Apoptosis resistance concomitant with the aberrant upregulation of pro-survival pathways is a main pathogenic mechanism in development and maintenance of chronic lymphocytic leukemia (CLL). Prior TOSO alias FAS apoptosis inhibitory molecule 3 (FAIM3) was identified to be specifically overexpressed in CLL, compared to healthy B cells and other B cell lymphomas. Interestingly, TOSO is thought to exert pro-survival signaling. However, its biological relevance for B cells *in vivo* urgently needs to be explored. Moreover, it remains still enigmatic, how TOSO is regulated and why TOSO is expressed extremely heterogeneous on different B cells entities. Interestingly, elevated TOSO expression was associated with progressive disease, including unmutated IgV_H status of the B cell receptor (BCR). Since the BCR is a driving force in B cell malignancies, TOSO expression was investigated after BCR crosslinking and resulted in increase of TOSO. To date, the TOSO promoter has not been described yet. In this work, the TOSO proximal region was identified to exert promoter activity. Moreover, *in silico* analysis and phylogenetic footprinting exhibited existence of transcription factor binding sites for NF-κB and BCL6. Here I have identified, that upregulation of TOSO after BCR engagement relies on direct binding of NF-κB and BCL6 to the TOSO promoter. In luciferase reporter assays, including targeted mutagenesis, NF-κB was confirmed as novel inducer of TOSO expression. Whereas BCL6 binding, confirmed by ChIP and luciferase assays, was shown to exert repressing activity on the TOSO promoter. Although it can explained now how TOSO is regulated by the BCR, the reason for its distinct basal expression levels in normal B cells and other B cell malignancies still remained unclear. My data reveal that methylation within the TOSO promoter controls basal TOSO expression level. Here, I firstly illustrate that DNA hypomethylation of the TOSO promoter is a conspicuous characteristic in CLL patients compared to the hypermethylated promoter in B cells from healthy donors. Indeed, the methylation status seems to play a major role, since the methylation level correlates with TOSO expression also in other B cell lymphomas. To investigate the downstream effects of TOSO, a B cell-specific TOSO knockout mouse model was generated via CD19Cre-mediated recombination. Peripheral blood of the TOSO deficient mice displayed decreased level of B lymphocytes, while other cells, like NK and T cells, remained unaffected. Microarray analysis revealed a TOSO dependent gene expression profile. Almost 500 genes were identified to be dependent on TOSO expression in B cells. Particularly conspicuous were two factors:

survival promoting B cell-activating factor receptor (BAFF-R) and the migration factor C-X-C chemokine receptor type 5 (CXCR5), which are known to play important roles also in CLL pathogensis. Deletion of TOSO in murine B cells resulted in decreased BAFF-R and CXCR5 levels, which might initially result in less trafficking to or impaired formation of B cell follicles, which usually provide pro-survival signals and initiate proliferation as well as cell differentiation. Moreover, loss of BAFF-R function is known to cause deprivation of B cells, originating from a lack of BAFF-R-mediated pro-survival signals. Thus, these results might reveal a new function of TOSO in migration, pro-survival signaling and blood cell homeostasis.

Taken together, this work reveal how TOSO is regulated in normal and malignant B cells and identifies novel TOSO downstream functions, which are an essential step towards elucidation of the underlying molecular causes for the development of CLL.