Spindle assembly checkpoint serine / threonine kinases BUB1 and BUB1B have distinct actions in castration-resistant and chemo-resistant prostate cancer

Background

Using a systems biology approach, we identified a clinically relevant androgen receptor (AR) variant-driven seven gene network[(1)]. This gene set includes BUB1 and BUB1B, serine threonine kinases, which are related proteins that exert different functions on the spindle assembly checkpoint (SAC). Although the expression of both BUB1 and BUB1B genes are upregulated in CRPC patient samples, little is known regarding their roles in PC progression or their link to the AR pathway.

Methods and Results

To understand BUB1 and BUB1B function within the seven gene network, we individually depleted both kinases and measured expression of the other gene set members. Depletion of BUB1B, but not BUB1, downregulated all but one member of the set, suggesting that BUB1B is of particular importance in regulating the gene network in CRPC. While all evaluated PC cell lines expressed similar amounts of BUB1 and BUB1B, individual depletion of these kinases resulted in decreased proliferation in CRPC but not androgen-dependent PC cells. The anti-proliferative effects of BUB1 and BUB1B depletion was associated with prolonged mitosis and cell cycle inhibition in CRPC cells. Depletion of BUB1 and BUB1B also decreased expression of specific AR and AR-V7 target genes in CRPC cells under androgen-depleted conditions suggesting that BUB1 and BUB1B enhance AR ligand-independent signaling. BUB1B knockdown resulted in decreased levels of AR and AR-V7 protein, but not mRNA, in CRPC cells. In contrast, neither BUB1 nor BUB1B depletion in androgen-dependent PC cells affected AR transcriptional activity or AR levels. Since SAC dysregulation is a well characterized mechanism of taxane resistance, we analyzed the expression of BUB1 and BUB1B in taxane sensitive (TxS), resistant (TxR) and cabazitaxel resistant (cabR) PC cell lines. Expression of both genes was higher in TxR and cabR compared to their chemosensitive counterparts. Furthermore, inhibition of BUB1 kinase activity (BAY1816032) sensitized TxR and cabR cells to docetaxel and cabazitaxel treatment.

Conclusion

Collectively, our data indicate that both BUB1 and BUB1B have important but distinct roles in CRPC. Our results suggest that BUB1B represents a vulnerability in CRPC since it participates in a positive feedback loop to AR signaling likely through post-translational regulation of AR and AR-V7. On the other hand, BUB1 plays a role in taxane resistance. These results support investigation of BUB1 and BUB1B as therapeutic targets in CRPC.

(1) Magani F, Bray ER, Martinez MJ, Zhao N, Copello VA, Heidman L, Peacock SO, Wiley DJ, D'Urso G, Burnstein KL. 2018. Identification of an oncogenic network with prognostic and therapeutic value in prostate cancer. Mol Syst Biol. 14(8): e8202. doi: 10.15252/msb.20188202.