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TUMORIGENESIS

# Hormonally driven

The ovarian hormones oestrogen and progesterone are inextricably linked to breast cancer. Not only do their levels influence disease risk and prognosis, but manipulating their activity also forms the basis for gold standard treatments. It is therefore surprising that little is known about how they influence breast tumour development.

The idea that mammary stem cells (MaSCs) respond to ovarian hormones is an appealing one, but one with an important caveat: MaSCs are oestrogen receptor-negative ($ER^-$) and progesterone receptor-negative ($PR^-$). In spite of this challenge, teams led by Rama Khokha and Jane Visvader sought to characterize the effect of ovarian hormones on MaSC function.

MaSCs are thought to lie dormant, mobilising only during the hormonal onslaughts that occur during puberty and pregnancy, but Joshi *et al.* asked whether they responded to hormonal fluctuations during the menstrual cycle. They showed that during the mouse dioestrus phase (analogous to the luteal phase in humans) when progesterone levels peak, the MaSC-enriched basal cell pool increased by sixfold, with a concomitant 14-fold increase in the number of MaSCs that repopulate a cleared mammary fat pad in a recipient mouse. Therefore, far from being quiescent, MaSCs are in fact highly responsive to hormone levels during the reproductive cycle.

Asselin-Labat *et al.* came to similar conclusions. They found that treating virgin mice with a cocktail of oestrogen and progesterone led to a substantial increase in MaSC number and outgrowth potential *in vivo*. Conversely, hormone deprivation by ovariectomy or letrozole (which inhibits oestrogen biosynthesis) severely depleted the MaSC pool, compromising outgrowth potential. They also showed an 11-fold increase in MaSC number during mid-pregnancy, when PR expression is at its highest — a finding that might help explain the increased risk of breast cancer following pregnancy.

But if MaSCs are $ER^-$ and $PR^-$, how are ovarian hormones signalling? Joshi *et al.* found an answer that lies in the luminal and basal cells surrounding the MaSC niche. Using reverse transcription PCR analysis, they showed that both these cell populations significantly increased PR expression following treatment with 17β-oestradiol and progesterone. Under the same conditions, they observed profound upregulation of *Wnt4* and *Rankl* in luminal cells as well as induction of their respective receptors *Lrp5* and *Rank* in the MaSC-enriched basal cell population. Tellingly, both the RANK and WNT4a pathways are known mediators of progesterone-driven paracrine effects in the mammary gland. Asselin-Labat *et al.* concurred: during mid-pregnancy, they found a marked increase in RANKL expression in the luminal cell population, and the RANK receptor and the RANK signalling target *Id2* were specifically upregulated in the MaSC-enriched basal cell subset. Crucially, treatment with a RANKL inhibitor suppressed the clonogenic activity of this population. So, RANKL from luminal cells binding to its receptor on MaSCs is the likely paracrine effector of progesterone.

Together, these findings identify MaSCs as crucial targets for ovarian hormones, and support a model in which surges of progesterone occurring during the reproductive cycle and pregnancy prompt MaSC proliferation — providing a window during which MaSCs are targets for oncogenic mutations.

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**ORIGINAL RESEARCH PAPER**
Asselin-Labat, M.-L. *et al.* Control of mammary stem cell function by steroid hormone signaling. *Nature* 11 Apr 2010 (doi:10.1038/nature09027) | Joshi, P. A. *et al.* Progesterone induces adult mammary stem cell expansion. *Nature* 5 May 2010 (doi: 10.1038/nature09091)