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The expression, activity and targeting of calcitonin receptor, a putative tumour suppressor in the deadly brain tumour glioblastoma

Calcitonin receptor (CTR) is highly expressed in the lethal brain tumour glioblastoma by glioma cells and glioma stem cells (1). Furthermore, evidence that CTR is a tumour suppressor in glioblastoma (2) is based on inactivating mutations that compromise the actions of an agonist. In view of the current consensus that glioma stem cells are highly invasive and provide resistance to conventional therapeutics, we investigated CTR as a potential therapeutic target on high grade glioma (HGG) cell lines that are similar to glioma stem cells. Pharmacological data from 4 HGG cell lines that express CTR show that 3 lines (JK2, PB1 & WK1) do not respond to calcitonin in contrast to SB2b, in which adenylyl cyclase is activated. Our group has developed monoclonal antibodies that (i) binds a specific epitope in the extracellular domain (ECD, mAb2C4), (ii) binds an epitope in the carboxyl terminus (mAb1H10) and (iii) that identifies the insert-positive isoform (mAb10G6). In contrast to the pharmacological inactivation, CTR protein was detected on immunoblots of cytosolic, nuclear and membrane fractions from the HGG cell lines with one exception, the membrane fraction from PB1. Immunotoxins (mAb2C4:dianthin and mAb2C4:gelonin) and an antibody:drug conjugate (ADC, mAb2C4:monomethyl auristatin E [MMAE]) were constructed and tested in HGG cell lines. When tested on JK2, SB2b and WK1, both immunotoxins were 250 times more potent than the ADC in the presence of the triterpene glycoside SO1861 that enhances endo-lysosomal escape (3). PB1, which expresses low levels of CTR in the membrane fraction, was resistant to the immunotoxins.

Biography

Peter Wookey completed his PhD from the Australian National University and postdoctoral studies at the University of Tübingen, Germany, supported by the Alexander von Humboldt Stiftung. He has spent many years in medical research at the University of Melbourne, where he manages a research group. He has developed antibodies that bind extracellular domains of GPCRs, conjugates for imaging programmed cell death and immunotoxins aimed at the treatment of glioblastoma. He has published more than 55 refereed manuscripts and filed patents granted in the US & EU with further patents pending. He is founder of two start-ups.

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