THE ROYAL FREE LONDON AND UNIVERSITY COLLEGE LONDON ARTERIOVENOUS MALFORMATION RESEARCH PROGRAMME

BACKGROUND

Arteriovenous malformations (AVMs) are rare vascular lesions caused by abnormal connections between arteries and veins. AVMs affect all age groups of the population and can occur anywhere in the body with over half of the cases involving the head and neck. Patients with AVMs suffer from various symptoms, including disfiguration, pain, life-threatening bleeding and organ failure. Clinical diagnosis, monitoring and management of patients with AVMs remains suboptimal. This is due to our very poor understanding of the disease mechanism. However, in spite of the COVID-19 pandemic and with generous funding from the Butterfly AVM charity, we have made great strides!

RECENT FINDINGS

Firstly, after correlating the serum levels of various mediators of angiogenesis (vessel sprouting) with AVM lesion volumes, we have identified angiopoietin 1 (Ang1) as a potential serum biomarker that could be used in monitoring the growth of AVMs and their responses to treatment. As shown in **Figure 1**, we found that the higher the levels of Ang1 in the bloods of patients with AVMs the smaller the lesions. Ang1 is involved in stabilising the endothelium, the layer that lines the inside of blood vessels, and is produced by mural cells or cells that surround and support the endothelium. We believe that fewer of these mural cells support vessels in AVMs and this causes the lesions to destabilise and increase in size. Indeed, Ang1 has been shown to inhibit vessel sprouting or angiogenesis in solid tumours by promoting vessel stabilisation. We are currently investigating this further.

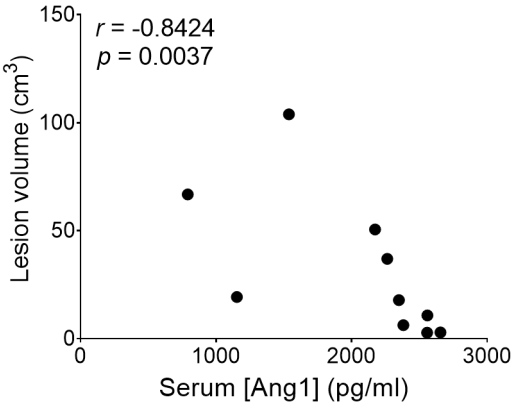

Figure 1: Negative correlation between serum concentration of Ang1 and lesion volume in patients with AVMs.

Secondly, we have successfully isolated and characterised endothelial cells (ECs) from AVM lesions to study their behaviour, comparing them with control ECs (**Figure 2**). We found that endothelial cells derived from AVM patients migrate quickly than those derived from healthy subjects (**Figure 3**). We believe that this facilitates the sprouting of new vessels and the growth of AVMs. This migratory behaviour of AVM endothelial cells could potentially be normalised to limit the growth of AVMs. Interestingly, fluorescence imaging revealed that AVM ECs possess more spike-like processes or filopodia, which are used by cells to migrate, than control ECs (**Figure 4**). This further supports our argument that ECs from AVMs exhibit a higher migratory capacity than control ECs.

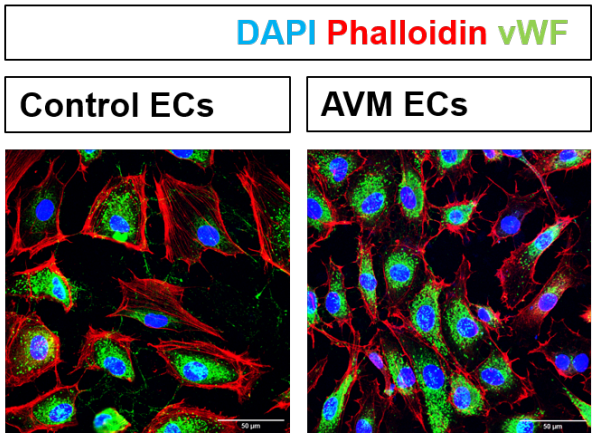

Figure 2: Characterisation of ECs isolated from a patients with AVM and a control subject. Von Willebrand factor (vWF) is a marker for ECs.

Thirdly, we found that AVM ECs produce less platelet-derived growth factor BB (PDGFBB) than control ECs (**Figure 5**). PDGFBB is a protein that attracts mural cells, including smooth muscle cells and pericytes to ECs and is therefore critical for vessel stabilisation. We believe that reduced pericyte recruitment secondary to diminished PDGFBB production in AVM ECs leads to vessel destabilisation and lesion growth in AVMs (**Figure 6**).

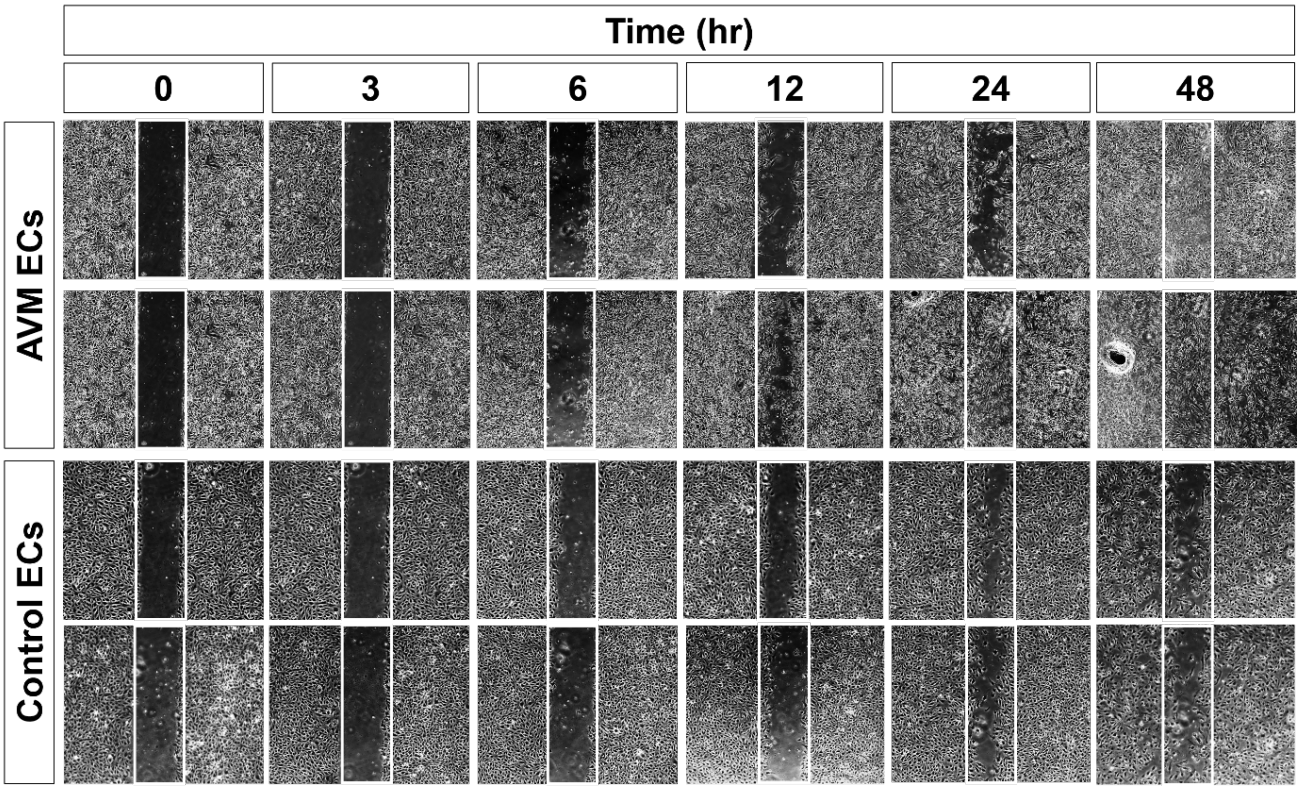

Figure 3: ECs from a patient with AVM move more quickly to cover the gap or scratch in the middle than ECs derived from control subjects.

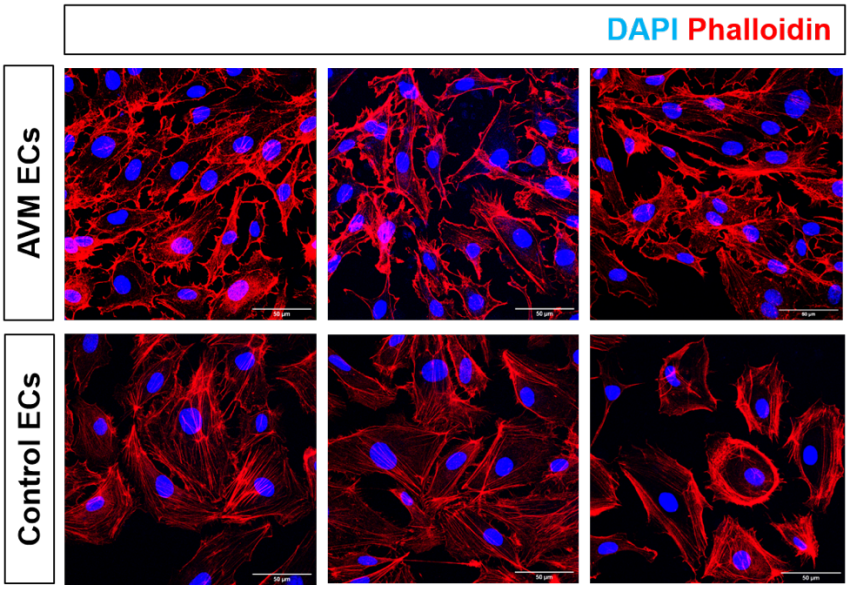

Figure 4: AVM ECs possess more spike-like processes called filopodia than control ECs. This underlies their increased migratory capacity.

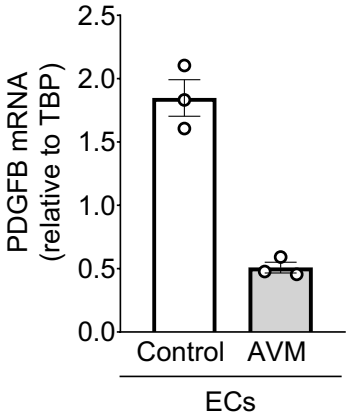

Figure 5: Reduced PDGFB gene expression in AVM ECs.

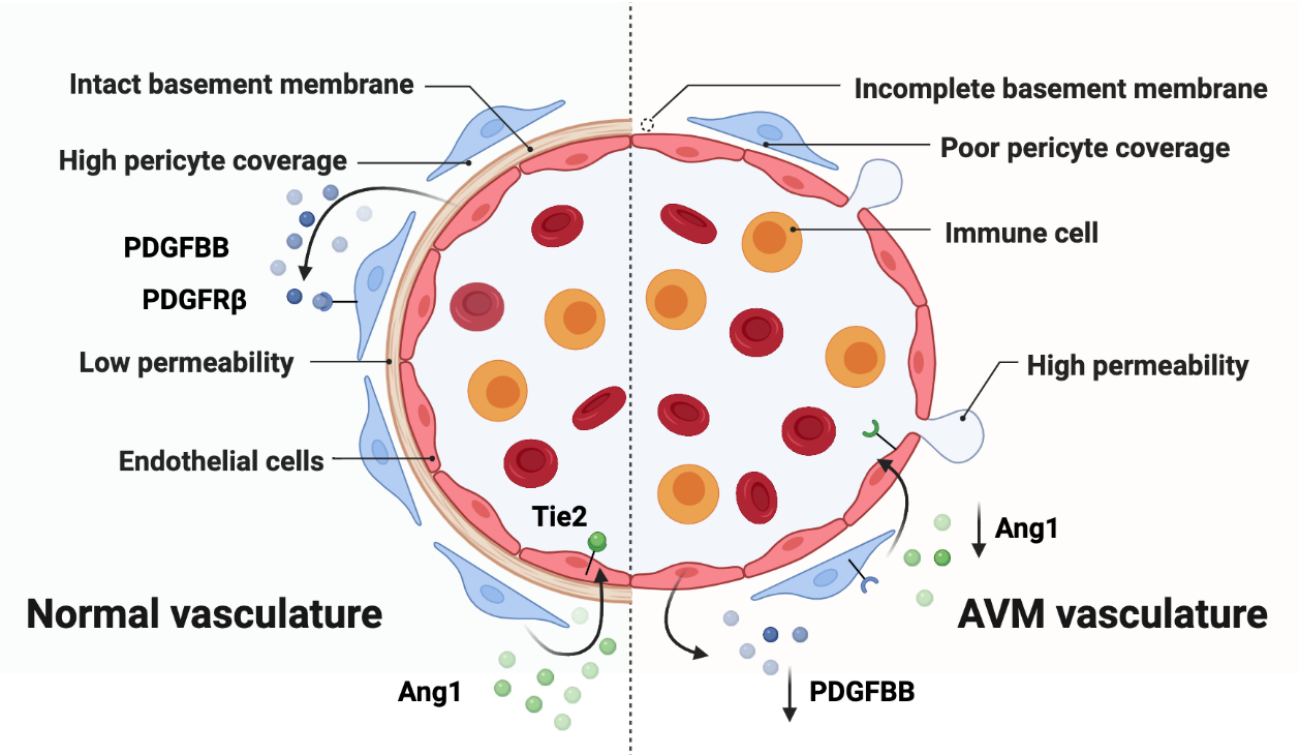

Figure 6: Our theory is that, in AVM vasculature, there is reduced pericyte recruitment to endothelial cells (ECs) and coverage of vessels due to the diminished production of platelet-derived growth factor BB (PDGFBB) in ECs. Moreover, pericytes produce angiopoietin 1 (Ang1), which signals via the Tie2 receptor in ECs, to strengthen the interactions of ECs with pericytes and reduce vessel permeability. Therefore, the reduced PDGFBB production in ECs as well as the reduced availability of Ang1 (due to the presence of fewer pericytes) leads to vessel destabilisation and lesion growth (swelling) in AVMs. These are possible avenues for targeted intervention.

NEWS AND UPDATES

First, Dr Caver Pang has passed his MPhil-to-PhD upgrade viva with flying colours and is now officially a PhD candidate.

Second, Medical student Alex Valnarov-Boulter joined the Vascular Anomalies group to investigate the role of inflammation and angiogenesis in the pathogenesis of congenital vascular malformations (CVMs) for his iBSc Research Project. With our support, Alex won an award from the Association of Clinical Pathologists. He contributed significantly to the analysis of the results presented in this report. Alex had this to say:

“Working on the project thus far has been interesting and exciting. This is due to two reasons in equal parts; the nature of the project and the support and way it is being handled despite the difficult times of the pandemic. AVMs are not very well understood and the research I have had the pleasure of being a part of is key in building up the bigger picture of how the disease works leading to us better being able to treat it. Using statistical software to analyse the data from home is not how I imagined my dissertation would be but fortunately the interactivity thanks to my supervisor Dr Jeries Abu-Hanna means I have never once felt bored or not engaged. From the weekly project meetings, to being a text away from answering any of my questions I could not have asked for a better supervisor. This project has certainly widened my interests in the field of vascular anomalies and surgery and I am interested in pursuing these interests with further research over the summer and in the further future.”

Third, we set up a collaboration with Prof Stavroula Balabani's lab at UCL Mechanical Engineering to use microfluidic systems to develop an *in vitro* model of AVMs, which will hopefully be a substitute to animal models and allow us to screen drugs for their usefulness in treating AVMs.

Last but not least, we are in the process of recruiting a PhD student to use multilevel omics to identify and validate biomarkers and potential drug targets for CVMs.