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Commentary

RANKL/OPG in Breast Cancer — Extending Its Territory to *BRCA* Mutation Carriers

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Receptor activator of nuclear factor-κB ligand (RANKL) and its decoy receptor osteoprotegerin (OPG) are established as essential determinants of bone health and a dysregulation of this system towards RANKL results in osteoporosis (Rachner et al., 2011). Based on these findings, denosumab, a monoclonal antibody directed against RANKL was developed and has now been approved for the treatment of osteoporosis and bone metastases (Rachner et al., 2011).

In the past years, an additional role of the RANKL/OPG system in mammary carcinogenesis has been recognized. Until now, most studies addressing this topic have focused on the role of RANKL as the direct effector molecule in this system. Two simultaneously published studies in 2010 convincingly provided evidence to show that RANKL mediates progestin-driven mammary carcinogenesis (Schramek et al., 2010; Gonzalez-Suarez et al., 2010). Upon exposure of mice to progesterone or progesterone derivatives the local expression of RANKL is highly increased in mammary cells. Increased carcinogenesis observed in the presence of medroxyprogesterone and the carcinogen 7,12-dimethylbenz(a)anthracene (DMBA) is prevented by both the genetic inhibition of RANK, which acts as the receptor for RANKL (Schramek et al., 2010) or by pharmacological inhibition of RANKL (Gonzalez-Suarez et al., 2010). In addition, tumour-infiltrating regulatory T cells have been shown to promote metastases by producing high levels of RANKL (Tan et al., 2011).

In this issue of *EBioMedicine*, Widschwendter and colleagues extend the scope of the RANKL/OPG system to women with BRCA-mutations (Widschwendter et al., 2015). BRCA-mutations occur infrequently and account for about 5 to 10% of all breast cancers and 15% of ovarian cancers (Campeau et al., 2008). The lifetime risk of developing breast cancer is drastically increased in women with a harmful mutation in *BRCA1* or *BRCA2* compared to non-mutation carriers, however a clear prediction with regard to cancer occurrence remains impossible.

In their analyses of almost 400 BRCA 1/2-mutation carriers, Widschwendter et al. found OPG serum levels to be lower, most notably in BRCA1-mutation carriers, compared to ~780 controls (Widschwendter et al., 2015). In addition, free RANKL serum concentrations were also decreased in BRCA-mutation carriers. To address this issue which may appear discrepant at first, further studies were conducted by comparing serum and tissue expression of RANKL and OPG in ovariectomised adult female cynomolgus macaques treated with no hormones, oestrogens or an oestrogen/progestin combination. While progestin treatment increased RANKL expression in the mammary gland there were no differences in serum RANKL. On the other hand lower levels of serum OPG following progestin treatment correlated with a decreased expression in breast tissue. These results indicate that – in contrast to RANKL – breast tissue derived OPG substantially contributes to serum levels.

Finally, associations were made for serum RANKL and OPG and the menopausal status as lack of ovarian function (i.e., postmenopausal status) is known to protect from breast cancer. Serum levels of OPG were higher in postmenopause as compared to premenopause, whereas an opposite tendency was observed for RANKL. Even more compelling evidence for a possible role of OPG in the risk prediction of breast cancer was provided by the analysis of about 220 patients with distinct BRCA mutations that are associated with different HR for breast cancer. Therein, OPG serum levels were inversely associated with breast cancer risk. In addition, low levels of OPG were associated with an increased proliferation in the mammary gland as assessed by Ki67 measurement.

These results underline a role of the RANKL/OPG system in the pathophysiology of breast cancer. Since the activity of RANKL is directly determined by the presence of OPG, it is important to assess the concentration of both proteins and the RANKL/OPG ratio has often been considered as a better indicator of RANKL activity than RANKL alone. However, serum levels do not always reflect the situation at the tissue level. This may be especially true for RANKL, where previous studies reported elevated levels of RANKL in the cells of the bone microenvironment in postmenopausal women, and while this increase was reversed in women receiving hormone replacement therapy in bone cells, no changes in serum RANKL were observed between the groups (Eghbali-Fatourechi et al., 2003).

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In the past two years, the challenges associated with the diagnosis of a BRCA mutation have received increased attention as a result of the "Angelina Jolie Effect" (Evans et al., 2014). Despite the increasing awareness, the uncertainty of the diagnosis with respect to breast cancer risk and the potential need for risk-reducing mastectomy remain a significant psychological burden for numerous young women. Thus, defining novel methods to better predict the risk of developing breast cancer and most importantly discover non-invasive preventive measures are urgently needed.

In summary, results from this study provide a clear rationale for further investigation of the RANKL/OPG system in breast cancer and specifically in patients with BRCA 1/2-mutations.

Conflict of interest

TDR has received grants or honorarium for advisory boards to the individual or the institution by Amgen, Novartis and Merck. MR has nothing to declare.

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