P61

The landscape of stemness-associated markers in the development of castration-resistant prostate cancer

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Federer-Gsponer J.R.[1], Müller D.C.[2], Zellweger T.[3], Ruiz C.[4], Seifert H.[2], Rentsch C.A.[2], Bubendorf L.[4], Le Magnen C.[1]

[1]University Hospital Basel, Institute of Pathology and Department of Urology, Basel, Switzerland, [2]University Hospital Basel, Department of Urology, Basel, Switzerland, [3]St. Claraspital, Department of Urology, Basel, Switzerland, [4]University Hospital Basel, Institute of Pathology , Basel, Switzerland

Introduction & Objectives: Putative castration-resistant stem-like cells (CRSC) have been identified based on their ability to initiate and drive prostate cancer (PCa) recurrence following castration *in vivo*. Yet the relevance of these CRSC in the course of the human disease and particularly for the transition from hormone naive (HN) to castration-resistance (CR) is unclear. Here we aimed at deciphering the prognostic and clinical significance of CRSC markers in PCa progression.

Materials & Methods: We constructed a tissue microarray (TMA) comprising 118 matched hormone-naive (HN) and castration-resistant (CR) tissues specimens derived from 57 PCa patients and including 113 prostate resections and 5 distant metastases. Expression of eight stemness-associated markers (ALDH1A1, ALDH1A3, ALDH3A1, BMI1, NANOG, NKX3.1, POU5F1, SOX2) was assessed by immunohistochemistry and scored as percentage of positive tumor cells. The resulting scores were statistically analyzed and compared to pathological and clinical data associated with the samples. Publicly available transcriptional datasets were interrogated to assess the expression of the factors *in silico*.

Results: Immunohistochemical assessment of paired samples revealed atypical patterns of expression and striking intra- and inter-tumor heterogeneity for most of the investigated markers. Notably, none of the markers showed significant changes in expression upon the development of castration resistance (CR vs. HN). Using unsupervised clustering approaches, we identified phenotypic subtypes based on the expression of specific stem-associated markers. In particular, we observed (i) frequent mutual exclusivity for ALDH1A1 and ALDH1A3 expression (52% of samples positive for one isoform only, 13% positive for both, 35% negative for both), (ii) phenotypic clusters associated with shorter time to castration resistance upon the initial treatment, (iii) loss of NKX3.1 expression in SOX2-positive neuroendocrine prostate cancers. *In silico* analyses of publicly available gene expression datasets supported similar findings at the transcriptomic level. Next, we will investigate prognostic significance and molecular features associated with distinct phenotypic subtypes, as well as relevance of CRSC factors in patient-derived organoid lines.

Conclusions: Our findings pave the way for futures studies aimed at further exploring the clinical implication and the functional relevance of CRSC populations in PCa progression.