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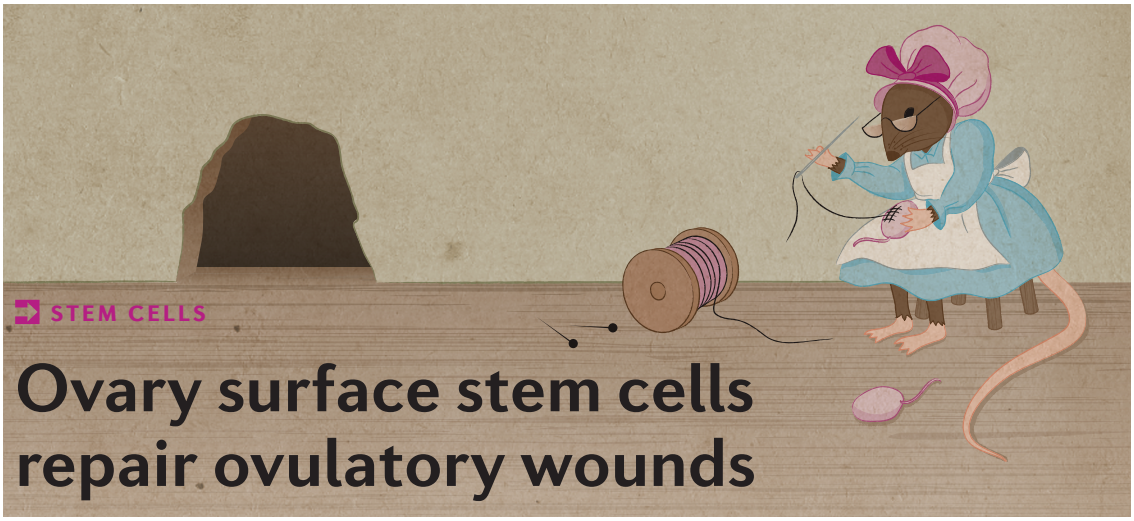

NPG/Vicky Summersby

STEM CELLS

Ovary surface stem cells repair ovulatory wounds

The epithelium of the ovary is subject to ovulatory rupture followed by repair throughout life. The nature and location of the stem cells that sustain regeneration of the ovarian surface epithelium (OSE) during ovulation has been debated. Now, Barker and colleagues identify Leu-rich-repeat-containing G protein coupled receptor 5 (LGR5)-expressing (LGR5$^+$) cells — located in the ovary surface layer — as stem cells that contribute to the ovary and oviduct epithelia during organogenesis, and that repair and maintain OSE homeostasis in the adult.

The WNT target gene *LGR5* has been reported as a marker for epithelial stem cells in several organs. Using conditional reporter mice that express *Lgr5–EGFP* (enhanced GFP), the authors observed LGR5$^+$ cells in the developing ovary from embryonic day 13.5 onwards. These cells were first detected in the ovary surface and subsurface layers, and later only in the epithelium of neonatal ovaries. In adult ovaries, LGR5$^+$ cells were observed in the OSE monolayer, in the distal oviduct epithelium and in the mesothelium lining of the mesovarian ligament (hilum; the junction area between the OSE and distal oviductal epithelium). LGR5$^+$ cells were detected throughout the OSE, but LGR5 expression was most prominent in ovulating regions where the OSE undergoes rupture. Importantly, the authors observed that in undamaged (non-ovulating) regions only a small proportion of dividing cells were LGR5$^+$, whereas in ovulating regions cycling LGR5$^+$ cells comprised a much higher proportion (~50%). These observations are consistent with a possible role of LGR5$^+$ cells in tissue repair.

To investigate the role of LGR5$^+$ cells during ovary development and regenerative repair, the authors carried out *in vivo* lineage tracing. LGR5$^+$ cell progeny marked with LacZ were followed over time, both during development and in adult ovaries. Embryonic and neonatal LacZ$^+$ clones expanded over time and ultimately contributed to the entire ovary surface, and to the adult oviduct and mesovarian ligament. Thus, embryonic and neonatal LGR5$^+$ cells are precursors of the adult ovary epithelial lineages. Moreover, reporter gene activity was maintained in the long term in adult tissues, which suggests that these LGR5$^+$ cells are also the source of adult stem cells that maintain OSE homeostasis.

In adult females, LacZ$^+$ clones of different sizes were found in the OSE. Small clones were distributed throughout the ovary surface around non-ovulating follicles, whereas the largest clones were consistently located at the periphery of ruptured follicles or in regions of repaired epithelia. Such observations indicate that most LGR5$^+$ cells in the adult OSE divide infrequently during normal epithelial turnover, but that multiple LGR5$^+$ cells are activated in response to ovulatory damage. Importantly, these lineage-tracing experiments also confirmed that LGR5$^+$ cells are capable of self-renewal and the generation of phenotypically different cell types, which are defining characteristics of stem cells.

Whereas previous studies had suggested that the hilum contained the stem cell reservoir for post-ovulatory repair of the entire OSE, this study showed that multiple LGR5$^+$ epithelial stem cells reside throughout the OSE. These findings may also be clinically relevant, as the OSE and tubal epithelia are thought to be the source of ovarian cancers, which raises the possibility that these malignancies may originate from LGR5$^+$ stem cells.

Kim Baumann

> “multiple LGR5$^+$ epithelial stem cells reside throughout the OSE”

ORIGINAL RESEARCH PAPER Ng, A. *et al.* Lgr5 marks stem/progenitor cells in ovary and tubal epithelia. *Nature Cell Biol.* http://dx.doi.org/10.1038/ncb3000 (2014)