The Importance of Wall Degeneration in Preclinical Aneurysm Models

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Commentary

Recently, King et al reported to have successfully established an extracranial aneurysm model in rabbits that reflects wall degeneration, capacity of growth and potential rupture.[1] These are fundamental biological characteristics of human intracranial aneurysms (IA). Developing an appropriate animal model is of utmost importance for the study of clinical conditions in a preclinical setting. To date, however, only a small minority of the many previously proposed preclinical extracranial aneurysm models[2 3] include decellularized and degenerated walls.

Unlike microsurgical clipping, which causes immediate mechanical occlusion, aneurysm healing after endovascular treatments depends on a biological response.[4] Coil materials are used to induce a thrombus in the aneurysm sac and immediately exclude the aneurysm from blood circulation. Long-term healing, however, relies on thrombus remodelling. A large number of cells are required to organise the early thrombus into mature scar tissue and eventually form a neointima.[5 6] These cells are predominantly recruited from the aneurysm wall and the parent artery.[7 8] In aneurysms with healthy walls, the pool of cells is sufficient to appropriately mediate the healing process. Therefore, experimental aneurysms with cell-rich walls have a strong tendency to self-heal[9] and are only of limited value for testing novel endovascular therapies.

Human histopathological series have long highlighted the underlying differences between ruptured and unruptured IA wall characteristics: specifically, that ruptured aneurysms are associated with acellular walls, degenerated extracellular matrix, and loss of endothelial cells.[10 11] This association becomes particularly important when considering recurrence rates following “successful” coil embolization. Large clinical series looking at long-term recurrence after endovascular aneurysm treatments have detected mean recurrence rates of 20% (range 5% - 27%) for unruptured aneurysms versus 30% (range 15% -52%) for ruptured aneurysms.[4 12 13] In addition to the reduced healing capacity of ruptured aneurysm, further growth of the aneurysm sac has been identified as an important contributor to IA recurrence after coiling.[14 15] Consequently, it is of paramount importance to test new endovascular devices and therapeutic concepts in an animal model with aneurysms featuring degenerated walls and hence an increased vulnerability for aneurysm growth.

With that clinical knowledge in mind, previous researchers attempted to mimic human pathophysiological conditions in the preclinical setting; namely aneurysms with degenerated walls and potential further growth during follow-up. A first successful attempt was reported following modification of a previously established sidewall aneurysm model in the rat.[7 16] The authors pre-treated arterial grafts with sodium dedoxylsulfate (SDS) which decellularizes the grafts but leaves extracellular matrix intact. In contrast to aneurysms with healthy cell-rich walls, decellularized aneurysms demonstrated insufficient thrombus organization and growth, and ultimately suffered from rupture. Unfortunately, translation of the same methodology of aneurysm decellularization to a larger animal model failed, as most of the SDS pre-treated aneurysms thrombosed spontaneously during the first 4 weeks after creation (for sidewall and bifurcation type aneurysms).[17] A more promising strategy in rabbits was reported in another study using elastase injection.[18] Upon harvesting the aneurysms after 2 and 12

weeks, the authors were able to detect various histological wall types as described for human IAs.[10] However, none of these experimental aneurysms were reported to exhibit growth or rupture.

In comparison, the study by King et al. represents a significant step forward. These researchers used a combination of SDS and elastase to alter the aneurysm wall. This combined pre-treatment seems to result in truly unstable experimental aneurysms which include wall decellularization, extra cellular matrix degradation, and chronic inflammatory reaction - and ultimately leads to aneurysm growth during 12-week follow-up. The presented aneurysm model is properly classified as an arterial vessel stump model.[2] In an advanced setting, a true bifurcation model would represent an even more physiological situation in terms of flow dynamics and wall shear stress. It would also be of much interest to evaluate if recurrence rates in King's model match that of human IA after endovascular therapy. If so, the proposed model could potentially significantly reduce the translational gap from bench to bedside and establish itself as a new preclinical standard.

In summary, a growing body of evidence suggests that rarefication of mural cells is key, not only to insufficient aneurysm healing after endovascular treatments, but also to further aneurysm growth. This must therefore be a prerequisite condition for adequate aneurysm models used for the testing of new therapeutic concepts. The study by King et al. represents a crucial step towards that goal.

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