Nature Reviews Urology | Published online 7 Sep 2016; corrected online 31 Oct 2016; doi:10.1038/nrurol.2016.173

George Diebold/Getty

TESTICULAR CANCER

In a spin — disorientated divisions disrupt germ cells

> spindle-associated RHAMM could not be detected

Testicular germ cell tumour and one of its main risk factors, hypofertility, that can precede tumorigenicity by many years, could be the result of defective planar divisions of undifferentiated germ cells, according to new data published in *Cancer Research*. These findings shed light on the common aetiology linking these two pathologies.

Li and colleagues observed that transcript levels of hyaluronan-mediated motility receptor (RHAMM, also known as HMMR) — which is involved in the regulation of mitosis and maintaining mitotic spindle integrity — were high in the seminiferous tubules of mouse testes and that it localized to the mitotic spindle of spermatogonia and spermatocytes. However, spindle-associated RHAMM could not be detected in 28 of 29 patient seminoma samples.

In vivo, homozygous matings of mice with mutated *Rhamm* ($hmmr^{m/m}$) resulted in decreased litter sizes as did matings of $hmmr^{m/m}$ males with wild-type females, indicating that these male mice were hypofertile. $hmmr^{m/m}$ male mice also had testes of reduced size and severe atrophy of the seminiferous tubules, apparent at 5 weeks old. The seminiferous tubules of these mice were either depleted of germ cells or were completely degenerated.

A significant number of $hmmr^{m/m}$ males >30 weeks old had high numbers of atypical germ cells in their seminiferous tubules, which displayed abnormal mitosis or apoptotic nuclear fragmentation resembling intratubular germ cell neoplasia, with a concurrent elevation in p53 expression. Ablation of p53 by mating $hmmr^{m/m}$ males with $Trp53^{-/-}$ mice did not completely rescue germ cell apoptosis, and 30% of the progeny had testicular atrophy. Atypical germ cells were localized to the adluminal area of the seminiferous tubules and seminoma occurred in 3.7% of a subgroup of $hmmr^{m/m}$ mice undergoing ongoing follow-up monitoring.

Spermatogonial spindle orientation angle (which should be parallel to the basal membrane of the seminiferous epithelium) in $hmmr^{m/m}$ mice aged 5–10 weeks was significantly increased, included spindles perpendicular to the membrane, and did not differ from random distribution. In differentiating germ cells (in which the spindle should be orientated perpendicular to the basal membrane) the average angle was significantly reduced. The aberrant distribution of spindle orientation in male $hmmr^{m/m}$ mice probably contributes to geometrical alterations of planar divisions of undifferentiated germ cells, divisions that are required for germ cell renewal and functional testes. Analysis of differentiation markers showed that undifferentiated spermatogonia were prematurely displaced from the niche, whereas differentiated spermatogonia were prevented from translocating into the lumen of the seminiferous tubule.

In human germ cells *in vitro*, missense variants did not affect spindle localization; however, *RHAMM* expression was significantly downregulated. RNA interference screening identified *CFIM25* as a *RHAMM* regulator, and it was also observed to be significantly downregulated in seminomas.

These data indicate that reduced *CFIM25* expression and consequent *RHAMM* downregulation result in testicular atrophy and hypofertility caused by depletion of germ cells from the seminiferous niche and cellular atypia, germ cell neoplasia, and seminoma owing to premature displacement of undifferentiated germ cells.

"So far, reduced RHAMM expression in cancer-initiating cells has either not been analysed or not taken into consideration as predictor of their oncogenic potential," commented corresponding author Aspasia Ploubidou. "This study identifies RHAMM as an intrinsic regulator of male germ cell fate, and suggests RHAMM dysfunction is a mechanistic cause and common molecular link underpining hypofertility and seminoma development." Ploubidou concludes: "Our study proposes a new paradigm, namely that premature exit of stem cells from their niche is an initiating event in seminoma development. This finding opens a new area of investigation on the consequences of premature niche exit in oncogenesis in different organs."

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ORIGINAL ARTICLE Li H. *et al.* Impaired planar germ cell division in the testis, caused by dissociation of RHAMM from the spindle, results in hypofertility and seminoma. *Cancer Res.* http://dx.doi.org/10.1158/0008-5472.CAN-16-0179 (2016)

CORRECTION

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Nature Reviews Urology **13**, 561 (2016)

In the fifth paragraph of this Research Highlight the text should have read "In differentiating germ cells (in which the spindle should be orientated perpendicular to the basal membrane) the average angle was significantly reduced." The text has been corrected in the html and PDF versions.