Nuclear matrix and matrix binding proteins play important role in regulating various cellular processes. Association of Matrix Attachment Regions (MARs) with Matrix Attachment Region Binding Proteins (MARBPs) maintains the chromatin architecture and matrix topology. Altered chromatin structure and function is observed during tumorigenesis due to dysregulation of MARBPs. SMAR1 is initially identified from T-cell and is been characterized as a MARBP. Smar1 gene is present at 16q24.3 locus and its tumor suppressor role is recently been highlighted. SMAR1 is also established as negative regulator of transcription at TCRβ locus and Cyclin D1 promoter. The present study focuses on understanding the mechanism of SMAR1 regulation and its in depth role in regulating the transcription and signaling pathways pertinent to breast cancer.

Our study shows that SMAR1 transcription is directly regulated by another tumor suppressor MARBP, p53 upon DNA damage through its response element. Further in human breast cancer samples SMAR1 was downregulated during the advanced stages. Reduced expression of SMAR1 was then correlated with increased Cyclin D1 expression in these breast cancer samples. Interestingly this was also correlated to the defective sub-cellular localization of p53 where acetylated p53 was observed in the nucleolar heterochromatin regions in Infiltrating Ductal Carcinoma grade II and grade III cases and thus was unable to activate SMAR1 transcription. This study also establishes that SMAR1 and p53 regulates each other through a positive feed forward loop.

Further by genomewide microarray analysis we show that SMAR1 overexpression results in downregulation of many genes involved in cell proliferation, cell migration and TGFβ signaling. Detailed investigation revealed that SMAR1 inhibits tumor cell migration and invasion through downregulation of TGFβ signaling and its target gene CUTL1. Interestingly this function of SMAR1 was p53 independent. SMAR1 also downregulated NFκB target gene expression as observed in microarray analysis. We have thus also studied the role of SMAR1 in modulating NFκB signaling.
and found that SMAR1 inhibits NFκB transactivation. Further we could establish that the repression mediated by SMAR1 is dependent on MARs present near the NFκB binding sites in the promoter regions of NFκB target genes. We show that SMAR1 downregulates IκBα transcription along with other NFκB target genes like CCL2, AGT1, AKT1, IL 10 and IFN-γ directly through its binding to MARs. By overexpression and siRNA studies we also show that SMAR1 inhibits the classical NFκB activation by TNFα.

Another important NFκB target gene CD40, involved in inflammation associated with tumorigenesis is also shown to be regulated by SMAR1. CD40 transcription is kept in check through SMAR1 in normal scenario. Upon activation with TNFα SMAR1 gets phosphorylated at serine 347 residue and translocates into the cytoplasm resulting in derepression of CD40 promoter. In the absence of SMAR1 repressor complex, STAT1 activator complex occupies the CD40 promoter and induces its expression.

In brief, the present study has revealed the mechanism of SMAR1 regulation by p53 and its implication in regulating TGFβ and NFκB signaling pathways that are well known to have role in breast cancer.