In vivo cerebral aneurysm models

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Cerebral aneurysm rupture is a devastating event resulting in subarachnoid hemorrhage and is associated with significant morbidity and death. Up to 50% of individuals do not survive aneurysm rupture, with the majority of survivors suffering some degree of neurological deficit. Therefore, prior to aneurysm rupture, a large number of diagnosed patients are treated either microsurgically via clipping or endovascularly to prevent aneurysm filling. With the advancement of endovascular surgical techniques and devices, endovascular treatment of cerebral aneurysms is becoming the first-line therapy at many hospitals. Despite this fact, a large number of endovascularly treated patients will have aneurysm recanalization and progression and will require retreatment. The lack of approved pharmacological interventions for cerebral aneurysms and the need for retreatment have led to a growing interest in understanding the molecular, cellular, and physiological determinants of cerebral aneurysm pathogenesis, maturation, and rupture. To this end, the use of animal cerebral aneurysm models has contributed significantly to our current understanding of cerebral aneurysm biology and to the development of and training in endovascular devices. This review summarizes the small and large animal models of cerebral aneurysm that are being used to explore the pathophysiology of cerebral aneurysms, as well as the development of novel endovascular devices for aneurysm treatment.

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primarily differ in the mechanisms of vessel wall weakening and hemodynamic stress induction (Fig. 1).

**Hemodynamic Stress and Vessel Wall Weakening**

Hemodynamic stress in the cerebral vasculature can be increased by hypertension and/or an increase in flow rate. Using the combination of hypertension and flow rate to induce hemodynamic stress, Hashimoto et al. created the first rodent CA model in rats. During a series of surgeries, hemodynamic stress was increased by ligation of the left common carotid artery (CCA) while hypertension was induced by unilateral nephrectomy, followed by subcutaneous injections of deoxycorticosterone acetate (DOCA) and the addition of 1% sodium chloride to the drinking water. Vessel walls were weakened by feeding the rats chow containing 0.12% β-aminopropionitrile (BAPN), a lysyl oxidase inhibitor, which prevents collagen and elastin cross-linking, leading to increased vessel fragility and a greater likelihood of aneurysm formation. Morimoto et al. later adapted this method for CA formation in mice and included bilateral ligation of the posterior branches of the renal arteries. Four months following surgery, CAs were observed at various stages of formation, located primarily at the bifurcation of the right anterior cerebral artery and the olfactory artery. Histological analysis revealed fragmented elastic lamina and media thinning suggestive of aneurysm formation in 78% of the treated mice. However, the CAs formed by this method are small with a few microaneurysms observable by light microscopy, while other aneurysms require electron microscopy for visualization. This method of CA formation suffers from slow aneurysm formation. Other adaptations to this protocol include ligation of the left renal artery, unilateral nephrectomy, and bilateral ligation of the posterior branches of the renal arteries during the same surgery.

**Elastase and Angiotensin II**

Early stages of aneurysm formation are associated with elastic lamina degeneration, which may contribute to aneurysm progression and rupture. Given this histological finding, Nuki et al. stereotactically injected elastase into the cerebrospinal fluid of the right basal cistern. To induce hypertension, angiotensin II was continuously administered via a subcutaneously placed microosmotic pump. CA formation was achieved in 77% of the mice within 2 weeks of treatment. Histologically, the aneurysms demon-
strated degeneration of the media layer and elastic lamina and infiltration of inflammatory cells.

**Intracranial Aneurysm Rupture Model**

The spontaneous aneurysm rupture model was introduced by Makino et al., who used a combination of elastase treatment to weaken cerebral blood vessels and hypertension. With this method, in a series of surgeries, hypertension is induced by unilateral nephrectomy, implantation of a DOCA-salt pellet, and the addition of 1% NaCl to the drinking water. During the same surgery as the DOCA-salt pellet implantation, the mice receive a single injection of elastase into the right basal cistern. With this method, CA formation occurs in >60% of the mice within 28 days of the aneurysm induction surgery. Additionally, spontaneous aneurysm rupture occurs in 50–60% of mice within 7–11 days following surgery. Hosaka et al. later modified this model with the addition of an increased vessel flow rate and fragility induced by ligating the left CCA and the right renal artery, followed 1 week later by the injection of elastase into the right basal cistern. Hypertension and vessel fragility were further enhanced by angiotensin II and by chow containing 8% NaCl and 0.12% BAPN. Using this method with elastase concentrations greater than 30 mU, 100% of the mice develop CAs.

With elastase, CAs are made and also rupture at predictable time points. With 25–30 mU of elastase, the majority of mice form aneurysms at 1 week without signs of rupture. However, approximately 80% of animals will have subarachnoid hemorrhage by 4 weeks. Similar to the histological changes observed in human CAs, the aneurysms formed by elastase display disruption of the elastic lamina, macrophage infiltration, loss or reduction of the endothelium, and smooth-muscle cell hyperplasia. This model is utilized extensively in the literature and has been used to test pharmacological inhibitors that decrease the incidence of aneurysm progression and rupture.

**Surgically Created Saccular Aneurysms**

The small animal size and the intracranial aneurysms formed preclude the use of rodent CA models for endovascular device testing. To circumvent this issue, Frösen et al. and Marbacher et al. surgically created saccular aneurysms using a donor thoracic aorta, which was surgically ligated end-to-side to the abdominal aorta in both mice and rats. These saccular aneurysms display inflammatory cell infiltration, endothelial denudation, thrombus formation, and intimal hyperplasia. Marbacher et al. expanded on this model with sodium dodecyl sulfate–induced decellularization of the donor thoracic aorta prior to aneurysm creation. The loss of mural cells led to an organized luminal thrombus, increased inflammation, and wall damage resulting in aneurysm growth and rupture. Although mice are too small, studies have been successfully conducted using the rat saccular aneurysm model for testing stents and coils.

**Perspectives and Limitations**

Rodent CA models offer a powerful tool for the investigation of aneurysm biology at a molecular, cellular, and physiological level. Excluding surgically created saccular aneurysms, rodent CA models do not require direct vessel manipulation and have an intracranial location. This leads to the question of what constitutes an aneurysm. In the early studies, aneurysm formation produced small microaneurysms that were rarely visible and only detectable by light or electron microscopy or histological alterations of the vessel wall. Some scientists do not believe these “microaneurysms” recapitulate human CA disease. In contrast, elastase treatment results in clear and defined outward bulging of the vessel walls of the circle of Willis and its major branches. Starke et al. defined an aneurysm as a bulge in the vessel wall whose diameter is >150% of the diameter of the parent artery. Similarly, Nuki et al. defined an aneurysm as a bulging of the vessel wall >150% of the diameter of the basilar artery. Although rodent CA models replicate many of the histological and molecular changes found in human CAs, there are certain pathologies observed in human CAs but not in the rodent CA models. For example, in human saccular CAs, lipids and oxidized lipids accumulate in the aneurysm wall and are associated with cell death, vessel wall weakening, and aneurysm rupture. Similarly, the complement inflammatory system is activated in human saccular CAs and is involved in aneurysm wall degradation and rupture.

The commercial availability of genetically modified mice has made rodent CA models a vital tool in investigating the molecular underpinnings of CA formation, progression, and rupture. Transgenic mice allow for the investigation of particular proteins that are altered in human CA disease. For example, tumor necrosis factor (TNF)–α, monocyte chemoattractant protein (MCP)–1, and nuclear factor (NF)–κB p50 subunit knockout reduces CA formation, whereas endothelial nitric oxide synthase (eNOS) and SOX17 knockout predisposes mice to CA formation. The cited studies are just a few of the many using transgenic mice to better understand CA biology in preclinical studies.

**Large Animal CA Models**

Large animal CA models have been made in numerous species but are primarily formed in rabbits, dogs, and swine. Aneurysm formation in large animals requires direct vessel manipulation through either microsurgical or endovascular intervention, and these aneurysms are typically formed using the CCA. Therefore, these models are extracranial in location and suffer from the effects of surgical creation at the aneurysm neck and dome. Despite these weaknesses, each model has particular characteristics that are either advantageous for or detrimental to the purposes of a particular study.

**Rabbit Aneurysm Models**

*Venous Graft Aneurysm*

To simulate arterial bifurcation aneurysms, a technique was developed to create venous pouch aneurysms using a jugular venous graft at a surgically induced bifurcation at the end-to-side anastomosis of the left CCA to the
Aneurysm formation in rabbits consists of exposing the right CCA. As the balloon is inflated, elastase is simultaneously injected, filling the artery. The artery is incubated with elastase for 20 minutes. The elastase and balloon are then removed, and the distal portion of the CCA is ligated, forming the aneurysm. Residual elastase and hemodynamic forces will cause the aneurysm to maturate over a period of several weeks following surgery. A digital subtraction angiography study shows a newly formed aneurysm to maturate over a period of several weeks following surgery. Aneurysm formation in rabbits (A) consists of exposing the right CCA. After gaining arterial access, a balloon is advanced to the origin of the CCA (A). As the balloon is inflated, elastase is simultaneously injected, filling the artery (B). The artery is incubated with elastase for 20 minutes. The elastase and balloon are then removed, and the distal portion of the CCA is ligated, forming the aneurysm. Residual elastase and hemodynamic forces will cause the aneurysm to maturate over a period of several weeks following surgery. A digital subtraction angiography study shows a newly formed aneurysm (C). Copyright Robert Starke. Published with permission.

Hemodynamic Stress–Induced Aneurysms of the Posterior Circulation

Studies by Hassler in 1963 and later by Gao et al. demonstrated that aneurysms can be formed in the posterior circulation of rabbits using hemodynamic stress alone without hypertension or vessel wall weakening. In this model, hemodynamic stress is increased in the basilar artery by unilateral or bilateral ligation of the carotid arteries. Using this technique, Hassler and Gao found histological changes in the arterial wall of the basilar terminus resembling nascent aneurysm formation characterized by a loss of internal elastic lamina, media thinning, and an outward bulge of the vessel lumen. This model has been expanded with the addition of the aneurysm risk factors of hypertension and estrogen deficiency. Hypertension is induced by unilateral nephrectomy combined with a high salt diet, and estrogen deficiency is induced by bilateral oophorectomy. The combining of hemodynamic stress with hypertension and estrogen deficiency induced changes in the circle of Willis, such as vessel length and tortuosity, as well as aneurysm lesion formation and vascular damage. Fusiform Aneurysm

Recently, Avery et al. developed a carotid artery fusiform aneurysm in rabbits. In this model, the right CCA is exposed and wrapped in gauze and isolated from surrounding tissue by placing the CCA-wrapped section into a cradle. The gauze is then soaked in elastase and CaCl₂ for 20 minutes. With this method, fusiform aneurysms, which were defined as vessel dilations greater than 50% of the proximal artery diameter, were formed in 100% of the animals at 6 weeks after aneurysm creation surgery. Histologically, these aneurysms demonstrate an almost complete loss of the internal elastic lamina, a reduction in the tunica media, and a thickening of the tunica intima. The long-term patency of this model was not investigated past 6 weeks.

Canine Aneurysm Models

Venous Pouch Model

The first reliable aneurysm model was developed in 1954 by German and Black, who used a venous pouch graft to create saccular aneurysms in dogs. This tech-
The technique has remained in use to date. The technique involves exposing the external jugular vein and sectioning a suitable length; one side of the venous segment is closed with a suture to create a venous pouch, which is then sutured to an arteriotomy created at any location of the investigator’s choice. Several modifications of this technique have been described including those for giant, wide-necked, and fusiform aneurysm creation (Fig. 3).

Generally, the CCA or cervical internal carotid artery is selected for the creation of aneurysms because of their similarity in caliber and blood flow to human cerebral vessels and the ability of the animal to tolerate the surgical procedure. The canine’s CCA is approximately 4 mm in diameter, similar to the human internal carotid artery, and the relatively long CCA in dogs (10–12 cm) affords easy surgical access.

Hemodynamic Stress and Arterial Wall Injury

More recently, Wang et al. described a novel method of CA formation by inducing hemodynamic stress in combination with arterial wall weakening. In this model, a new branch in the CCA is surgically constructed by attaching the proximal segment of one CCA to the proximal sidewall of the contralateral CCA. Hypertension is induced, and elastase is delivered externally to the apex of the newly created bifurcation.

Swine Aneurysm Models

The procedure for aneurysm production in swine is similar to that described by German and Black for aneurysm formation in canines. This method was slightly modified by using a longer venous segment and a side-to-side anastomosis to construct giant aneurysms, which were more prone to rupture if left untreated than smaller sized aneurysms.

Elastase was introduced by Goericke et al. to create saccular aneurysms. As in rabbit models, the CCA is exposed and occluded at the origin, and elastase is injected into the CCA and incubated for a period of time. As in both the rodent and rabbit CA models, elastase weakens the arterial wall, triggering an initial inflammatory response as well as activation of endogenous proteinases to break down elastin and collagen, resulting in vascular dilation.

Perspectives and Limitations

Large animal CA models offer broad utility for investigating endovascular therapeutic interventions, healing, and endovascular training. Among the large animal models, the venous pouch aneurysm model allows for the selection of aneurysm size, morphology, and location, and the aneurysm can be created in vessels with a caliber and blood flow similar to those of human cerebral vessels. However, the venous pouch model suffers in terms of the surgical trauma and suture material involved in aneurysm formation, nonarterial aneurysm composition, and an artificial neck. Despite these drawbacks, large animal models allow for testing of endovascular devices as well as endovascular training. However, the preferred CA model for endovascular training is still up for debate.

A major disadvantage of the rabbit elastase aneurysm model is that it lacks an inflammatory response and does not spontaneously rupture, but it does have coagulation and
thrombolyis profiles similar to those of humans, which is critical for testing new materials for use in endovascular devices for aneurysm occlusion. A major disadvantage of the swine CA venous graft model is a tendency for spontaneous thrombosis and healing with or without embolization. Another disadvantage of the large animal models is the presence of viable mural vascular smooth-muscle cells, which are significantly reduced or absent in human CA tissue. Marbacher et al. demonstrated that decellularized aneurysm grafts formed an unorganized luminal thrombus and had increased inflammation and wall damage resulting in aneurysm growth and rupture. Therefore, the healing response in CA models with normal cellularization of the aneurysm wall would be enhanced and thereby potentially enhance the healing response in device studies.

Silicone Aneurysm Models

The recent advancement in and accessibility to 3D printed technologies has allowed for the fabrication of patient-specific true-to-scale arterial replicas. These 3D printed models serve as education tools for presurgical assessment or can be further processed using silicone-casting technology to form a hollow, silicone-walled artificial vasculature. There is an increasing volume of literature in which artificial CA models have been used for endovascular device testing and training, surgical clip ligation training, presurgical assessment, and fluid dynamics studies, and they have also been surgically implanted into swine and cadaveric human heads for neurosurgical training. Although this model offers an excellent alternative to animals in endovascular training, it does not fully replicate the natural arterial biology, which may greatly affect testing results.

Clinical Translation and Conclusions

Animal models of CA have been and continue to be an invaluable tool for investigating the molecular, cellular, and physiological aspects of CA pathophysiology as well as for testing novel endovascular devices. Ideally, the CA model will replicate the hemodynamic forces, wall shear stresses, and cellular and tissue responses observed in human CAs. However, no animal model perfectly replicates the human disease being investigated. Therefore, each investigator must consider the strengths and weaknesses of each model in order to best replicate the aspect of CAs that is being investigated. In general, rodent CA models are useful for investigating the molecular and cellular mechanisms of aneurysm formation, growth, and rupture with the goal of finding druggable targets for therapeutic intervention and translational potential. In contrast, large CA animal models are primarily used in the development and refinement of new endovascular therapies and in the assessment of novel therapeutic interventions, as was done with Gamma Knife radiosurgery. Large animal models also allow for the investigation of aneurysm healing following therapy. No current CA model perfectly replicates human CA disease. Therefore, further work is needed to create a CA model that more closely replicates the histological and pathophysiological features of human CA disease.

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