Pathological angiogenesis and lymphangiogenesis are a hallmark of cancer and both serve as the major routes for cancer cell dissemination and metastasis. The tumor-vasculogenic process is the result of the interaction between endothelial and tumor cells and requires the coordinated actions of growth factors with both angiogenic and lymphangiogenic properties. Unrevealing the potential mediators able to modulate this complex process would provide the basis for the development of molecularly targeted therapeutics directed against both tumor and tumor-associated endothelial cells. The multifunctional peptide endothelin-1 (ET-1) and its receptors have been correlated with invasiveness and metastasis and have been shown to be markedly increased in the vasculature of several cancers. ET-1/HIF-1α pathway has been shown to be significantly upregulated in several cancers and is able to amplify the results of the interaction between endothelial and tumor cells, suggesting that a positive interregulation of ET-1 and its receptors is controlled by VEGF and hypoxia in both endothelial and tumor cells. ET-1 induces events that are important for the interaction with the miRNA 1285 which binds to the 3′UTR of target genes. Furthermore, we show that Mxi-2/Ago2 is an important for the interaction with the miRNA 1285 which binds to the 3′UTR of target genes. Furthermore, we show that Mxi-2/Ago2 is complex interplay with VEGF family members. Furthermore, expression of ET-1 and its receptors is controlled by VEGF and hypoxia in both endothelial and tumor cells, suggesting that a positive interregulation between ET-1/HIF-1α, VEGF and hypoxia is able to amplify the neovascularogenic response. The better mechanistic understanding of these complex interactions is gradually paving the way toward the rationale exploitation of the ET-1/ET receptor signaling pathway as a therapeutically active target for neoplastic disease characterized by active neovascularisation.

Increased endothelin-1 decreases PKC alpha (PKCα), resulting in high miRNA 15a levels in kidney tumors. Breast cancer cells treated with ET-1, α-estrogen, Tamoxifen, Tamoxifen + α-estrogen and Tamoxifen + ET-1 were analysed regarding miRNA 15a expression. Significantly increased miRNA 15a levels were found after ET-1 treatment, becoming further increased in Tamoxifen + ET-1 treated cells. Our group already showed that miRNA 15a induces MAPK p38 splicing resulting in a truncated product called Mxi-2, whose function has yet to be defined in tumors. We described for the first time in ET-1 induced tumor cells that Mxi-2 builds a complex with Ago2, a miRNA binding protein, which is important for the localization of miRNAs to the 3′UTR of target genes. Furthermore, we show that Mxi-2/Ago2 is an important for the interaction with the miRNA 1285 which binds to the 3′end of the tumor suppressor gene p53, being responsible for the downregulation of p53. Tissue arrays from breast cancer patients were performed, analysing Mxi-2, p53 and PKCα. Since the Mxi-2 levels increase in Tamoxifen + ET-1 treated cells, we claim that increasing ET-1 levels in Tamoxifen treated breast cancer patients are responsible for decreasing p53 levels. In summary, ET-1 decreases nuclear PKCα levels, while increasing the amount of miRNA 15a. This causes high levels of Mxi-2, necessary for complex formation with Ago2. The newly identified Mxi-2/Ago2 complex interacting with miRNA 1285 leads to increased 3′UTR p53 interaction, resulting in decreased p53 levels and subsequent tumor progression. This newly identified mechanism is a possible explanation for the development of ET-1 induced tumors.