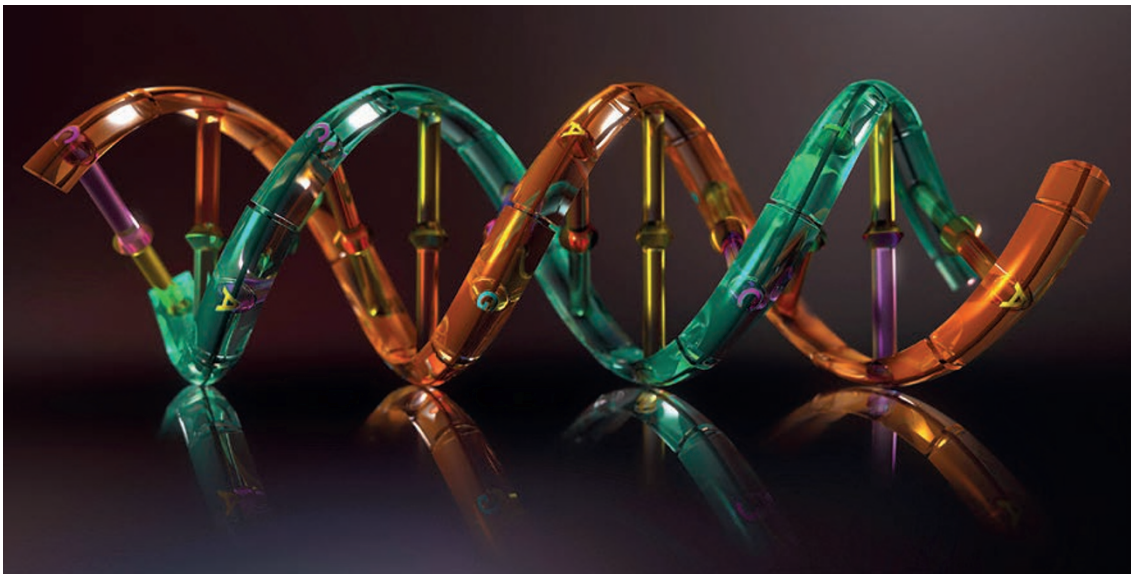
Nature Reviews Drug Discovery | Published online 22 Jul 2016; doi:10.1038/nrd.2016.152



Ikon Images/Alamy Stock Photo

ANTICANCER AGENTS

Osteoporosis drug shows potential for breast cancer prevention

Women harbouring germline mutations in *BRCA1* commonly develop breast tumours at an early age with poor prognosis. The development of a preventive strategy remains a key therapeutic goal. Now, writing in *Nature Medicine*, Nolan and colleagues report that inhibition of receptor activator of NF-κB ligand (RANKL) delays breast cancer development in mouse models and inhibits breast epithelial cell proliferation in humans carrying a *BRCA1* mutation.

RANK–RANKL signalling regulates the proliferation and differentiation of mammary epithelial cells and has been implicated in the development of hormone-induced breast cancer. Moreover, RANKL has emerged as an important mediator of hormonal signalling to mouse luminal progenitor (LP) cells, which are thought to be the major cellular target for neoplastic transformation in *Brca1*-mutant breast tissue. Given this, Nolan and colleagues set out to explore the potential role of RANK–RANKL signalling in the initiation of *BRCA1*-mutant breast cancer.

First, the authors analysed histologically normal breast tissue from *BRCA1*-mutation carriers and identified a RANK$^+$ subset of LP cells. *In vitro* analysis of these RANK$^+$ cells showed them to be highly proliferative, strongly susceptible to DNA damage and to exhibit a molecular signature similar to that of basal-like breast cancer.

Next, the authors investigated the effect of inhibiting RANKL signalling on cell proliferation. Treatment of *ex vivo* three-dimensional breast organoids, derived from pre-neoplastic (histologically normal) *BRCA1*-mutant tissue, with denosumab (a RANKL monoclonal antibody that is FDA-approved to treat osteoporosis) blocked progesterone-induced proliferation.

Furthermore, a small pilot study involving three premenopausal women carrying the *BRCA1* mutation demonstrated the anti-proliferative effect of RANKL inhibition *in vivo*. Analysis of pre- and post-treatment biopsy samples revealed that 3 months of denosumab treatment (administered subcutaneously on days 1, 15, 28 and 56 of the study) significantly reduced breast epithelial cell proliferation in each of the subjects.

Finally, inhibition of RANKL was demonstrated to delay tumour development in *Brca1*-deficient mouse models. RANKL inhibition, through injection of osteoprotegerin-Fc (osteoprotegerin (OPG) is the natural inhibitor of RANKL) three times per week, significantly delayed tumour onset in a *Brca1*-deficient mouse model, with 65% of mice not developing tumours by the experimental end point of 250 days. A similar delay in tumour growth was seen in *Brca1*-deficient mice treated with a RANKL-specific antibody.

In addition, treatment of a RANK$^+$ patient-derived xenograft that was established from a *BRCA1*-mutation carrier with docetaxel plus OPG-Fc significantly attenuated tumour growth, suggesting that RANKL may also serve as a therapeutic target in established RANK$^+$ tumours.

In summary, these findings indicate an integral role for the RANK pathway in tumour initiation in *BRCA1*-mutation carriers and support the repurposing of denosumab as a novel preventive therapeutic strategy.

Sarah Crunkhorn

ORIGINAL ARTICLE Nolan, E. *et al.* RANK ligand as a potential target for breast cancer prevention in *BRCA1*-mutation carriers. *Nat. Med.* http://dx.doi.org/10.1038/nm.4118 (2016)