GENETICS

Gains and losses

Aneuploidy — gains or losses of whole chromosomes — is a common feature of tumours, but it is not clear how this defect occurs, or whether it is a cause or simply a by-product of transformation. Sandra Hanks *et al.* report that mutations in the spindle-checkpoint gene *BUB1B* cause aneuploidy and contribute to an inherited cancer-predisposition syndrome.

The mitotic-spindle checkpoint is a surveillance mechanism that maintains the correct chromosome number during cell division. A large number of proteins, including members of the BUB and MAD family, regulate this process, delaying anaphase until the kinetochores of each chromosome pair have successfully attached to the spindle.

In a search for genetic defects that might cause mosaic variegated aneuploidy (MVA), a recessive condition characterized by aneuploidies and other chromosome defects, Hanks *et al.* identified mutations in both *BUB1B* alleles in five out of eight families with a history of this rare disease. MVA causes several developmental defects as well as a high risk of malignancy, with rhabdomyosarcoma, Wilms' tumour and leukaemia reported in several cases. Five individuals who were found to carry biallelic truncating and missense mutations in *BUB1B* had phenotypes typical of MVA, and two of these cases developed cancer. No such mutations have been detected in tumour cells collected from patients with other types of cancer, or from normal cell samples.

In mice, reduced expression of BUB1R, the protein encoded by *BUB1B*, results in defective spindle-checkpoint activation, aneuploidy, and predisposition to lung and colon cancers. In some human cancers, *BUB1B* has been shown to be epigenetically downregulated. So, aneuploidy, when caused by a functional disruption of the mitotic-spindle checkpoint, seems to be an important contributing factor to human cancer. Further studies will reveal whether defects in other spindle-checkpoint genes also contribute to aneuploidy-associated cancers.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Hanks, S. *et al.* Constitutional aneuploidy and cancer predisposition caused by biallelic mutations in *BUB1B*. *Nature Genet.* 10 Oct 2004 (doi:10.1038/ng1449)

FERTILITY

Against the odds

More than 90% of girls and young women with childhood cancer can now be cured with aggressive chemotherapy, radiotherapy and bone-marrow transplantation. However, the ovaries are very sensitive to cytotoxic treatment and women can be left infertile. Jacques Donnez *et al.* now report the first livebirth after orthotopic transplantation of ovarian tissue.

Ovarian tissue was taken from a 25-year-old woman with stage IV Hodgkin's lymphoma, the stromal tissue was removed and 70 samples of cortex were cryopreserved.

The patient then received MOPP/ABV combination chemotherapy and radiotherapy and was later shown to be disease free but amenorrhoeic and infertile.

Six years later, when the patient decided that she wanted to try for a child, the surgeon first created a peritoneal window beneath the right ovary to induce angiogenesis and neovascularization. Both ovaries were confirmed to be atrophic. At a second laporoscopy 7 days later, half of the cortical tissue samples, which all contained surviving primordial follicles, were thawed and re-implanted into the peritoneal window, which was now clearly vascularized. There is a potential risk of re-implanting malignant cells with this technique, but in this case no evidence of cancer was seen 5 months after re-implantation.

Concentrations of luteinizing hormone and follicle-stimulating hormone (FSH) decreased after re-implantation, indicating follicular development, but they then increased again to castrated levels and there was no sign of ovarian activity. At a third laparoscopy 4 months later to check the graft, a viable follice outside the atrophic right ovary was seen. The surgeon also re-implanted the remaining cubes of cryopreserved tissue. Over the next 4 months, follicle development followed by corpeus-luteum formation was seen with restoration of regular menstruation. Then, after a surge of FSH — which probably favoured follicle recruitment — the concentration of human chorionic gonadotrophin increased and a viable pregancy (by natural fertilization) was confirmed. A healthy girl was born in September 2004.

There is convincing evidence that the pregnancy originated in the transplanted tissue, particularly because the right ovary never showed any ovarian activity, the only follicle seen was in grafted tissue, and a pre-ovulation follicle was seen at the re-implantation site during the cycle leading to the pregnancy.

The authors conclude that all young women diagnosed with cancer should be given the option to have their ovarian tissue cryopreserved. Another option, which is not technically possible yet, would be to re-implant primordial follicles; this would decrease the risk of re-implanting malignant cells.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPER Donnez, J. *et al.* Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. *Lancet* **364**, 5000–5005 (2004)