Regulation of Smad3 binding by FoxA1/2 in lung adenocarcinoma cells

Kazunobu Isogaya[1], Daizo Koinuma[1], Shuichi Tsutsumi[2], Hiroyuki Aburatani[2], Kohei Miyazono[1]

[1]Department of Molecular Pathology, Graduate School of Medicine, University of Tokyo

[2]Genome Science Division, RCAST, University of Tokyo

FoxA1 and FoxA2 (FoxA1/2) are members of the Forkhead box family transcription factors. They are called “pioneer factors”, for they are able to open closed chromatin structure and recruit other transcription factors. FoxA1/2 play very important role during development as well as tumorigenesis. FoxA1 works as oncogene in thyroid, breast, and lung adenocarcinoma, but it is also reported to be tumor suppressor gene in hepatocellular carcinoma and pancreatic adenocarcinoma. In breast and prostate carcinoma, FoxA1 cooperates with ER and AR, and regulates expression of their target genes. On the other hand, little is known about how FoxA2 works during tumorigenesis. Recently, FoxA2 is found to be frequently down-regulated in lung adenocarcinoma, and FoxA2 prevents epithelial mesenchymal transition (EMT) by suppressing Slug expression in lung adenocarcinoma cell lines.

Here we determined time-course changes of Smad3 binding regions in A549 lung adenocarcinoma cells by ChIP-sequencing. We identified enrichment of FoxA binding motif in a subset of Smad3 binding regions. Only a transient binding of Smad3 to target gene loci was observed when Smad3 co-localizes with FoxA1/2. TGF-beta signaling also changed FoxA1/2 binding regions as well as their binding strength. These results suggest that Smad3 and FoxA1/2 cooperate to regulate transcriptional level of target genes possibly through alteration of chromatin conformation.