Novinky v biomedicínském výzkumu
Biomedical Research News

Estrogen receptor in breast cancer: surprising regulation leading to an innovative, new treatment strategy

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1. LÉKAŘSKÁ FAKULTA
Univerzita Karlova

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Des Richardson

Professor Richardson is a multidisciplinary medicinal chemist, biochemist and pharmacologist whose career has spanned medicinal chemistry, drug design, development, commercialization, cancer biology, and neurobiology. He holds the Alan Mackay-Sim Distinguished Chair of Cancer Cell Biology at Griffith University (Inaugural Chair – First Named Chair at Griffith University in its 50-year history), Nathan, Brisbane, and he is a National Health and Medical Research Council (NHMRC) of Australia Senior Principal Research Fellow.

He published more than 460 articles, reviews, patents, chapters etc. with H-index: 101; >44,700 citations over entire career. He was recently honored by the international Otto Krayer Award in Pharmacology 2022 from the American Society of Pharmacology & Experimental Therapeutics (ASPET). He is Executive Editor of BBA-General Subjects and have served on the Ed. Boards of 49 journals, including: JBC, Antioxidants Redox Signaling, Biochem. J., Free Radic. Biol. Med., Pharmacol. Res., J. Clin. Pathology (Assoc. Ed.), Int. J. Biochem. Cell Biology, BBA-Mol. Cell. Res., Mol. Pharmacol., Pharmacol. Res., Cancers, etc.

His major translational research achievement is development of the redox active anticancer and antimetastatic drug, DpC, which overcomes P-glycoprotein-mediated resistance and up-regulates the metastasis suppressor, NDRG1. This has led to commercialization of DpC and the international company, Oncochel Therapeutics LLC, USA and its Australian subsidiary, Oncochel Therapeutics Pty Ltd. Notably, DpC entered multi-centre Phase I clinical trials for advanced and resistant cancer. These anticancer drugs target the lysosome via the P-glycoprotein transporter.

14.15 Registration for students

14.30–15.30 Estrogen receptor in breast cancer: surprising regulation leading to an innovative, new treatment strategy

Estrogen receptor-α (ER-α) is a key driver of breast cancer (BC) targeted by tamoxifen. However, tamoxifen resistance is a major problem. An important mechanism of resistance is the activation of EGFR/HER2/HER3 signaling and other hormone receptors (androgen receptor, progesterone receptor, prolactin receptor that intrinsically activate ER-α. Hence, therapeutics targeting multiple receptors, rather than ER-α alone, would be extremely useful and may overcome tamoxifen resistance.

This study examined the activity of di-2-pyridylketone-4,4-dimethyl-3-thiosemicarbazone (Dp44mT) and di-2-pyridylketone-4-cyclohexyl-4-methyl-3-thiosemicarbazone (DpC), on the expression and activation of crucial hormone receptors, their cofactors, and key resistance pathways in ER-α-positive breast cancer.

Strikingly, DpC differentially regulated 106 estrogen-response genes with Sankey diagram analysis demonstrating this was linked to decreased mRNA levels of 4 central hormone receptors involved in breast cancer pathogenesis, namely androgen receptor, progesterone receptor, prolactin receptor.

In conclusion, through a bespoke non-hormonal mechanism, Dp44mT and DpC disrupt multiple key inter-receptor interactions that act with ER-α to promote breast cancer constituting an innovative therapeutic approach.

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Přednáškové odpoledne je součástí kurzu „**Novinky v biomedicínském výzkumu**“, který je jedním z doporučených povinně volitelných kurzů pro Ph.D. studenty oboru **Biochemie a patobiochemie** (Oborová rada 04) a **Fyziologie a patofyziologie člověka** (Oborová rada 05). Účastníci na konci kurzu získají zápočet. Kurz je sestaven z přednášek zahraničních a domácích světově uznávaných odborníků zabývajících se molekulovými mechanismy etiologie, patogeneze a terapie chorob. Vítáni jsou i studenti jiných oborů a zájemci z řad vědeckých pracovníků a lékařů.