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International Conference on
Pediatrics & Gynecology

Interplay between BRCA1 and RHAMM regulates epithelial apicobasal polarization and may influence risk of breast cancer

Chris A Maxwell

Child and Family Research Institute, University of British Columbia, Canada

Differentiated mammary epithelium shows apicobasal polarity, and loss of tissue organization is an early hallmark of breast carcinogenesis. In *BRCA1* mutation carriers, accumulation of stem and progenitor cells in normal breast tissue and increased risk of developing tumors of basal-like type suggest that BRCA1 regulates stem/progenitor cell proliferation and differentiation. However, its function in this process and the link to carcinogenesis remain unknown. Here we depict a molecular mechanism involving BRCA1 and RHAMM that regulates apicobasal polarity and, when perturbed, may increase risk of breast cancer. Starting from complementary genetic analyses across families and populations, we identified common genetic variation at the low-penetrance susceptibility *HMMR* locus (encoding for RHAMM) that modifies breast cancer risk among *BRCA1*, but probably not *BRCA2*, mutation carriers: n = 7,584, weighted hazard ratio (wHR) = 1.09 (95% CI 1.02 – 1.16), *ptrend* = 0.017; and n = 3,965, wHR = 1.04 (95% CI 0.94 – 1.16), *ptrend* = 0.43; respectively. Subsequently, studies of MCF10A apicobasal polarization revealed a central role for BRCA1 and RHAMM, together with AURKA and TPX2, in essential re-organization of microtubules. Mechanistically, re-organization is facilitated by BRCA1 and impaired by AURKA, which is regulated by negative feedback involving RHAMM and TPX2. Taken together, our data provide fundamental insight into apicobasal polarization through BRCA1 function, which may explain the expanded cell subsets and characteristic tumor type accompanying *BRCA1* mutation. It also provides rationale for inhibition of AURKA in the basal- like tumors associated with these mutations.

Biography

Dr Maxwell completed his Ph.D from the University of Alberta (Canada), followed by postdoctoral studies from Lawrence Berkeley National Laboratory (Berkeley, USA) and the Catalan Institute of Oncology (Barcelona, Spain). He is now an Assistant Professor in the Department of Pediatrics at the University of British Columbia and a Scientist within the Child and Family Research Institute. His research focuses on the molecular regulators of microtubule organization and centrosome polarity during mitotic spindle assembly, cell polarity and migration.