Institute of Pathology

Gene Expression Profiling and SNP Analysis of B Cell Lymphoma of the Gastrointestinal Tract

Head: Peter Möller

As a national reference center for lymphoma diagnostics, the Institute of Pathology at Ulm University has been engaged for many years in the characterization of Hodgkin and non-Hodgkin lymphoma. Based on a large collection of fresh-frozen lymphoma tissue, the aim of the project is to analyze oncogenesis and the progression of extranodal marginal zone B cell lymphoma (MZBL) of the gastrointestinal (GI) tract by means of gene expression profiling and SNP analysis of microdissected lymphoma tissue.

MZBL, consisting of small cells, and aggressive diffuse large B cell lymphoma (DLBCL) of the GI tract are extranodal lymphomas with immunological, cytogenetic and clinical features that differ from nodal B cell lymphomas. It is well known that indolent MZBL and aggressive DLBCL can coexist in the GI tract. Within an inflammatory context caused by *Helicobacter pylori* infection, clonal evolution from the small to the large cell variant has been proven by means of molecular cytogenetics.

The Team:
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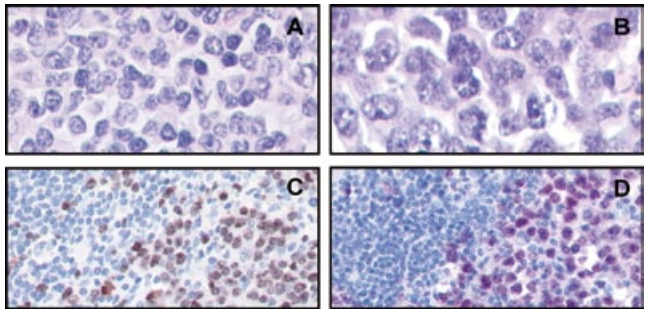

Composite lymphoma of an extranodal marginal B cell lymphoma of the stomach.
A: Hematoxylin-Eosin staining of the small cell component of a composite B cell lymphoma of the stomach. Cells have a lymphocytic appearance.
B: Hematoxylin-Eosin staining of the large cell component of the same lymphoma.
C: Immunostaining with the proliferation marker Ki-67. The large cell compartment shows a higher proliferation index than the small cell areas.
D: Immunostaining with an antibody specific for Bcl6. The small cell compartment is negative, while the large cell compartment shows strong expression of the Bcl6 protein.

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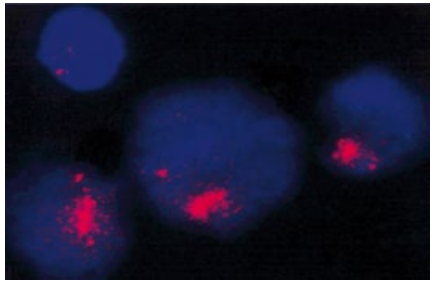
Therefore, these tumors are referred to as “composite lymphoma” and represent a model of lymphoma progression. In a former study, we showed by transcriptional profiling that there is a close relationship between GI MALT lymphoma and their large cell variants. From these results, we concluded that DLBCL of the GI tract is a blastic, aggressive variant of MZBL.

We have identified that *c-REL* and *BCL6*, as candidate genes for lymphoma progression, can be activated by gene amplification or translocations. We have shown that an amplification of *c-REL* is frequently accompanied by a nuclear accumulation of *REL* protein in the nucleus of lymphoma cells. Our goal is to further characterize this finding of GI B cell lymphomas by using Affymetrix platforms for gene expression profiling and SNP analysis. Our aim is to identify specific markers associated with lymphoma progression from MZBL to DLBCL.



FISH with a probe for *c-REL* on a large B cell lymphoma of the stomach. The cloudy red signals reflect massive amplification on 2p16 that includes the *c-REL* gene.

Selected Publications:

- *Flossbach L, Antoneag E, Buck M, Siebert R, Mattfeldt T, Möller P; Barth TFE (2011) BCL6 gene rearrangement and protein expression are associated with large cell presentation of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue, Int J Cancer 129, 70-7.*
- *Leeman JR, Weniger MA, Barth TF, Gilmore TD (2008) Deletion analysis and alternative splicing define a transactivation inhibitory domain in human oncoprotein REL, Oncogene 4, 6770-81.*