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Wnt-DP103-GSK3β cascade promotes Wnt/β-catenin signaling in parental and stem cells from triple negative breast cancer

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Despite recent advances in breast cancer therapeutics, mortality of highly metastatic triple negative breast cancer (TNBC) subtype remains high; due to their lack of hormone receptors expression for targeted therapy. Therefore, there is a pressing need to identify new prognostic markers and therapeutic targets for this group of breast cancers. Aberrant activation of Wnt/β-catenin signaling has been associated with breast cancers; where 40% of total breast cancers have elevated β-catenin levels and/or Wnt activity. Herein, we identify DEAD-box RNA helicase DP103 as a novel driver of Wnt/β-catenin pathway in TNBC. The link between DP103 and Wnt/beta-catenin signaling was further validated using in vivo Zebrafish models, where disruption in DDX20 gene splicing mechanisms resulted in severe early embryonic developmental defects which phenocopies loss of Wnt/beta-catenin signaling during gastrulation. Interestingly, we also show DP103 drives breast cancer stem cell (CSC) formation, a process regulated by the Wnt/beta-catenin pathway. Depletion of DP103 led to a marked reduction in the percentage of CSC-enriched mammospheres with reduced tumor-initiating ability. Mechanistically, we show DP103's role in driving Wnt/beta-catenin pathway is independent of casein kinase I activity but highly dependent on GSK3β activity. More interestingly, from molecular docking data, we found DP103 protein has to be phosphorylated at threonine residue 552, when it interacts with GSK3β. Surprisingly, induction of Wnt/β-catenin signaling also significantly increased DP103 expression, indicating a possible positive feedback loop. Collectively, our data suggest a novel regulatory role of DP103 in the Wnt/β-catenin signaling pathway in parental and CSC derived TNBC.

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Talking to children and young people about hereditary breast cancer

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Many families with a family history of breast or ovarian cancer will request genetic testing to ascertain whether family members carry the gene mutation. The gene test results will indicate whether women need to undergo additional screening measures and receive prophylactic treatments to reduce their risk of developing cancer. Whilst many families welcome the opportunity to receive this additional surveillance a major concern that continues is when and how parents should talk to their children about the cancer and hereditary risks. We carried out semi-structured qualitative interviews with 11 families, which included parents, children (7-11years) and young people (12-18 years) to learn more about families' experiences about managing these sensitive conversations and the effect upon their family functioning and coping with the risk information. The interview transcripts were coded and thematically analyzed. Four themes emerged from the data on family communication, perception of cancer risk, managing risk and the impact of genetic risk upon children and young people's decision-making. Our findings showed that parents were worried for their children but only discussed a limited amount of information about the cancer risk and particularly about the psychological effects of prophylactic measures. Children and young people often did not realize implications of prophylactic procedures, especially bilateral mastectomy and breast reconstruction. With contemporary Western society's acceptance of cosmetic surgery, many children and young people focused predominantly on the perceived positive benefits without realizing more fully the physical and psychological consequences of managing the risk information and the outcomes of surgery.

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