

How can we stop the blood supply to cancer cells?

I haven't written about VEGF before, not because it's not important, it is, in fact VEGF has been shown to be important in a whole range of solid (i.e. lump forming) tumours, these include:

- Bladder
- Breast
- Cervical
- Colorectal (bowel)
- Esophageal (food pipe)
- Glioblastoma multiforme (brain tumour)
- Head and neck cancer
- Lung cancer
- Ovarian cancer
- Pancreatic cancer
- Renal cell carcinoma

Generally speaking, if you have a lot of VEGF it's a bad sign (or in medical speak "a poor prognosis"). As you might expect given the list of cancers above, a lot of labs and drug companies are researching VEGF. It will also not surprise you to learn that VEGF biology is very complicated. None the less I want to write about a paper that appeared in the *Journal of Cell Science* called "[Expression of pro- and anti-angiogenic isoforms of VEGF is differentially regulated by splicing and growth factors](#)". This paper is the work of several research labs in Bristol. If you want to know more about this research visit <http://www.ladomerylab.org>

Before I start discussing any paper, I like to make sure I understand the title, that's where I'll start.

So what is VEGF?

VEGF stands for vascular endothelial growth factor A.

Okay, what does that mean?

Vascular means a system of tubes to move fluids around your body, in this case the tubes are blood vessels and the fluid is blood. Endothelial is a fancy name for a type of cell that makes the inside of blood vessels. A growth factor is a chemical in the body that makes things grow. So in this case, VEGF is a protein that makes blood vessels grow. We all have VEGF inside us, we need it to live, for example if you cut yourself you need to form new blood vessels to repair the damage.

pro and anti- angio what?

Angiogenic is scientist speak for growing new blood vessels

- Pro-angiogenic means it encourages the growth of new blood vessels
- Anti-angiogenic means it stops the growth of new blood vessels

What does isoform mean?

Isoform means "different types". In this paper it means different types of the protein VEGF.

Okay and what is differential regulation?

Differentially is a fancy way of saying different, and regulation is another way of saying control. So differentially regulated means that different things control what happens inside the cell. For example you could control the temperature in your house by

1. Turning down the temperature on your thermostat
2. Turning down a radiator
3. Opening a window

These are all examples of "differentially regulating" the temperature in your house, i.e. they are all different ways of doing the same thing (controlling the temperature in your house). Inside a cell you can control the amount of VEGF protein in different ways

1. By splicing
2. By growth factors

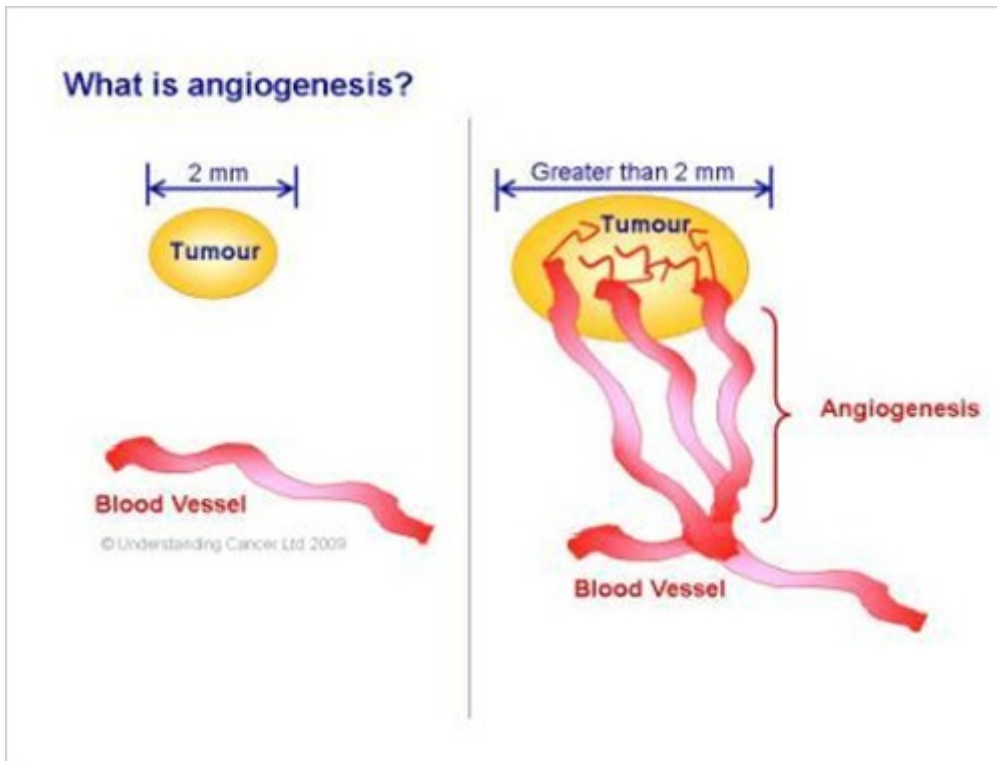
What is splicing? it sounds painful...

Splicing means joining things together to form a new combination. A fisherman may fix his fishing nets by splicing two bits of rope together or an electrician may splice two bits of wire together. Your body does the same thing with genes, it makes different proteins by chopping up DNA and rejoining them together in different combinations. The bits that are cut out are called "introns" (go figure), the bits that are left in are called "exons". Different exons can be stuck together in different combinations. This all sounds very haphazard and random, but it's not. It's a very specific and controlled process.

So to sum up - Expression of pro and anti-angiogenic isoforms of VEGF is differentially regulated by splicing and growth factors means... **There are two types of VEGF in your body, one that makes blood vessels grow and one that makes blood vessels stop growing. The type of VEGF in your cells is controlled by (at least) two different things, splicing and growth factors.**

What has all this got to do with cancer?

Cancer needs blood vessels to grow. Most tumours would not grow bigger than a couple of millimetres if they didn't attract their own blood supply. When a tumour attracts new blood vessels into it this is called "angiogenesis". There are new drugs available that block VEGF and stop tumours growing. Unfortunately, after a couple of months the tumours get used to these drugs and start growing again. We need to understand why this happens and that is why this research paper is important.



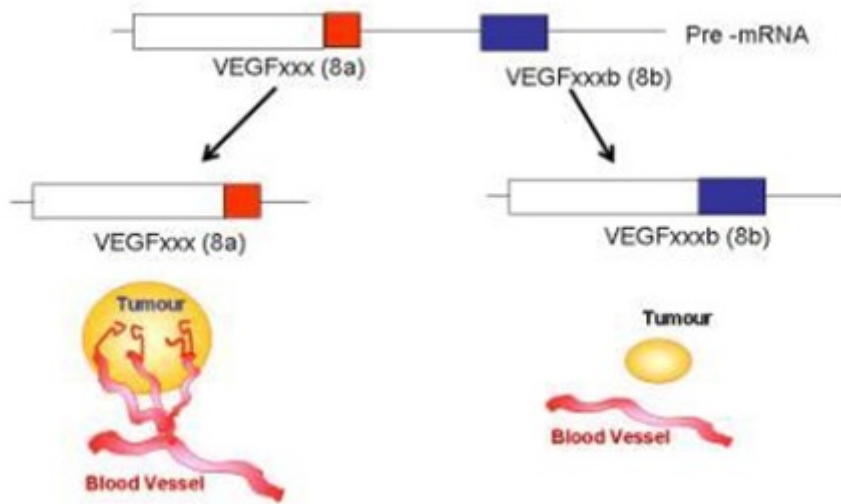
This picture shows the formation of new blood vessels (angiogenesis). On the left is a small tumour that has not attracted any blood vessels. On the right is a larger tumour that has attracted its own blood supply.

The research in this paper describes how VEGF can have different effects, some types can inhibit (stop) blood vessels growing and other types can encourage blood vessels to grow. Your body controls which type of VEGF and how much VEGF is inside you by controlling growth factors and splicing factors. The control of new vessel formation is complicated and involves at least 50 other proteins as well as VEGF.

So how do you get different types of VEGF?

You get different types of VEGF by a process called splicing, this is when the VEGF gene is cut up and reassembled in different combinations. In the picture below, the rectangles represent the pre mRNA (which comes from the VEGF gene). If the sequence in the red box is included then the protein will be called VEGFxxx and it will encourage new blood vessels to grow. If the sequence in the blue box is included then the protein will be called VEGFxxx_b and it will inhibit new blood vessel formation (and prevent tumours growing).

Vascular Endothelial Growth Factor (VEGF) - Exon 8



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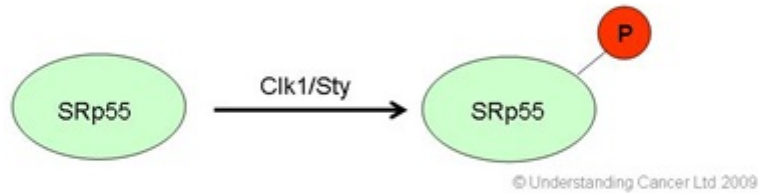
So if you have a tumour, you want less of the VEGFxxx with the red box and more of the VEGFxxx with the blue box because this will stop the tumour gaining a blood supply. How does your body control this? How do you control gene splicing?

There are a whole host of other proteins in your body that control splicing, this research is the first to show that splicing factors can alter which type of VEGF your cells make. The scientists carried out experiments to show that something called SRp55 controls the amount of VEGFxxx.

So what is SRp55 then?

SR stands for serine-arginine, serine and arginine are amino acids and the SR class of proteins contain lots of these two amino acids. The "p" of p55 means protein and the "55" means that when you look at the protein in the lab, on a gel, then its size is 55 kDa's. In the picture below the SR protein is shown as a green circle. This protein (like many others) is turned on by phosphorylation (shown in the picture by a red circle with a "P").

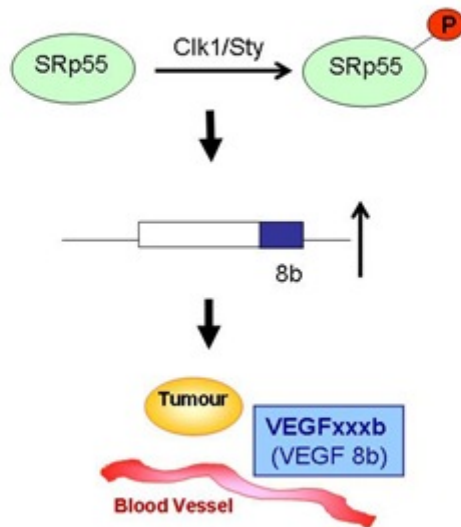
Splicing Factors



So what have we learnt about this splicing factor from this research?

We now know, that splicing factor SRp55 increases the amount of VEGF_{xxx}b and that this type of VEGF stops new blood vessels growing. The scientists then went on to do other experiments to show that SRp55 is controlled by another protein called TGF beta via the p38 pathway. This is brand new research; nobody in the world knew that this happened before these experiments were done. We now know there is a pathway inside cells that leads from the splicing factor (the green circle in the picture below), to the VEGF mRNA (the rectangles) that affects the amount of VEGF_{xxx}b. This controls how much blood a tumour gets.

Splicing Factor SRp55 and VEGF_{xxx}b (Exon 8b)

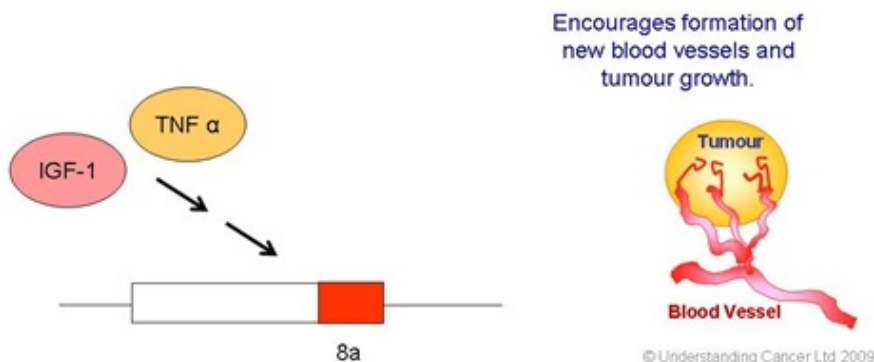


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So what about the other one? The VEGF_{xxx} what do we know about it?

The scientists show that different proteins control the amount of VEGF_{xxx}, in particular two proteins called TNF α and IGF-1 were shown to increase the amount of VEGF_{xxx}. This encourages new blood vessels to form.

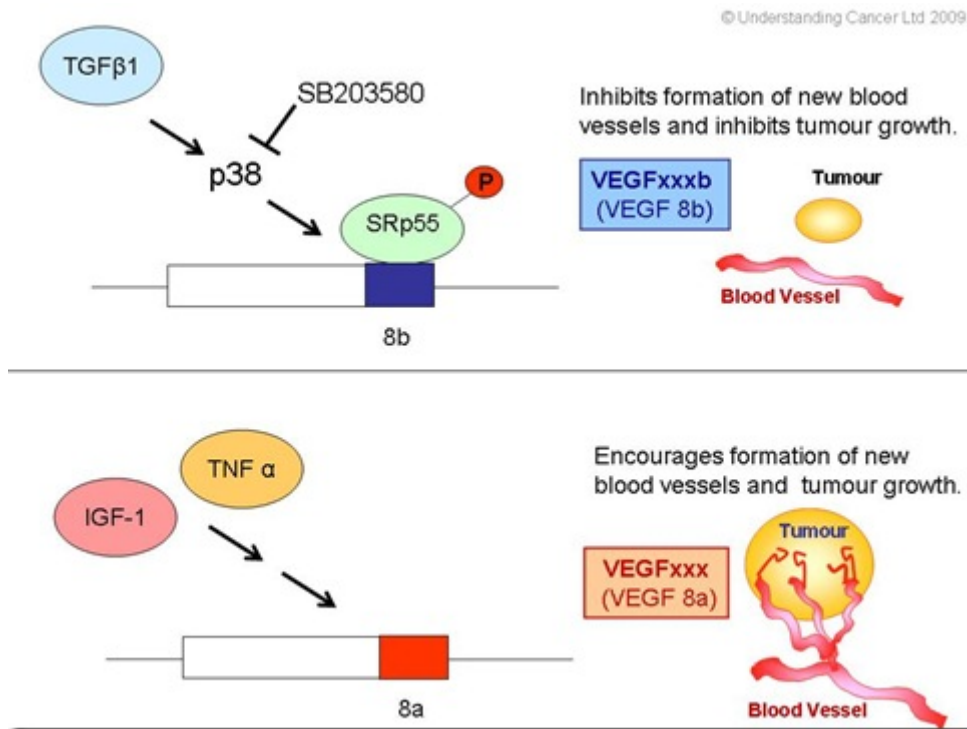
What increases the amount of VEGF_{xxx}?



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So all in all what did this new research show?

This research tells us for the first time, that a splicing factor can control which type of VEGF you have inside your cells. The splicing factor that controls this is called SRp55 and this is in turn controlled by another protein called TGF beta via the p38 pathway. This research also tells us that a different form of VEGF (one that encourages new blood vessels to grow) is controlled by two other proteins called TNF alpha and IGF-1.



Why is all this important?

Lots of other proteins in the body are spliced. So it is likely that other proteins could have this "dual control" which means that sometimes they turn something on (e.g. blood vessel formation) and sometimes they turn something off. The ratio of these proteins is probably important, so if you have lots of VEGFxxx (the blue rectangle) relative to the amount of VEGFxxx (the red triangle) then your tumour doesn't grow.

This is pure speculation on my part, but perhaps the new drugs that target VEGF, only work on the VEGFxxx (the red box). We have already discovered a way to stop the VEGFxxx working, maybe now we need to find a drug that can increase the levels of VEGFxxx (the blue box).

This sort of research is called basic research, because it is done in a lab on cells in a dish and it is trying to work out the basic biology of how normal cells (and cancer cells grow). As you can see this sort of research is complicated and we need to fund more of it, if we want to find out how this alternative splicing affects cancer cells (see my post [We can afford to fund bankers but not scientists](#) for more on my views on science funding in the UK). This sort of study is not limited to cancer as other diseases are also caused (at least in part) by blood vessels growing where they shouldn't, this includes diseases like diabetes, kidney disease, arthritis and heart disease.

What if you are having treatment for cancer now?

This research was carried out in a lab, in cells in a dish. It hasn't been tested in people. This sort of basic research is at least a decade away from being used in a clinic or hospital. That doesn't mean it's not important, hopefully knowing more about how VEGF alters the blood supply to tumours will allow us to develop new drugs (with fewer side effects) that will stop tumours growing.

Notes

Understanding Cancer Ltd are based in the North East of Scotland. We offer courses and tutorials on cancer to the general public and to healthcare professionals.

Understanding Cancer courses are designed and delivered by Avril Morrison a research scientist with a PhD in Cell Biology. Avril has worked for the Association for Cancer Research and the American Institute for Cancer Research on breast cancer, leukaemia and Wilm's tumour. Visit <http://understandingcancer.co.uk> for more information.

Other leaflets are available in this series including "What is a normal blood count" please see <http://understandingcancer.co.uk> for further information.

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