Fernandez *et al.*[12] found that TIMP-2 blocks the growth of endothelial cells in an MMP-independent way. This inhibition requires a peptide at the carboxy-terminal end of TIMP-2, which was superior to an amino-terminal TIMP-2 fragment (which blocks MMP activity) in inhibiting angiogenesis.

Now, Stetler-Stevenson's group (Seo *et al.*) brings further insight into the MMP-independent activity of TIMP-2. The authors show that TIMP-2 silences two growth-factor receptors — one that detects VEGF, and one for fibroblast growth factor-2 (FGF-2). They also offer clues to how this happens.

Many angiogenic factors, such as VEGF and FGF-2, bind to receptors on endothelial cells, causing the receptors to self-activate by adding phosphate groups to tyrosine amino acids in their intracellular portion[13]. This leads to a sequence of events that promotes endothelial-cell proliferation and migration, and hence angiogenesis. This process is partly regulated by enzymes that remove phosphate groups, such as SHP-1 and other 'protein tyrosine phosphatases', which prevent the receptors from transmitting further signals[14].

Seo *et al.* show *in vitro* that a modified form of TIMP-2, which can no longer interact with MMPs, causes SHP-1 and other unidentified protein tyrosine phosphatases to associate with VEGF and FGF-2 receptors. This occurs in a remarkably indirect way: TIMP-2 binds to a neighbouring receptor on endothelial cells, called $\alpha_3\beta_1$ integrin, with which phosphatases usually associate. This binding causes the phosphatases to move from the integrin to the VEGF and FGF-2 receptors (Fig. 1). The cells are thereby rendered resistant to VEGF and FGF-2 — an effect that Seo *et al.* also observed in a mouse model of angiogenesis. The authors further show that inhibitors of protein tyrosine phosphatases largely block the anti-angiogenesis effects of TIMP-2. The discovery of such receptor crosstalk reveals a high degree of coordination between proteinase inhibitors, integrins and growth-factor receptors. It also provides insight into how signalling from VEGF receptors is terminated — a poorly understood process.

What are the medical implications of these exciting findings? As mentioned above, the development of synthetic MMP inhibitors for cancer treatment has been based, at least in part, on the observation that TIMP-2 and other TIMPs inhibit tumour growth in animal models[1–4]. As a consequence, several MMP inhibitors have been extensively evaluated in clinical trials, but with disappointing results. But these inhibitors were selected for their TIMP-like ability to block the proteolytic activity of MMPs — and the findings of Seo *et al.*[5] imply that the anti-angiogenic function of TIMP-2 stems primarily from its MMP-independent activity.

This conclusion needs to be confirmed. And it must be reconciled with gene-inactivation studies[15] showing that TIMP-2's main function *in vivo* is to activate pro-angiogenic MMP-2, and with the finding that, for certain cancers, high levels of TIMP-2 predict poor (not, as one might expect for an angiogenesis inhibitor, good) prognosis. If Seo and colleagues' findings prove correct, however, it might be bad news for the strategy of using synthetic MMP inhibitors in the clinic. The good news, though, is that we now have other ideas for angiogenesis inhibitors: it might, for instance, be worth investigating analogues or fragments of TIMP-2 that induce phosphatases to silence the angiogenic growth-factor receptors. ■

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1. Overall, C. M. & Lopez-Otin, C. *Nature Rev. Cancer* **2,** 657–672 (2002).
2. Brinckerhoff, C. E. & Matrisian, L. M. *Nature Rev. Mol. Cell Biol.* **3,** 207–214 (2002).
3. Egeblad, M. & Werb, Z. *Nature Rev. Cancer* **2,** 161–174 (2002).
4. Coussens, L. M., Fingleton, B. & Matrisian, L. M. *Science* **295,** 2387–2392 (2002).
5. Seo, D. W. *et al. Cell* **114,** 171–180 (2003).
6. McCarthy, M. *Lancet* **361,** 1959 (2003).
7. Murphy, A. N., Unsworth, E. J. & Stetler-Stevenson, W. G. *J. Cell Physiol.* **157,** 351–358 (1993).
8. Qi, J. H. *et al. Nature Med.* **9,** 407–415 (2003).
9. Stetler-Stevenson, W. G., Krutzsch, H. C. & Liotta, L. A. *Matrix* **1** (Suppl.), 299–306 (1992).
10. Valente, P. *et al. Int. J. Cancer* **75,** 246–253 (1998).
11. Hajitou, A. *et al. Cancer Res.* **61,** 3450–3457 (2001).
12. Fernandez, C. A., Butterfield, C., Jackson, G. & Moses, M. A. *J. Biol. Chem.* published online 4 August 2003 (doi:10.1074/jbc.M306176200).
13. Schlessinger, J. *Cell* **103,** 211–225 (2000).
14. Ostman, A. & Bohmer, F. D. *Trends Cell Biol.* **11,** 258–266 (2001).
15. Wang, Z., Juttermann, R. & Soloway, P. D. *J. Biol. Chem.* **275,** 26411–26415 (2000).

Clarification

Readers may have been misled by the phrasing of the penultimate paragraph in David Gems and Joshua J. McElwee's News and Views article "Ageing: Microarraying mortality" (*Nature* **424,** 259–261; 2003). The article dealt with a paper by C. T. Murphy *et al.* in the same issue (**424,** 277–284; 2003), which described the use of microarrays and RNA interference to identify *Caenorhabditis elegans* longevity genes that are regulated by insulin/IGF-1 signalling. The phrase concerned was "Seeking insight into the biochemistry of ageing, Murphy *et al.* panned their mine of microarray data for genes that fit existing expectations — an approach sometimes referred to as 'fishing'". This did not refer to the choice of genes for functional investigation with RNAi, which, with the exception of *ins-7*, involved testing clones with the greatest expression change and/or the highest overall statistical significance. Rather, the comment was directed to the discussion of the biochemical significance of the overall data.

100 YEARS AGO

The Scottish Sanitary Congress was opened at Stranraer on Thursday last… Prof. Glaister, in the course of his remarks, urged that men of science and local authorities should realise the detrimental effect of atmospheric pollution, and together grapple with the subject. The prejudicial effects of town living could not be better demonstrated than in the depreciated physique of the third and fourth generations of many of those who had proceeded from the country to the towns. One of the significant features of present-day statistics, and one calling for the serious consideration of sanitarians, was the high prevailing rate of infantile mortality in populous centres. If the state of the principal English towns for 1901 be considered, it will be found that the infantile death rate varied from 126 per thousand up to 226 per thousand. These figures exhibited a great wastage of infantile life. He affirmed that it was a preventable wastage, and, therefore, worthy the reflections of sanitarians. Such high rates of infantile mortality were bound in the future to become a serious national concern in view of the diminution of the birth rate which had been progressively taking place for the last few decades.
From *Nature* 10 September 1903.

50 YEARS AGO

In an imaginative but well-authenticated article, Nigel Balchin, the well-known psychologist and author, examines the way in which the growth of industry has affected the outlook and philosophy of those who work in large or small industrial undertakings… A comparison is made between the life of the agricultural worker and of the individual whose working life is confined to the factory, and Balchin concludes that the impact of industry upon the worker has been to destroy the simple and direct significance of work done and hence to sever the mental link between 'work' and life. In these circumstances 'work' is liable to become something which has no logic or point in itself. The impact of the huge and complicated industry structure on the worker has been to confuse the mind as to his real desires and requirements and to leave him with a vague impression that man exists for industry rather than *vice versa*.
From *Nature* 12 September 1953.