THE ROLE OF THE MEMBRANE ANDROGEN RECEPTOR OXER1 IN ANDROGEN INDUCED CALCIUM CHANGES

Athanasios A. Panagiotopoulos, Konstantina Kalyvianaki, Evangelia Konstantinou, George Notas, Elias Castanas*, Marilena Kampa*

Laboratory of Experimental Endocrinology, University of Crete, School of Medicine, Heraklion, Greece
**e-mails: Marilena Kampa (kampam@uoc.gr), and Elias Castanas (castanas@uoc.gr)*

In prostate cancer, calcium homeostasis plays a significant role in the disease's development and progression. Intracellular calcium changes are an important secondary signal, triggered by a variety of extracellular stimuli, that controls many cellular functions. One of the main events affecting calcium is androgen signaling. Androgens can induce rapid calcium increases, mainly independently of the classical androgen receptor. Several studies have reported an effect mediated via G protein-coupled membrane receptors. In the present work, we have explored the role of OXER1 (a receptor of 5-oxo-ETE-arachidonic acid metabolite and a membrane androgen receptor, as we have previously reported in intracellular, androgen-induced, calcium increases in prostate cancer cells. Moreover, we report the specific signaling cascade(s) involved.Calcium was assayed using Fura 2-AM and/or Fluo-4-AM. Specific siRNAs and OXER1 agonists (5-oxo-ETE) and antagonists (GUE-1654) for OXER1 involvement. Downstream signaling was identified using specific kinase inhibitors and siRNAs. OXER1 expression was assayed by qPCR.Treatment of DU-145 cells with testosterone-BSA (a membrane impermeable analog) rapidly increased intracellular calcium, mainly from intracellular stores (as shown by nifidepine and U73122 -an inhibitor of L-type Ca^{2+} channel and phospholipase C, respectively). This effect was mediated by a GPCR (pertussis toxin- inhibited). The involvement of OXER1 was verified by OXER1 silencing and GUE-1654 inhibition. Surprisingly 5-oxo-ETE also specifically and dose dependently reverted the effect of testosterone-BSA. Additionally, it was found that both $G\alpha i$ (without cAMP signaling) and $G\beta\gamma$ signaling via PI3K/Akt, FAK, c-Src and RACK-1 have a critical role in testosterone effect. Our findings clearly indicate OXER1 as the GPCR receptor involved in testosterone-induced calcium changes by activating specific $G\alpha/G\beta\gamma$ signaling cascade(s), and illustrate, once again, an important interaction between androgens and lipid metabolites for tumor cell fate regulation.

Bibliography

1. Panagiotopoulos, A. et al. OXER1 mediates testosterone-induced calcium responses in prostate cancer cells. Molecular and Cellular Endocrinology (2022) 539: 111487.
2. Kalyvianaki, K. et al. Antagonizing effects of membrane-acting androgens on the eicosanoid receptor OXER1 in prostate cancer. Scientific reports (2017) 7: 44418.

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