Master of puppets in prostate cancer: heat shock protein 27 is pulling androgen receptor's strings

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The androgen receptor (AR) has been reported as one of the major factors promoting initiation and progression of prostate cancer (PC). Although inactivation of AR functionality is state of the art chemotherapy, the resulting benefit for PC patients appears temporary and chemoresistance occurs with increasing frequency. The discovery of complex AR regulating pathways more and more changed the view of AR targeting therapy. Prospectively, the development of new drugs inhibiting co-factors of AR signaling pathways will take on increasing importance for achieving novel PC treatment options. The present research highlight provides an insight into our current research efforts focused on the identification of clinically relevant AR mechanisms and interactions with other molecular factors, recently being associated with PC therapy resistance: heat shock protein 27, microRNA 1 and ErbB3-binding protein-1. Our recent data indicate so far unknown possibilities of interfering AR functionality far from current treatment regimes.

Keywords: Prostate cancer; androgen receptor; heat shock protein 27; microRNA-1


Since androgen depletion therapy is the main strategy in prostate cancer (PC) treatment [1], in recent years attention has turned towards targeting up-stream signaling pathways of androgen receptor (AR) regulation. As a member of the nuclear receptor family, AR is responsible for PC genesis and progression. Although nearly all PC treatment regimes base on direct (inhibition of AR activity) or indirect (inhibition of androgen synthesis) attenuation of oncogenic AR properties, the patient's benefit is temporary until castration resistance arises. As one reason for resistance and therapy relapse it has been shown that AR expression and AR activity is dysregulated in castration-resistant PC cells [2].

During investigation of the AR protein complex, more than 130 binding proteins and therefore putative co-regulators have already been identified [3]. Beyond this manifold potential regulatory network it is of great interest that heat shock proteins have been demonstrated to be vital elements in modulation of AR turn-over and activity. Our recent research focuses on the regulatory interference between AR and heat shock protein 27 (HSP27). The latter one, which is highly expressed in PC tissue, takes a pivotal role in tumor cell growth and survival. Whereas HSP27 was previously shown to regulate a variety of AR functions including receptor stability, nuclear shuttling and AR transactivation [4, 5], we demonstrated that HSP27 is furthermore involved in the regulation of AR expression on the level of mRNA synthesis. Down-regulation of HSP27 in the AR positive cell line LNCaP by HSP27-specific siRNA, caused diminished levels of AR protein as well as AR mRNA. Moreover, the over expression of HSP27 protein in AR negative PC cell line PC-3 significantly enhanced AR mRNA transcription, however, re-expression of functional AR protein was not detectable. Our observations indicated...
that HSP27 regulatory properties control AR expression by stimulated synthesis of AR transcripts [6].

AR is forms with variable truncated COOH-terminal regions and hence lacking the ligand-binding domain exhibit ligand-independent and therefore constitutive transcriptional activity. Generation of these short receptor is forms has been proposed by mutations, alternative splicing and proteolytic cleavage [7, 8, 9]. Due to detection in primary PC patients, samples, it has been suspected, that short AR is forms cause resistance to AR-antagonistic therapy [10]. As HSP27 appeared to be involved in regulating AR expression, we investigated the impact of HSP27 on the expression of short AR is forms in the PC cell line 22Rv1, which express at least two COOH-terminally deleted AR is forms [11]. The over expression of HSP27 protein in 22Rv1 cells induced the expression of short AR is forms, whereas an HSP27 knock down diminished short AR levels. Taken together these results highlight a so far widely unknown but extensive influence of HSP27 on cellular AR regulation pattern. Surprisingly, there was no evidence for differential regulation of short and full-length AR is forms by HSP27.

As AR functionality appears to be influenced by HSP27 in a very particular way the question of further effectors within the HSP27/AR pathway arises. MicroRNA (miR)-1 was former described to act as a tumor-suppressor in solid tumors and most interestingly histological studies showed miR-1 amount being negatively correlated with HSP27 expression in primary PC tissue [12]. Our data from in vitro studies confirmed these observations and moreover, clearly indicated that HSP27 operates as a regulator of miR-1 [13]; HSP27 induction diminished miR-1 synthesis in PC cells. We could verify, that the previously described miR-1 tumor suppressor skills arised at least in part from miR-1-driven modulation of AR expression. Particularly, expression of miR-1 mimicking RNA in AR-positive PC cells led to down-regulation of AR expression. Our studies also demonstrated that the expression of all AR isoforms (AR long and the shortened, constitutively active AR isoforms) is negatively affected by miR-1 the same way [11]. Most interestingly, inhibition of miR-1 synthesis in AR-negative PC cells caused a significant increase of AR mRNA vice versa. Another interesting subject of our current research is the AR inhibitor ErbB3-binding protein-1 (Ebp1), which is part of epidermal growth factor (EGF) signaling cascades. Ebp1 was formerly identified to attenuate AR expression and activity, next to Ebp1 functionality which is involved in chemotherapy failure [14, 15]. Based on these findings we suggested a possible correlation between Ebp1 and the HSP27/miR-1 signaling axis in form of a HSP27- and miR-1-driven control of Ebp1 expression in PC cells. Notwithstanding, we could not establish any HSP27/miR-1 driven effect on Ebp1 expression [16]. Thus, it appears more likely that Ebp1 signaling is completely independent from HSP27 and miR-1 pathways and stresses the complex AR regulation mechanisms throughout PC cells.

In conclusion, beneficial and sufficient anti-PC treatment warrants a better understanding of AR capacity by which castration resistant cellular growth is promoted. During the past years, new insights have been made into mechanisms of AR functionality and AR-regulated gene expression - nevertheless, the identification of AR-regulating factors and the underlying regulation pathways must be proceeded to ensure a prospective development of potent targeted therapy approaches. The newly identified signaling axis HSP27/miR-1/AR represents such a new promising resource throughout PC treatment ready to maintain prospective and more ambitious pharmacological studies.

Conflicting interests

The authors have declared that no competing interests exist.

References


