

Androgen receptor function in prostate cancer

Androgens are important in several steps of male development including sexual differentiation, initiation and maintenance of spermatogenesis or development and maintenance of secondary male characteristics. In target cells, androgens act via binding to androgen receptor (AR), a ligand-dependent transcription factor that directly regulates gene expression and belongs to the nuclear receptor superfamily. It is well known that in males prostate cancer is associated with abnormal AR structure and function. Adenocarcinoma of the prostate is the second leading cause of cancer deaths among men and becomes the greatest in men after the age of 75 years in Europe and the US. In the initial growing phase prostate tumours grow androgen dependent and respond favorably to androgen suppressing therapy. After an initial androgen dependent growth phase, most prostate tumours enter in a so called androgen independent growth phase and are stimulated by estrogens, progestins, and antiandrogens. Once the tumour has entered the androgen independent growth phase there is no cure and very little treatment options. In general, very little is known about the specific molecular mechanisms controlling the transcriptional activity of the AR in normal prostate and in pathologic situation such as androgen independent prostate tumour growth. In this project, we focused on specific molecular mechanisms involving protein-protein interactions and signaling pathways that control AR transcriptional activity. Importantly, we have identified a novel signaling pathway which is, at least in part, responsible, for androgen independent prostate tumour growth. The identification of this yet undescribed signaling pathway allows us to identify novel therapeutic targets for highly specific pharmaceutical interventions and diagnosis of prostate cancer.

Characterization of LIM-only coactivators and their regulation by second messenger signaling pathways

The control of target gene expression by nuclear receptors requires the recruitment of multiple cofactors. One possible mechanism to achieve specific gene regulation is the selective interaction of tissue-restricted cofactors with individual nuclear receptors. In our previous work (Müller et al. 2000) we characterized FHL2 (DRAL/Slim3) as the first LIM-only coactivator of the androgen receptor (AR). FHL2 consists of four and a half LIM domains and exhibits a unique tissue-specific expression pattern. In the adult FHL2 protein is expressed in the myocardium of the heart and in the epithelial cells of the prostate, where it colocalizes with the AR in the nucleus. Interestingly, it is also well expressed in the ovary and bone. FHL2 specifically binds to the AR and selectively increases its transcriptional activity in an agonist- and AF2-dependent manner. Currently, we are interested in the regulation of the transcriptional activity of FHL2. We therefore test the influence of various signal transduction pathways on the transcriptional activity of FHL2 in pathophysiological situations, such as heart hypertrophy, dilated cardiomyopathy and metastasis. Furthermore, we functionally analyze FHL2 interacting proteins and study their roles in growth and differentiation. The establishment of mice deficient of FHL2 and transgenic mice overexpressing FHL2 in different tissues allowed us to create suitable animal models and to analyze these question in detail.