Identification of new inhibitors of the androgen signaling axis to counteract prostate cancer resistance to castration.

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Abstract:

Resistance to castration is one of the major causes of death in prostate cancer patients. It is often linked to mechanisms that are dependent on the androgen receptor (AR) such as amplification or mutations of the receptor, expression of AR splice variants, in particular AR-V7, that are constitutively active because of a lack of the ligand binding domain, or overexpression of coactivators that stimulate AR transcriptional activity. Strategies to counteract resistance to castration have primarily focused on the identification of more specific and more potent AR antagonists leading to the approval of enzalutamide or darolutamide. However, fewer studies investigated other mechanisms that regulate AR transcriptional activity including the targeting of AR coactivators, probably because they were considered as undruggable targets and also because of their extensive number.
Our project aims at the identification of new molecules that can impair the transcriptional activity of full-length AR or AR-V7 by screening chemical libraries of diverse origins. They include the Prestwick Chemical and Natural Compounds) libraries and a library from the National Museum of Natural History that is composed of extracts from 80 different strains of endophitic fungi of brown algae with a unprecedented chemical diversity. For these purposes, we have generated dedicated cell lines stably expressing AR or AR-V7 and a luciferase reporter system allowing the quantification of AR transcriptional activity by using Promega product “Dual-Luciferase® Reporter Assay System”. We also implemented several models allowing us to measure the effect of specific coactivators on AR activity in order to identify specific inhibitors of these coactivators using dedicated two-hybrid screening models. We will present the preliminary results of our screening and on the identification of FHL2, a coactivator of both AR and AR-V7 receptors, as a potential target. Identification of new inhibitors of the androgen axis and/or AR coactivators may be useful to potentiate the effect of AR antagonists currently used in the clinic to overcome resistance to castration.

Keywords:

Prostate cancer, androgen receptor, coactivators, resistance to castration, drug screening.