UCL-Royal Free AVM Newsletter 2022

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. Mounting evidence, including data generated in our lab, suggests the involvement of various inflammatory cells in the development of AVMs. Despite the restrictions imposed by the COVID-19 pandemic, we have progressed considerably and continue to make great strides!

Recent findings

Almost half of patients with AVMs complain of debilitating pain. However, the cause of this pain remained elusive until now! We have identified strong associations between the levels of inflammatory blood markers (e.g. TNFα, IL-1β, IL17, IFNγ) and pain in patients with AVM (**Figure 1**), irrespective of the size of the lesion, suggesting that the cause of pain in patients is likely to be inflammatory and that the patients may benefit from anti-inflammatory therapy to relieve this clinical manifestation of AVMs. We have also shown inflammatory cell infiltration (**Figure 2**) of surgically resected AVM tissues and are currently trying to identify the immune cell subsets that mediate this inflammation. These data have also led us to contemplate the use of immunosuppressants in the treatment of patients with AVMs.

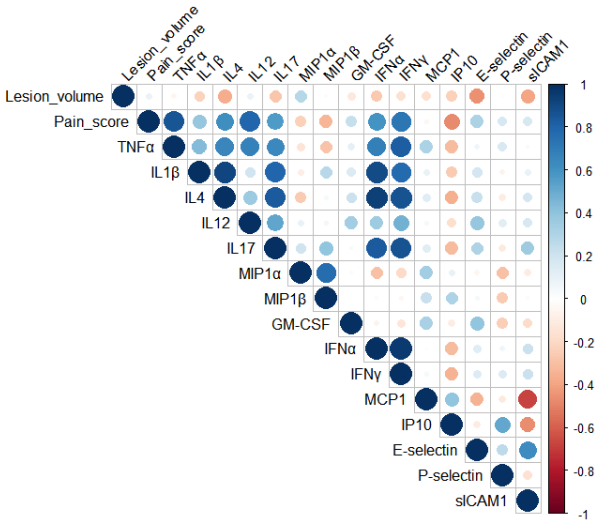
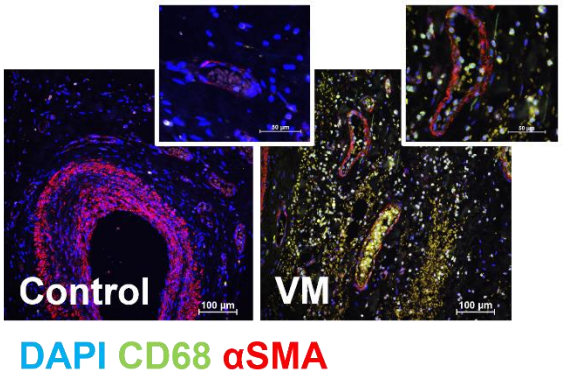


Figure 1: Correlation matrix showing strong associations (blue dots) between pain scores reported by patients and blood markers of inflammation.



DAPI CD68 αSMA

Figure 2: AVM tissues contain more macrophages (green), particularly around vessels (red), than control tissues.

To infiltrate AVM tissues, immune cells circulating in the bloodstream need to be attracted and transported across the walls of blood vessels. Once recruited to tissues, immune cells can undergo maturation to produce tissue inflammation. Endothelial cells (ECs), the key cellular players in AVMs, mediate this immune cell recruitment and maturation, through the release of chemoattractants and other pro-inflammatory proteins. We found that ECs from AVM vessels are better able at recruiting immune cells than ECs from healthy vessels. ECs from AVM vessels also encourage the maturation of immune cells into pro-inflammatory cells (**Figure 3**).

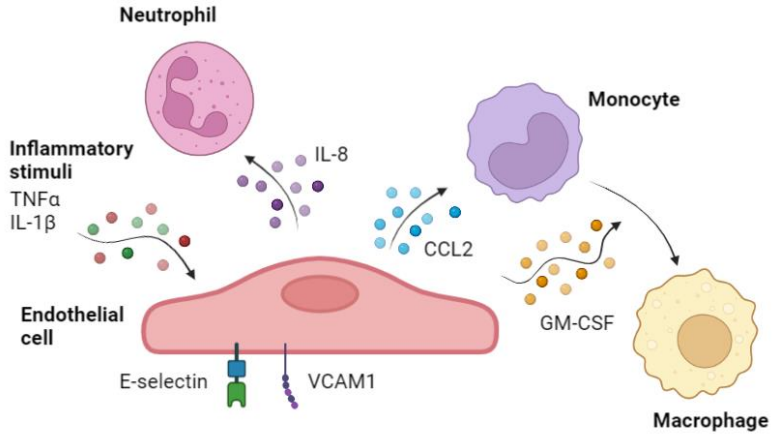


Figure 3: In response to inflammatory stimulation, ECs create a microenvironment within AVM lesions conducive to the recruitment and maturation of inflammatory cells.

News and updates

Our AVM team is increasingly expanding, underpinning the growing interests shown by both basic scientists and clinicians in this understudied disease.

First, Dr Jeries Abu-Hanna presented a poster on promising diagnostic and prognostic biomarkers for AVMs at the Vascular Discovery 2021 virtual conference (attached) and is soon submitting a paper reporting his findings on inflammatory endothelial cell activation in AVMs.

Second, Mr Ahmad Shuwhi has recently joined the group as a PhD student to investigate the role of inflammation in driving the progression of AVMs.

Third, Mr Omar Hamza has also elected to carry out his MSc project on thrombosis (clotting) in AVMs. Patients with AVMs exhibit coagulopathy but this aspect of the disease remains poorly understood. Omar's project will help shed light on the processes underlying this hypercoagulable phenotype of patients with AVMs.

Fourth, Mr Alex Valnarov-Boulter has completed his BSc research project in our lab investigating the roles of inflammation and angiogenesis in the pathogenesis of AVMs and graduated with a First-Class Honours degree. Alex has also decided to pursue his doctoral studies researching AVMs and has applied for the prestigious UCL MB PhD programme to join our group in the next academic year. We congratulate Alex and wish him the very best of luck with his MB PhD application. We look forward to welcoming him back to the AVM team.

Finally, Dr Calver Pang will be presenting his research at the Surgical Research Society Meeting in Nottingham in March and has also submitted an abstract to the International Society for the Study of Vascular Anomalies (ISSVA).

In addition to our growing AVM team, our biobank of samples from patients with AVMs has grown substantially in the past year and contains over 170 samples!

Go Team AVMs!

← Our very own Consultant Vascular Surgeon Mr Chung Sim Lim handing over a surgically resected kidney with an AVM. We are very lucky to have such a kind and caring surgeon on our AVM team!

Our MSc student Omar Hamza expertly culturing endothelial cells for his project on thrombosis in AVMs. →

← Dr Calver Pang, our surgeon in training and PhD student, preparing for patient blood withdrawal. Our growing biobank of patient samples would not have been possible without Calver's tireless efforts in collecting patient samples.

Medical student Alex Valnarov-Boulter looking very smart in his lab coat during his time in our lab. →

← Dr Jeries Abu-Hanna, our resident postdoctoral scientist, isolating endothelial cells and vascular smooth muscle cells from AVM lesions.

Future work

We aim to undertake deeper immune profiling of patients with AVMs to better understand the immune-mediated nature of the inflammatory response in patients. We will utilise novel single-cell techniques, including single-cell transcriptomic and proteomic analysis. This will allow us to identify inflammatory immune cell subsets associated with AVMs that could be targeted in the clinic to alleviate AVM symptoms, including pain, and possibly even reduce lesion growth.

We thank the Butterfly AVM Charity very much for their invaluable support and in helping us realise our ambitions of starting a world-leading AVM research group at UCL.

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