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ANGIOGENESIS

Natural inhibition

Although a large amount of research has been focused on tumour factors that promote angiogenesis, little is known about natural angiogenesis inhibitors. In the June issue of *Cancer Cell*, Raghu Kalluri and colleagues report that tumstatin — a cleavage fragment of collagen IV — functions not only as an endogenous inhibitor of angiogenesis, but also as a tumour suppressor.

Tumstatin is a proteolytic product of the $\alpha 3$ chain of type IV collagen (**ColIV $\alpha 3$**) — one of the components of vascular basement membranes. This cleavage fragment has been detected in the circulation, and has also been shown to have anti-angiogenic properties. Little is known, however, about its *in vivo* function.

Kalluri and colleagues therefore studied ColIV $\alpha 3$ -deficient mice. Although these mice did not produce tumstatin, they did not have any detectable defects in embryonic development or wound healing — processes that are known to involve angiogenesis. They did, however, have defects in pathological angiogenesis. When three different tumour types were implanted into either wild-type or ColIV $\alpha 3$ -deficient mice, they were found to grow at the same rate in all mice until they reached a volume of 500 mm³. At this point, tumour growth and tumour blood-vessel formation accelerated rapidly in the ColIV $\alpha 3$ -deficient mice, compared with wild-type mice. This effect was reversible, as administration of recombinant

tumstatin reduced tumour growth rates back to wild-type levels.

So, how does tumstatin specifically block tumour angiogenesis? Tumstatin has been previously shown to be a ligand for $\alpha v\beta 3$ integrin — a receptor that is expressed by tumour-associated blood vessels. Kalluri and colleagues observed that tumstatin was not able to inhibit tumour-associated blood-vessel formation of $\beta 3$ -integrin-deficient mice, indicating the requirement for this receptor in tumstatin signalling. Blood vessels that are associated with healing wounds, alternatively, expressed only the $\beta 1$ integrin, which might explain their lack of response to tumstatin. The $\beta 3$ integrin was also primarily expressed by blood vessels that are associated with large tumours (500 mm³ or greater).

The matrix metalloproteinase (**MMP**)-9 is known to be responsible for liberating tumstatin from ColIV $\alpha 3$. Kalluri's group showed that Mmp-9-deficient mice have lower circulating levels of tumstatin, resulting in accelerated growth of large tumours. MMP-9, however, has been implicated as a positive regulator of the angiogenic switch and of tumour growth, so why would it also be involved in production of an angiogenesis inhibitor?

The authors suggest that MMP-9 has opposing actions on neoplasia at different stages of tumour progression — whereas it can promote the angiogenic switch that leads to the initial burst of tumour growth, it eventually

restrains tumour growth by generating endogenous inhibitors of angiogenesis, such as tumstatin. In this regard, tumstatin might have therapeutic potential as a specific inhibitor of late-stage tumour growth. Further experiments are required to determine if its formation or function is disrupted in cancer patients.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Hamano, Y. *et al.*

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FURTHER READING Kalluri, R. Angiogenesis: Basement membranes: structure, assembly and role in tumour angiogenesis. *Nature Rev. Cancer* 3, 422–433 (2003)

WEB SITE

Raghu Kalluri's lab:

http://www.researchmatters.harvard.edu/people.php?people_id=108