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Session 2: Oncology

The endothelin axis: A new player in tumor angiogenesis and lymphangiogenesis

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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 kinds of tumors and associated with tumor grade and poor prognosis. ET-1 acts in both blood and lymphatic endothelial as well as in tumor cells through its G-protein coupled receptors, ETA and ETB, to promote angiogenesis and lymphangiogenesis. The mechanism by which ET-1 promotes these processes is beginning gradually defined. During tumor progression ET-1 exerts crucial roles in the vasculogenic switch promoting, via ETBR, endothelial cell proliferation, migration, protease production and morphogenesis, and, via both receptors, vascular endothelial growth factor (VEGF) release. Moreover, ET-1 stimulates highly aggressive tumor cells to form vessel-like networks that do not involve endothelial cells. The ET-1-induced vasculogenic effects, progress through the induction of the transcriptional hypoxia-inducible factor (HIF)-1α and HIF-2α, and through a 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 interegulation between ET-1/HIF-1α, VEGF and hypoxia is able to amplify the neovasculogenic 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 attractive target for neoplastic disease characterized by active neovascularisation.

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Endothelin-1 induced Mxi-2/Ago2 complex formation resulting in P53 downregulation promoting breast cancer development

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Increased endothelin-1 decreases PKC alpha (PKCα), resulting in high miRNA 15a levels in kidney tumors. Breast cancer cells treated with ET-1, β-estrogen, Tamoxifen, Tamoxifen + β-estrogen and Tamoxifen + ET-1 were analysed regarding miRNA 15a expression. Significantly increased miRNA 15a levels were found after ET-1, 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 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.

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Tamoxifen treatment in breast cancer induces a cytoplasmic complex consisting of endothelin-1, estrogen receptors, and Tamoxifen leading to nuclear transmigration, and transcription of target genes involved in metastatic spread

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Tamoxifen therapy of invasive breast cancer has been associated with increased levels of endothelin-1 (ET-1) so that an endothelin-1 receptor (ETR) blockade has been suggested as a new therapeutic approach. This study analyzed the relationship between Tamoxifen and ET-1 signalling in invasive breast cancer. Using paraffinized tissue from 50 randomly chosen cases of invasive and in-situ ductal carcinoma from our archive, the expression of ETRs was analyzed by immune histology. ETRs were regularly detectable in normal breast tissue, but rarely in adjacent tumor areas (3/50 cases). By immunoprecipitation, a complex was found consisting of ET-1, estrogen receptors and Tamoxifen. Consequently, transcription of several target genes of ET-1 and estrogen receptors was detectable (interleukin-6, wnt-11 and a vimentin spliceform). In particular, the combination of Tamoxifen, ET-1, and estrogen receptors induced further increasing levels of these target genes. Some of these genes have been found upregulated in metastatically spreading breast cancer cells. We conclude: i) ETRs do not play a role in invasive or in-situ ductal breast cancer; ii) estrogen receptors and Tamoxifen build a complex with ET-1; and iii) upregulated transcription of target genes by ET-1–estrogen receptor–Tamoxifen complex may negatively influence breast cancer prognosis. These results indicate a role for ET-1 in Tamoxifen treated breast cancer patients leading to a potentially worsening prognosis.

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