Heat shock protein 70 inhibitors suppress androgen receptor expression in LNCaP95 prostate cancer cells

Masayuki Shiota¹, Kazuaki Kita², Masako Tanaka³, Hiroshi Iwao⁴, Katsuyuki Miura⁵, Tatsuya Nakatani², Shuhei Tomita⁶

¹Res. Sprt. Platf., Osaka City Univ. Grad. Sch. Med., Japan, ²Dept. Urol., Osaka City Univ. Grad. Sch. Med., Japan, ³Dept. Life Sci. Med. BioSci., Sch. Sci. Eng., Waseda Univ., Japan, ⁴Dept. Edu, Shitennoji Univ., Japan, ⁵Dept. Appl. Pharmacol. Ther., Osaka City Univ. Grad. Sch. Med., Japan, ⁶Dept. Pharmacol., Osaka City Univ. Grad. Sch. Med., Japan

Androgen deprivation therapy is initially effective for treating patients with advanced prostate cancer; however, the prostate cancer gradually becomes resistant to androgen deprivation therapy, which is termed castration-resistant prostate cancer (CRPC). Androgen receptor splice variant 7 (AR-V7), one of the causes of CRPC, is correlated with resistance to a new-generation AR antagonist (enzalutamide) and poor prognosis. Heat shock protein 70 (Hsp70) inhibitor is known to decrease the levels of full-length AR (AR-FL), but little is known about its effects against CRPC cells expressing AR-V7. In this study, we investigated the effect of the Hsp70 inhibitors quercetin and VER155008 in the prostate cancer cell line LNCaP95 that expresses AR-V7, and explored the mechanism by which Hsp70 regulates AR-FL and AR-V7 expression. Quercetin and VER155008 decreased cell proliferation, increased the proportion of apoptotic cells, and decreased the protein levels of AR-FL and AR-V7. Furthermore, VER155008 decreased AR-FL and AR-V7 mRNA levels. Immunoprecipitation with Hsp70 antibody and mass spectrometry identified Y-box binding protein 1 (YB-1) as one of the molecules regulating AR-FL and AR-V7 at the transcription level through interaction with Hsp70. VER155008 decreased the phosphorylation of YB-1 and its localization in the nucleus, indicating that the involvement of Hsp70 in AR regulation might be mediated through the activation and nuclear translocation of YB-1. Collectively, these results suggest that Hsp70 inhibitors have potential anti-tumor activity against CRPC by decreasing AR-FL and AR-V7 expression through YB-1 suppression.