IN THE NEWS

One for the boys

There are many unsubstantiated myths about the effects of masturbation but, according to a team of Australian researchers, there is some encouraging news for men — frequent ejaculation can help protect against prostate cancer.

Graham Giles and colleagues from The Cancer Council Victoria surveyed 1,079 patients with prostate cancer and 1,259 healthy men, asking them about their sexual habits. When they compared the data from each group, they found that the more men ejaculated between the ages of 20 and 50, the less likely they were to develop prostate cancer. The results were most significant for men in their twenties, as ejaculation more than five times a week by men in this age group reduced their risk of prostate cancer by one-third.

According to Giles, "It's a prostatic stagnation hypothesis". Frequent ejaculation prevents the build up of harmful carcinogens in the testes and "The more you flush the ducts out, the less [carcinogen] there is to hang around and damage the cells that line them" (*CNN*, 17 July 2003).

Previous studies have indicated that multiple partners or a high frequency of sexual activity actually increases the risk of prostate cancer. However, Giles suggests these results probably reflect study design, which defined sexual activity as sexual intercourse, rather than number of ejaculations. "Had we been able to remove ejaculations associated with sexual intercourse, there should have been an even stronger protective effect of other ejaculations." claims Giles (*NewScientist*, 16 July 2003). So, it looks like men might have a way to beat prostate cancer.

Emma Croager

EXTRACELLULAR MATRIX

Breaking free

If we sometimes feel trapped and stuck in a rut, friends might say that we should make a change and take charge of our own destiny. Cancer cells do exactly that when they are restricted by a three-dimensional (3D) extracellular matrix. Stephen Weiss and colleagues, reporting in *Cell*, show that the cancer cells produce a protease that allows them to degrade the surrounding matrix and continue proliferating.

The role of proteases in regulating tumour-cell growth has proved difficult to pin down, as much of the work has been done in two-dimensional (2D) *in vitro* systems that might not replicate the physiological situation. To address this, Weiss and colleagues investigated the effects that protease inhibitors had on the growth of cancer cells in both 2D and 3D (in a matrix of type I collagen) conditions. Although the inhibitors had no effect on cell proliferation in 2D, the TIMP2 matrix metalloproteinase (MMP) inhibitor was found to specifically inhibit growth in 3D.

So, which MMP is important for this growth? By expressing different MMPs in MDCK cells, the membrane-anchored MMP MT1-MMP was shown to specifically enhance proliferation in a 3D matrix, and this could be suppressed by TIMP2. This is thought to be a direct effect, as expression of active forms of MT1-MMP targets — MMP2 and MMP13 — could not enhance the proliferation induced by MT1-MMP in a co-culture experiment. Cancer cells use the same strategies to increase proliferation, as transfection of MT1-MMP enhanced the growth rate of SCC-1 cancer cells by 2.5-fold in a 3D collagen matrix. This increased activity correlates with an increase in cyclin-D3-dependent kinase activity.

The authors next examined which domains of MT1-MMP were important for this ability. They deleted either the cytosolic tail or the transmembrane domain — neither of which affect its ability to become processed into the active form — and found that only the transmembrane-deleted form was unable to enhance growth, so it is important that the protein is present at the cell surface.

To further confirm that the effects of MT1-MMP were physiologically relevant, SCC-1 cells expressing low, medium or high levels of MT1-MMP were injected beneath the skin of mice. Tumour mass correlated with the expression level of MT1-MMP, and the increase was due to more proliferation, not less apoptosis, as the number of PCNA-positive cells increased, but the number of TUNEL-positive cells remained the same.

In considering what might be the proteolytic target of MT1-MMP, the authors first ruled out some possibilities. MT1-MMP can not increase proliferation of cells in soft agar or Matrigel, so it is unlikely to be a cell-dependent target. It is also unlikely to be through inactivation of a diffusible repressor, as co-culture of untransfected cells next to MT1-MMP-expressing cells did not increase the proliferation of the untransfected cells. The αvβ3 ligand gelatin is derived by MT1-MMP-induced cleavage of collagen, but its inhibition with monoclonal antibodies did not prevent growth.

So, the authors were left with the possibility that collagen itself needed to be degraded for cells to proliferate, and this was confirmed using a collagen mutant that was not susceptible to proteolytic degradation. In fact, collagen seems to enmesh cells in a cage, so that they are unable to change morphology by spreading and rearranging their cytoskeleton in response to growth signals — these changes are needed before cells can enter the cell cycle. MT1-MMP mediates this process by degrading collagen and allowing cells to spread.

MT1-MMP therefore directly regulates cell growth, by allowing cells to grow through the 3D matrix. Despite problems with MMP inhibitors in clinical trials, this study shows once again that MMPs should be pursued as therapeutic targets.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Hotary, K. B. *et al.* Membrane type I matrix metalloproteinase usurps tumor growth control imposed by the three-dimensional extracellular matrix. *Cell* **114**, 33–45 (2003)

WEB SITE

Stephen Weiss's lab:
http://www.med.umich.edu/cmb/faculty/weisssj.htm