CANCER

RANKL inhibition—a new weapon against breast cancer?

The receptor activator for nuclear factor κB (RANK) and its ligand RANKL represent an important molecular link between progesterone and breast cancer, which suggests that RANKL inhibition may be used to prevent or treat breast cancer.

In 1999, the RANKL knockout mouse provided the first genetic proof that the RANKL system is essential for osteoclast development. "At the same time, we had a strange finding in the lab," recollects Josef Penninger, senior author of one of two studies on RANKL recently published in *Nature*. All the offspring born to RANKL knockout mice died shortly after birth.

The researchers ignored it, thinking the mice were too unwell to care for their offspring. However, one day, someone mentioned a possible epidemiological association between bone loss and breast cancer in humans, which prompted Penninger to check the mammary glands of the mutant mothers. "To our surprise, we found that RANKL controls growth of mammary epithelial cells in response to pregnancy hormones, such as prolactin and progesterone."

Shortly after, several studies reported that hormone replacement therapy increases the risk of breast cancer. The idea was born that RANKL/RANK might be the missing link between sex hormones and breast cancer.

Using an experimental mouse model for sex-hormone-driven breast cancer, Penninger's group found markedly decreased incidence and delayed onset of breast cancer when RANK was inactivated in the mammary epithelium.

In a second study, Gonzalez-Suarez *et al.* published their findings on a transgenic mouse with RANK gain-of-function, which exhibited accelerated and increased mammary tumor formation. Similar to Penninger's findings, the researchers also found that pharmacological RANKL inhibition reduced the development of sex-hormone-induced mammary cancer from 100% to 10% in wild-type mice.

"Our data might have some intriguing implications," comments Penninger, as "mammograms used for screening detect microcalcifications. Since RANKL/RANK have key roles in bone metabolism, one could speculate that RANKL/RANK contributes to the calcification of such lesions, and its measurement could one day replace mammographies."

Moreover, denosumab, which blocks RANKL, has already been approved to treat osteoporosis. This agent could be evaluated in phase III trials for the treatment or prevention of breast cancer. As Penninger puts it, RANKL inhibition represents "a unique chance to potentially prevent breast cancer in millions of women—not in 20 years, but right now."

Linda Koch

Original articles Schramek, D. *et al.* Osteoclast differentiation factor RANKL controls development of progestin-driven mammary cancer. *Nature* **468**, 98–102 (2010) | Gonzalez-Suarez, E. *et al.* RANK ligand mediates progestin-induced mammary epithelial proliferation and carcinogenesis. *Nature* **468**, 103–107 (2010)