**Linking HOXB2, MMP-11, and E2 signaling: What a Developmental Gene Tells the Cancer Cells**

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Homeobox transcription factor, HOXB2, is aberrantly expressed in many solid tumors. Boimel and coworkers suggested the tumor suppressive role of HOXB2 in close association with the tumor microenvironment. The proposed tumor suppressor role of HOXB2 was explored using transcriptomic profiling after HOXB2 knockdown in MCF-7 cells. HOXB2 depletion affected the extracellular matrix remodeling process and related genes, including metalloproteinases (MMPs). GSEA analysis showed enrichment of several hallmark pathways, including the TGF pathway, estrogen early response, ECM genes, and EMT pathways. Previous work from our lab found HOXB2 to be suppressed by estrogen via ERα in ER-positive breast cancer cells. We hypothesized that HOXB2 could mediate a subset of E2-regulated genes via which it manifests its role as a tumor suppressor. The transcriptomic regulation of MMPs by HOXB2 was explored using siRNA-mediated HOXB2 knockdown. Also, the E2-regulated MMPs were identified after treating MCF-7 with estrogen. Few MMPs, including MMP-11, were found to be E2 targets mediated potentially via HOXB2. **This led us to hypothesize that HOXB2, MMP-11, and estrogen-ER signaling are functionally connected.** Metalloproteinase 11 (MMP-11), an ECM remodeler, is highly expressed in breast tumors and promotes cancer progression. MMP-11 was induced upon HOXB2 knockdown and suppressed by estrogen. The E2-mediated regulation involved ERα binding to the ERE locus within the MMP-11gene. **ERα knockdown also induces MMP-11.** Our findings suggest that the functional link between HOXB2 with the E2-ERα signaling pathway may be crucial for preventing EMT phenotype and maintaining ECM homeostasis in ER-positive breast cancer.

**Keywords**

Estrogen signaling, Breast Cancer, Metalloproteinases, Transcriptomic profiling, Developmental gene