Blood vessels: from friend to foe

Fascinated by the cellular and molecular mechanisms that shape disease pathogenesis, Dr Marie Jeansson explains the complex roles played by blood vessels and how this understanding is leading toward the development of novel treatments.

What motivated you to study the role of endothelial cells in health and disease, and what interests you most about this work?

Vascular endothelial cells line all of the blood vessels throughout our body and are the interface between the blood in the lumen and the rest of the vessel wall. Endothelial cells are the building blocks of our vascular system and their dysfunction is a hallmark of many diseases, including diabetes, kidney disease, malaria and cardiovascular diseases. In many ways, the endothelium acts as a sort of ‘gate keeper’ to the rest of the tissue in all of our organs.

My main interest is capillaries, the smallest of blood vessels. I find it fascinating how the endothelium in capillaries can have different properties depending on the specific task the organ has. For example, in the kidney, a large amount of blood is filtered to remove waste products; hence, in this setting, the endothelium is allowing passage of large amounts of water while still retaining large molecules in the blood.

How are the protein growth factors, angiopoietins, helping you to better understand disease pathogenesis?

The dysfunction of blood vessels is central to many diseases, and a better understanding of the factors that endothelial cells rely on – in both health and disease – can teach us a lot about the disease and possible treatments, or preventive measures. Over the years, we have developed genetic models where we can change the production of angiopoietins in mice. These models are very useful and can be utilised to study experimental models of diseases and how angiopoietins may be involved. Many diseases are dependent on a whole organ perspective, as inflammation, different cell interactions and blood flow are important factors in the disease, and difficult to mimic in other ways.

More specifically, you are investigating the role of angiopoietins in tumour growth and metastasis, as well as kidney diseases. Can you provide some insight into this work?

In most cancers, tumours need new blood vessels to continue growing as their demand for oxygen and nutrients increases. Drugs that inhibit pathways that are important for blood vessels’ growth have been used for cancer patients for a number of years now. Angiopoietins are important for the growth of new blood vessels, and there are ongoing clinical trials that are trying to target the angiopoietin system in cancer.

There is still a lot not known about how blood vessels and how their endothelial cells behave in a tumour or when there is metastasis. My research group is interested in the changes to angiopoietin and how they affect endothelial cells and blood vessels in cancer.

Fibrosis is also a key research interest for you at present. As it is linked with many other conditions, such as atherosclerosis, cirrhosis and asthma, how might your work contribute to treatments for both fibrosis and other diseases?

There are dozens of fibrotic diseases, including heart fibrosis, scleroderma and pulmonary fibrosis – as well as those previously mentioned. Fibrosis is a complicated process but, encouragingly enough, it seems there are some common processes despite its presence in different organs. This means that if we are able to understand the fibrotic processes better in one organ and one disease, this knowledge could potentially be applied to other organs and fibrotic diseases as well. So, while we are working with a specific focus on kidney fibrosis, the mechanisms that we find there could be the same, or at least similar, to other fibrotic diseases.

Are there any factors that have specifically benefited your work?

A supportive research environment is extremely important. Throughout my research career I have been very fortunate to work with some great collaborators and mentors. There have been many times when the advice, support and constructive criticism I received have been critical for my own professional development.

I think it is important to acknowledge that great mentors have a substantial impact on your research and your career.
The effects of angiopoietins on disease mechanisms

Scientists at Uppsala University, Sweden, are investigating blood vessels and how they work in health and disease. Their research includes studies on the role of angiopoietins in response to injury and their function in fibrosis, with the ultimate goal of improved patient care.

**Blood Vessels Are** remarkable. They are tubular structures responsible for transporting blood throughout the human body. There are three major types: arteries, which carry blood away from the heart; capillaries, which enable the exchange of water and chemicals between blood and tissues; and veins, which carry the blood from the capillaries back towards the heart.

The human body contains a staggering amount of blood vessels. If they were stretched out and laid end to end, they would have an approximate total length of 100,000 km (or 62,000 miles) — enough for them to be wrapped around the circumference of the Earth two and a half times.

Despite their essential role in keeping us alive and enabling our bodies to function effectively, blood vessels also play a significant role in almost every medical condition. Cancer, for example, could, in most cases, not grow unless the tumour were capable of formulating new blood vessels (a process known as angiogenesis) to supply the malignant cells with the nutrients and oxygen they need to thrive. Because blood vessels often play a fundamental part in disease, they are of special interest to researchers around the world. Increasing knowledge of blood vessels and how they work in both health and disease enables an understanding of the underlying mechanisms in a range of conditions, thereby boosting the potential for the development of better treatments and preventive measures.

**Protein Growth Factors**

Led by Dr. Marie Jeansson, researchers at Uppsala University in Sweden are performing multiple investigations to better understand blood vessels and their mechanisms. Much of the laboratory’s work is concerned with angiopoietins, which are protein growth factors intrinsically linked to blood vessels.

In one investigation, Jeansson and her collaborators studied Ang1, with relation to the tyrosine kinase receptor, Tek, and its function in blood vessel development. It has been identified and the most studied to date are Angiopoietin-1 (Ang1) and Angiopoietin-2 (Ang2). Whereas Ang1 is an agonist, that is, a chemical that initiates a physiological response when coupled with a receptor, Ang2 is, in most cases, a competitive antagonist or inhibitor of physiological response.

**The Function of Angiopoietin-1**

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THE ROLE OF ANGIOPOIETINS IN FIBROSIS

OBJECTIVE
To understand the cellular and molecular mechanisms behind the development of diseases, with a specific focus on fibrosis in order to develop novel treatment strategies.

KEY COLLABORATORS
Professor Christer Betsholtz, Uppsala University, Sweden
Professor Susan E Quaggin, Northwestern University, USA

FUNDING
Swedish Research Council
IGP Young Investigator Grant
Åke Wiberg Foundation
Magnus Bergvall Foundation

CONTACT
Dr Marie Jeansson
Assistant Professor
Vascular Biology
Department for Immunology, Genetics and Pathology
Uppsala University
Dag Hammarskjöldsvagen 20 751 85 Uppsala Sweden
T +46 70 167 9182
E marie.jeansson@igp.uu.se


Increasing knowledge of blood vessels and how they work in both health and disease enables an understanding of the underlying mechanisms of a range of conditions

suggested that Ang1 is essential in maintaining the stability of mature blood vessels, but the team wanted to understand more about its precise functions. The researchers were able to determine that Ang1 is critical for regulating both the number and diameter of developing vessels and, in doing so, demonstrated that it is essential in mouse vasculature during its development and in response to injury.

In addition to these findings, the study was able to ascertain that when there was a deficiency of Ang1, combined with injury or microvascular stress, the result was profound organ damage. Ultimately, these findings have redefined our understanding of the biological function of Ang1 for, while it has been shown to be dispensable in dormant vessels, it has the powerful ability to influence the vascular response to injury. These conclusions serve to highlight the importance of Ang1 in improving response to injury, but could also have implications for the treatment of diseases; if the condition affects blood vessels, then it might be possible to adjust the angiopoietin system and stifle the effect of disease.

FIBROTIC DISEASES
Another key focus of Jeansson’s research is fibrosis, where excess connective tissue is formed in either an organ or tissue. It is similar to scarring, where stimulated cells grow tissue in order to help the wound heal – but fibrosis is a wound-healing process that fails to stop, even when the initial reason for its onset has been removed. The majority of us have experienced some scarring of the skin during our lifetime, which is almost always a necessary and harmless condition of healing. However, when this scarring takes place in an organ, the consequences can be extremely severe. For example, when fibrous connective tissue replaces normal tissue in an organ, its function gradually declines, which can ultimately lead to organ failure.

There are a wide range of conditions where fibrosis is a crucial component, but there is currently no effective treatment for it, so Jeansson and her team have investigated the cellular and molecular mechanisms behind the development of fibrosis. Their specific interest has been on understanding the role angiopoietins play in kidney fibrosis. “Our studies suggest that the loss of Ang1 promotes more fibrosis compared to when angiopoietin levels are normal,” explains Jeansson. “As we continue working on elucidating the mechanisms of angiopoietins and their signalling in fibrosis, my hopes are that we and other groups are laying the groundwork for the development of new therapies.”

In studying the role of angiopoietins in the development of fibrosis, the team will be able to define the precise mechanisms behind its development, enabling the identification of new therapeutic targets. This, in addition to their continuing work on the role of angiopoietins in tumour growth and metastasis, as well as in kidney disease, has far-reaching implications for the creation of new, highly effective treatment strategies.