Cell Therapy for Intracranial Aneurysms: A Review

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Key words
- Aneurysm recurrence
- Cell therapy
- Intracranial aneurysms
- Endovascular coiling
- Stem cells

Abbreviations and Acronyms
ECM: Extracellular matrix
EPC: Endothelial progenitor cell
MMP: Matrix metalloproteinase
MSC: Mesenchymal stem/stromal cell
ROA: Route of administration
TGF: Transforming growth factor
VSMC: Vascular smooth muscle cell

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One in five patients undergoing endovascular coiling (the current standard of care for treating intracranial aneurysms) experience a recurrence of the aneurysm as a result of improper healing. Recurrence remains the only major drawback of the coiling treatment and has been the focus of many studies over the last two decades. Cell therapy, a novel treatment modality in which therapeutic cells are introduced to the site of the injury to promote tissue regeneration, has opened up new possibilities for treating aneurysms. The healing response that ensues aneurysm embolization includes several cellular processes that can be targeted with cell therapy to prevent the aneurysm from recurring. Ten preclinical studies involving cell therapy to treat aneurysms were published between 1999 and 2014. In this review, we summarize the results of these studies and discuss advances, shortcomings, and the future of cell therapy for intracranial aneurysms.

INTRODUCTION

Most saccular intracranial aneurysms are treated with endovascular coiling, a minimally invasive procedure in which the aneurysm is packed with thrombogenic embolic coils to prevent blood from entering the aneurysm, thereby alleviating the risk of rupture.[1,2] Compared with the surgical clipping approach, which requires a craniotomy, endovascular coiling has a significantly lower long-term risk for disability and death.[3] However, it bears one major drawback: the relatively high rate (~20%) of aneurysm recurrence, which could result in rebleeding or require retreatment.[4] This has prompted many to investigate the underlying processes that cause an embolized aneurysm to recur and to explore possible modifications to the current coiling treatment procedure to prevent it.

Some of these modifications, including using larger diameter coils such as DeltaMaxx (Codman Neuro, Raynham, Massachusetts, USA) or PC 400 (Penumbra, Alameda, California, USA) to increase packing density, or coating coils with either biodegradable polymers (to cause a more severe healing response) or expandable hydrogels (to achieve a higher packing density), have shown little or no success in randomized clinical trials.[5] Using flow-diverting stents instead of coils has been successful in terms of preventing recurrence but is subject to other limitations as a result of the reported episodes of late hemorrhage and the need for long-term antiplatelet therapy, which would exacerbate the consequences of any rerupture.[5]

An alternative approach to improve healing and prevent the events that lead to recurrence is cell therapy, wherein therapeutic cells are introduced to the site of the aneurysm. Cellular therapies have shown promising results in preclinical and early clinical studies for other cardiovascular indications, such as myocardial infarction[6,7] and ischemic stroke.[8]

In this report, we discuss different cell types that have been evaluated for the treatment of intracranial aneurysms and review related preclinical studies published from 1999 to 2014. Throughout this review, the term aneurysm refers to saccular intracranial aneurysms, unless specified otherwise.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched PubMed and Google Scholar for articles published in English with the keywords "intracranial aneurysms," "cell therapy," "cellular therapy," "smooth muscle cells," "fibroblasts," "endothelial progenitor cells," "mesenchymal stem cells," and "mesenchymal stromal cells" in various combinations. Preclinical cell therapy studies aimed at treating intracranial aneurysms were selected. Most of the selected articles had been published in the previous 5 years. Older publications were included if they were widely cited or if they were deemed significant for the purpose of this review. Relevant studies that were cited in any of the initially selected articles were also included. Gene therapy studies were excluded. The last online search was performed in October 2015.

SACCULAR INTRACRANIAL ANEURYSMS

The initial disease develops when an unusually high hemodynamic stress overwhelms repair and remodeling mechanisms within the arterial wall.[9,10] The ongoing inflammation that ensues dilates the aneurysm through the degeneration of the extracellular matrix (ECM) mediated by matrix metalloproteinases (MMPs) and apoptosis.[9,11-13] Histopathologic studies on surgically resected

human aneurysms have indicated loss of elastic lamina in the vessel wall as a hallmark in the formation of aneurysms.[14] Loss of lamina, in turn, puts more hemodynamic stress on the remaining collagen fibers, making them more prone to degeneration.[15]

The goal of a coiling procedure is to stop blood from flowing into an aneurysm by forming an intraluminal thrombus.[1] Clotting also triggers a healing response that transforms the clot into a fibrous tissue and regenerates the wall of the parent blood vessel over the course of several months.[16] The aneurysm healing process, to some extent, resembles the well-studied wound healing phenomenon and is attributed to several cellular processes, most prominently formation of an endothelialized neointima and resynthesis of the ECM by proliferating vascular smooth muscle cells (VSMCs).[16-18]

Ideally, once an aneurysm has healed, a neointimal layer covers the neck of the aneurysm, causing it to be permanently sealed off from the parent vessel. However, this is not always the case. Occasionally, the neointima may push into the lesion, instead of closing it off, leaving the neck open and creating a residual blood-filling space inside the lumen of the aneurysm.[19] If this happens, the hemodynamic stress caused by blood flow starts to cause inflammation, progressively expanding the residual blood-filling space toward the aneurysm fundus, effectively recreating the aneurysm. Contraction of the fibrous tissue that covers the coils (a phenomenon known as coil compaction) also contributes to recurrence by making more space available for blood to collect within the aneurysm.[17,19,20]

As shown in animal studies, it is the pathologic hemodynamic conditions at the site of the aneurysm that lead to disruption of endothelial function, infiltration of inflammatory macrophages, and apoptosis of VSMCs, resulting in the formation or recurrence of an aneurysm.[11,15,21,22] The dynamics of these processes include interactions between several cell types and can be altered via cell therapy to prevent formation, progression, or recurrence of aneurysms. For example, infiltration of macrophages is likely facilitated by the loss of endothelial function at the aneurysm neck, because synthesis of nitric oxide by healthy endothelium has been shown to protect the arterial wall against inflammation and inhibit aneurysm formation.[23] Therefore, re-endothelialization of the aneurysm neck, a process that could be enhanced through cell therapy, may serve to prevent recurrence of a treated aneurysm.

VSMCs could be another target for cell therapy. They are the constituting cellular component of blood vessels that provide structural integrity and regulate local blood flow by contracting and causing vessel constriction or relaxing and causing vessel dilation.[24] During development of an aneurysm, degeneration of the elastic lamina puts more stress on the collagen fibers of a vessel wall and consequently on the VSMCs responsible for their synthesis and maintenance. To make matters worse, infiltrated macrophages induce apoptosis in medial VSMCs by secreting interleukin-1β, reduce collagen synthesis by producing nuclear factor κB, and accelerate the breakdown of existing collagen fibers by releasing MMP-2 and MMP-9.[11,15,25] The increase in collagen degeneration coupled with the decrease in collagen production contributes to aneurysm growth. A possible therapeutic approach could be to replenish the lost VSMCs with exogenous VSMCs to reestablish the balance in collagen production and stop formation or recurrence of the aneurysm. Mesenchymal stem/stromal cells (MSCs) may also hold great therapeutic potential because they inhibit production of MMP-2, MMP-9, and interleukin-1β and have been reported to have the ability to differentiate into a VSMC phenotype.[26-29] MSCs have also been shown to inhibit production of tumor necrosis factor, a proinflammatory cytokine that is upregulated in injured cerebral vessels and plays a key role in aneurysm formation.[30-33]

CELL THERAPY FOR SACCULAR INTRACRANIAL ANEURYSMS

Recurrence of aneurysms involves several cellular processes that can be targeted for therapeutic purposes. In the following sections, preclinical cell therapy studies with VSMCs,[34,35] fibroblasts,[36-38] endothelial progenitor cells (EPCs),[39-42] and MSCs[43,44] are reviewed for their efficacy in treating intracranial aneurysms.

VSMCs

VSMCs are heterogeneous in terms of phenotype, with contractile or differentiated VSMCs at one extreme of the spectrum and synthetic VSMCs at the other.[24,45] Although contractile VSMCs are the dominant functional smooth muscle cell type in normal adult arteries, synthetic VSMCs are active in response to injury and during development. VSMCs retain some plasticity and can switch back and forth between different states. On injury, contractile VSMCs change their phenotype to a more synthetic state, migrate to the site of the injury, and start proliferating and synthesizing ECM, thereby supporting regeneration.[24]

During formation and recurrence of aneurysms, loss of ECM and local VSMCs results in an imbalance between ECM production and ECM degeneration, which contributes to aneurysm growth. Studies on VSMCs isolated from intracranial aneurysmal tissue and cultured in vitro[46] have shown that aneurysmal VSMCs have assumed a more synthetic phenotype, indicating their role in repairing the affected vessel. In 1999, Raymond et al.[18] studied healing of experimental aneurysms in pigs, an animal model that shows an unusually high tendency toward healing and is therefore protected against recurrence.[47] The results showed that a thick neointimal layer, mainly composed of VSMCs, was responsible for healing of porcine aneurysms.[18] Later that year, the same group[35] investigated the possible benefits of implanting VSMCs on the healing and occlusion of aneurysms in dogs. In contrast to pigs, but similar to humans, dog and rabbit aneurysm models are often affected by aneurysm recurrence.[47] The experimental aneurysms were occluded using a mix of Gelfoam (Pfizer, New York, New York, USA) and fibrinogen with or without VSMCs. Three weeks after treatment, the VSMC-treated group showed a significant increase in neointima thickness (average thickness 342.5 μm in treatment group vs. 97.63 μm in control group) and a nonsignificant improvement in angiographic scores. The investigators[35] concluded that VSMC grafts can improve the outcome of embolization treatment.

Results of a large-scale animal study on the impact of VSMC implantation on neointima formation were published in 2014.[34] In this study, Marbacher et al. showed that removing VSMCs from the aneurysmal tissue aggravates degeneration of the wall, even in occluded (i.e., treated) aneurysms. These investigators further showed that implanting VSMCs inside occluded aneurysms reduces angiographic recurrence