

 PREVENTION

RANKLing with breast cancer development

Prophylactic mastectomy can be recommended for women carrying *BRCA1/2* mutations, owing to their high risk of breast cancer, particularly aggressive, ‘basal-like’ disease. Now, new findings highlight inhibition of RANK ligand (RANKL) as a potential alternative preventive strategy.

Luminal progenitor cells are the probable cell-of-origin for *BRCA1*-mutated breast tumours, with aberrant progesterone signalling seemingly involved in tumorigenesis. RANKL is induced by, and has a key role in, progesterone signalling. “Thus, we were keen to understand whether RANK signalling is perturbed in the ‘culprit’ luminal progenitor subset in *BRCA1*-mutation carriers,” explains Geoff Lindeman.

Lindeman and co-workers identified RANK⁺ and RANK⁻ luminal progenitors in *BRCA1/2*-mutated prophylactic mastectomy specimens and ‘normal’ reduction mammoplasty samples. Notably, RANK⁺ cells were more abundant in *BRCA1*-deficient than in wild-type or *BRCA2*-mutated tissues, and were highly proliferative and DNA-damage prone, “even in the *BRCA1* heterozygous state in ostensibly normal breast tissue.” Moreover, RANK⁺ cells had molecular profiles

akin to those of basal-like tumours, and were highly clonogenic.

“We were very excited to find that we could ‘switch off’ the clonogenic activity of progenitors from *BRCA1*-mutation carriers using the RANKL inhibitor denosumab,” says co-senior author Jane Visvader. RANKL inhibition also prevented or delayed the onset of basal-like tumours in *Brc1*-deficient mouse models. Importantly, in a pilot study (termed ‘BRCA-D’) of preventative denosumab therapy in *BRCA1*-mutation carriers, breast epithelial cell proliferation was markedly reduced in the first three patients following 3 months of treatment.

Denosumab is approved for patients with osteoporosis or solid-tumour bone metastases. Thus, Lindeman concludes: “it may be possible to repurpose denosumab for use as a breast cancer prevention drug. If successful, this approach could offer a strategy for preventing hormone-receptor-negative breast cancer.”

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