SELECTED TALK:

Dr. Mads Daugaard

Regulation and targeting of chondroitin sulfate glycosaminoglycans in prostate cancer

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Most solid tumors undergo reconfigurations of glycosaminoglycans during disease initiation and progression. Lineage plasticity of prostate cancer is associated with resistance to androgen receptor (AR) pathway inhibition (ARPI) and supported by a reactive tumor microenvironment. Here we show that changes in chondroitin sulfate (CS), a major glycosaminoglycan component of the tumor cell glycocalyx and extracellular matrix, is AR-regulated and promotes the adaptive progression of castration-resistant prostate cancer (CRPC) after ARPI. AR directly represses transcription of the 4-*O*-sulfotransferase gene CHST11 under basal androgen conditions, maintaining steady-state CS in early-stage prostate adenocarcinomas. When AR signaling is inhibited by ARPI or lost during progression to non-AR-driven CRPC as a consequence of lineage plasticity, CHST11 expression is unleashed, leading to elevated 4-*O*-sulfated CS levels. Inhibition of the tumor cell CS glycocalyx delays CRPC progression, and impairs growth and motility of prostate cancer after ARPI. In pre-clinical models, this functional shift in CS composition towards a 4-*O*-dominated CS signature can be targeted by recombinant lectins with specificity to highly-sulfated 4-*O*-CS chains for drug-delivery. Thus, a reactive CS glycocalyx supports adaptive survival and treatment resistance after ARPI in prostate cancer and represents a therapeutic opportunity in tumors with elevated presentation of 4-*O*-sulfated CS glycosaminoglycans.