymphoma and DLBCL, and that the ectopic expression of NKX2-3 in mouse B lymphocytes recapitulates the main features of the human lymphoma counterparts.

Our hypothesis is that lymphomagenesis is induce by stimulation between B cell and T cell. NKX2.3 can produce changes in the surface cell markers. We would like to transfect human cell line with a regulable vector. After induce NKX2.3 expression, we will study how surface markers are involve in B cell and T cell presentation. Also we

want to study the citotoxic effect of different agonist of these markers in human cell lines.

If we received the award, we could study deeply how this gene is involve in with SMZL, MALT lymphoma and DLBCL, and consequently we will be able to try a better and more specific therapy for the patients.