Stephen Assinder et al., J Cancer Sci Ther 2015
http://dx.doi.org/10.4172/1948-5956.S1.041

OMICS International
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World Congress on
Breast Cancer

August 03-05, 2015 Birmingham, UK

Does copper transporter 2 (CTR2) quaternary structures and subcellular localisation determine sensitivity of breast cancer cell lines to platinum-based chemotherapies?

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Influx of reduced copper into cells is mediated by the copper transporters CTR1 and CTR2. CTR1 and 2 are also thought to be responsible for the influx of platinum-based cytotoxic drugs used in the treatment of cancers. Evidence suggests that the sensitivity of a cell to such drugs (eg. cisplatin) might relate to the amount of CTR2 present. Immunohistochemical analysis of breast cancer tissue microarrays demonstrated an increased amount of CTR2 relative to CTR1 in both invasive ductal and invasive epithelial carcinomas as compared to normal breast tissue.We than tested the hypothesis thatgreater amounts of CTR2 reduced sensitivity of breast cancer cells tocisplatin. Levels of CTR2 proteins were assayed in a normal breast epithelial cell line (184B5), and 3 representative breast cancer cell lines (MCF7, HCC1806, MDA-MB-468) by western blot. Western blot analysis detected monomeric and dimericCTR2. In the relatively cisplatin insensitive MCF7 cell line (IC_{50} > 20 μmol.L^{-1}) there is predominantly dimeric form. Cisplatin sensitive HCC1806 and 184B5 (IC_{50}=5 μmol.L^{-1}), have predominantly monomeric CTR2. The highly cisplatin sensitive (IC_{50}=0.5 μmol.L^{-1}) MDA-MB-468 breast cancer cells have significantly less total CTR2 protein, butsimilar amounts of CTR2 monomer and dimer. Confocal imaging demonstrated that cisplatin resistant MCF7 cells exhibit peri-nuclear CTR2 while more sensitive cell linesshow an unexpected CTR2 nuclear localisation. We conclude that the amount of total CTR2, its quarternary structure and sub-cellular localisation may determine cisplatin sensitivity. Dimerisation of CTR2 might prevent localisation to the nucleus in turn preventing cisplatin from trafficking to the nucleus and resultant DNA damage and apoptosis.

Biography

Stephen Assinder completed his Doctorate studies at the University of Bristol, UK in 1996. He now leads the Bosch Institute's Andrology Research Group, at the University of Sydney. Research interests include: the roles of structural proteins in cancer development; signaling pathway integration and dysregulation in cancers; the actions of oxytocin in both benign and malignant prostate disease; identification of prognostic markers of prostate disease and treatment. He is also a founding member of the Copper Biology Research Group which is focused on chemotherapeutic implications of copper transproters.

Notes: