These relatively new topics for the HHT field were discussed in an interactive, joint clinical and scientific workshop. The known HHT pathogenic gene variants (in ENG, ALK1 and SMAD4) affect proteins expressed on endothelial cells, but it is often overlooked that all three proteins are also co-expressed by other cell types, including the hemangioblasts [1] that give rise to endothelial, myeloid and lymphoid lineages, and in macrophages following the process of monocyte-macrophage differentiation [2].

**IMMUNITY:** The first workshop section considered immuno. In an illustrative exercise, HHT pathogenic variants in ENG and ALK1 were initially postulated to modify immune responses in different ways based on the higher prevalence of brain abscesses and other unusual infections in HHT1/ENG patients. The importance of recognizing potential confounders was then emphasized:

(i) Brain abscesses and other deep-seated infections are predominantly found in HHT patients with PAVMs [3,4] and PAVMs are more common and severe in HHT1 patients;
(ii) Bacteremia (infected blood) is normal after dental and other procedures [5] with PAVM-associated abscesses attributed to impaired pulmonary capillary removal of infected blood-borne particles [3,4];
(iii) In the general population, bacterial infections are more severe in the setting of high iron levels [6], which, counterintuitively, are often found in HHT patients who use iron treatments and have transient iron overload states [4].

Nevertheless, the infections observed are unusual, and the discussion concluded with laboratory data demonstrating lesser magnitude responses by lipopolysaccharide (LPS)-stimulated macrophages from a myeloid-specific ENG knockout model (Engfl/fl LysMCre mice): The ENG-deficient macrophages demonstrated lower expression of proinflammatory cytokines IL-1, IL-12, IL-6, CCL-20, and thrombospondin 1 compared to those with normal ENG expression [7].

The workshop presentations increased the proportion of participants who considered that HHT immunity was weaker than normal from 19 to 37%, although the most common response from patients was that in their day-to-day experience, their immune systems seemed stronger.

**INJURY:** The second section reviewed laboratory data that injury increases endothelial expression of ENG and ALK1 [8,9] and that vascular repair is abnormal if ENG or ALK1 are deficient [8].

(i) HHT-independent injuries (such as external trauma [9] mechanical stretching of vessels during respiration and peristalsis; gastrointestinal tract acidity; infection), and
(ii) HHT-specific injuries were discussed. The latter include locally modified flow through HHT vessels, generally increased flow through all vessels in response to the high cardiac outputs [10] and the emerging evidence that therapeutic iron treatments required by most HHT patients may directly injure the endothelium [11]. In unbiased, replicate surveys, approximately 1 in 20 HHT patients using the treatments reported that iron tablets or infusions precipitate nosebleeds [12,13].

The presentations increased the proportion of participants considering HHT patients respond less well to injury from 44 to 66%, but the most common response from patients was that their responses were no different to normal.

**INFLAMMATION:** In the final workshop section, inflammation was discussed in more detail.

Impaired resolution of inflammation in pan-ENG heterozygous mice, in a chronic colitis model [14] is now supplemented by similar findings in mice with myeloid-specific ENG deficiency [7]. ENG-deficient macrophages from Engfl/fl LysMCre knockout mice displayed reduced cytokine expression in response to peritoneal LPS (as noted above), and reduced phagocytic activity [7]. While the ENG-deficient mice were more likely to develop spontaneous infections by opportunistic bacteria, they also demonstrated better survival in the LPS/Septic shock model, attributed to less exuberant inflammatory responses [7].

The take-home messages from the workshop were:
- the importance of future immunophenotyping of HHT patients, and
- incorporation of the discussed processes into HHT pathogenic models:

85% of attendees thought that immunity and inflammation would influence the development of abnormal blood vessels in HHT.
References


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