REVIEW

Endogenous animal models of intracranial aneurysm development: a review

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Abstract

The pathogenesis and natural history of intracranial aneurysm (IA) remains poorly understood. To this end, animal models with induced cerebral vessel lesions mimicking human aneurysms have provided the ability to greatly expand our understanding. In this review, we comprehensively searched the published literature to identify studies that endogenously induced IA formation in animals. Studies that constructed aneurysms (i.e., by surgically creating a sac) were excluded. From the eligible studies, we reported information including the animal species, method for aneurysm induction, aneurysm definitions, evaluation methods, aneurysm characteristics, formation rate, rupture rate, and time course. Between 1960 and 2019, 174 articles reported endogenous animal models of IA. The majority used flow modification, hypertension, and vessel wall weakening (i.e., elastase treatment) to induce IAs, primarily in rats and mice. Most studies utilized subjective or qualitative descriptions to define experimental aneurysms and histology to study them. In general, experimental IAs resembled the pathobiology of the human disease in terms of internal elastic lamina loss, medial layer degradation, and inflammatory cell infiltration. After the early 2000s, many endogenous animal models of IA began to incorporate state-of-the-art technology, such as gene expression profiling and 9.4-T magnetic resonance imaging (MRI) in vivo imaging, to quantitatively analyze the biological mechanisms of IA. Future studies aimed at longitudinally assessing IA pathobiology in models that incorporate aneurysm growth will likely have the largest impact on our understanding of the disease. We believe this will be aided by high-resolution, small animal, survival imaging, in situ live-cell imaging, and next-generation omics technology.

Keywords Animal model · Cerebral aneurysm · Intracranial aneurysm · Natural history · Vascular disease · Review

Introduction

Intracranial aneurysm (IA) is a multifaceted disease that is characterized by pathologic outpouchings of the cerebral vascular wall. An estimated 3–5% of the general population harbors an IA [1], but the exact prevalence is unknown because most are asymptomatic. The rupture of an IA is the most common cause of nontraumatic subarachnoid hemorrhage, a devastating event that carries high rates of mortality, morbidity, and disability, as well as high health care costs [2]. Although IAs are a major public healthcare concern, their pathogenesis and natural history remain poorly understood. Aside from studies involving imaging, the only investigations of human IA pathobiology have been performed using precious clinical samples that are rarely obtained from autopsy or clipped IAs. Furthermore, their examination has only provided biological information about the aneurysm's endpoint, not its genesis or development over time, which limits delineating

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mechanisms of natural history. To this end, animal models with induced cerebral vessel aneurysm mimicking the human disease have shown the ability to expand our understanding of IA, affording opportunities to unravel disease mechanisms, identify biomarkers, and develop potential pharmacotherapies.

Generally, animal models of IA can be categorized into two classes. The first class induces aneurysmal lesions spontaneously in the cerebral vasculature in response to manipulations that incite risk factors relevant to the disease. These are what we are calling endogenous IA models. The second class surgically creates an aneurysm pouch, typically in extracranial arteries. These models include the creation of vein pouches and elastase-treated, distally ligated extracranial artery stumps [3–5]. Such surgical models have been integral in evaluating endovascular IA interventions (e.g., aneurysm coiling and stenting). As they have been thoroughly reviewed elsewhere [6–8], they will not be discussed here. Instead, this review will focus on endogenous IA models, which have provided the most knowledge of aneurysm pathobiology to date.

Nearly six decades of research have been devoted to the development and implementation of endogenous IA models in various animal species. In the last 20 years, extensive use of these models has led to a deeper understanding of the biological and molecular basis of IA formation and development.

Materials and methods

For this review, we comprehensively searched the published literature. In PubMed, we used Medical Subject Headings (MeSH) terms to identify studies that used animal models with endogenously induced IAs between 01/01/1960 and 12/31/2019 (Fig. 1). We included the MeSH terms "intracranial aneurysm," "cerebral aneurysm," "animal model," "animal model, experimental," and "animal model, laboratory," and excluded MeSH terms "surgical," "structure, surgically created," and "medical device." Next, we excluded review articles, as well as re-analyses of existing datasets, letters and commentaries, published datasets, and other articles that did not meet our search terms. In all, we identified 174 original publications between 1960 and 2019 (Table 1), from which we extracted the animal species, the method for aneurysm induction, the definition of aneurysmal lesion(s), IA evaluation methods, aneurysm characteristics, the IA formation and rupture rates, and the developmental time course.

In this review, we present a brief history of endogenous IA models and summarize the methods that have been employed for induction, investigation, and characterization of experimental IAs. We will also discuss the strengths and weaknesses of the various approaches and the relevance of these models to human disease.

Results

A history of endogenous IA model development

Endogenous animal models of IA have been studied over the last 60 years. While clinical IA studies during that time largely focused on epidemiologic analyses and interventions, experimental IA investigations have tried to understand the disease pathophysiology, unravel mechanisms of IA formation, identify molecular targets for potential pharmacological therapies, and understand IA rupture. Figure 2 illustrates the chronology of the introduction of aneurysm models in terms of three aspects that will be discussed in this review: the animal species, the factors used to induce aneurysms, and the technology used for manipulation or assessment.

The earliest report of an endogenous IA animal model was published by White et al. in 1961 [9]. In this study, various noxious chemical solutions, i.e., hyaluronidase (150 or 300 USP units/mL), sodium morrhuate (10% or 5%), plasmocid (1 or 5 mg/mL), and nitrogen mustard (0.5 or 2 mg), were injected into the wall of the left internal carotid artery (ICA) of mongrel canines to induce IA. Hypertonic saline produced the best results, mimicking many features of human IAs, including loss of internal elastic lamina (IEL) and degradation of the medial layer. In 1963, motivated by observations that IAs form in high blood flow regions in the cerebral circulation, Hassler et al. [10] used unilateral common carotid artery (CCA) ligation in rabbits of unspecified strain to induce flow-mediated cerebrovascular damage. The resulting vascular changes were described as "consistent with aneurysms," including bulging, media thinning, and loss of IEL at the basilar terminus (BT) and other bifurcations. Then in 1978, seeking a small animal model of IA, Lee et al. [12] created micro-aneurysms in rats via hypertension (a known IA risk factor [182]) induced by unilateral nephrectomy, deoxycorticosterone acetate (DOCA) treatment, and high salt diet. They found lesions throughout the vasculature of the cortex and basal ganglia 14 weeks after inducing hypertension. From these early, simpler models, multi-modal models (i.e., models inducing multiple risk factors) began to emerge in the 1970s in an effort to increase the incidence of IA formation [13; 14]. Notably, in 1974, Uchida et al. [11] built upon Hassler's model [10] by combining β-aminopropionitrile (BAPN) with either unilateral or bilateral CCA ligation in rabbits. With this approach, they were able to produce larger and more rapidly developing lesions at the BT [11].

One of the most important milestones in IA model development was the rat model created by Hashimoto et al. [14] from Kyoto University in Japan. In 1978, this group combined flow increase via unilateral CCA ligation, hypertension induced by renal ligation and DOCA (2.5 mg/100 mg body

Table 1 174 studies involving endogenous animal models of IA

First author	Year	Journal abbreviation	Animal	Manipulation					Number of experimental animals	Aneurysm rate	Rupture rate	Max. Time of evaluation (days)
				Flow modification	Hypertension	Estrogen manipulation	Connective tissue weakness	Genetics				
White [9]	1961	J Neurosurg	Canine				X		10	30%	NR	21
Hassler [10]	1963	J Neurosurg	Rabbit	X					NR	NR	NR	150
Uchida [11]	1974	Kumamoto Med J	Rabbit	X			X		NR	NR	NR	63
Lee [12]	1978	J Pathol	Rat		X				14	71%	NR	98
Kido [13]	1978	Neuroradiology	Rabbit		X				4	100%	0%	NR
Hashimoto [14]	1978	Surg Neurol	Rat	X	X		X		55	11%	4%	60
Hashimoto [15]	1979	Surg Neurol	Rat	X	X		X		30	37%	3%	147
Hashimoto [16]	1979	Surg Neurol	Rat	X	X		X		NR	NR	NR	147
Nagata [17]	1979	Surg Neurol	Rat	X	X		X		NR	NR	0%	90
Hashimoto [18]	1979	Neurol Med Chir	Rat	X	X		X		45	NR	NR	NR
Hashimoto [19]	1979	Nihon Geka Hokan	Rat	X	X		X		NR	NR	NR	NR
Nagata [20]	1980	Surg Neurol	Rat	X	X		X		NR	50%	32%	112
Hashimoto [21]	1980	Surg Neurol	Rat	X	X		X		72	40%	NR	147
Suzuki [22]	1980	J Neruosurg	Rat	X	X	X	X		43	14%	0%	70
Zhou [23]	1985	Chin Med J	Rat	X	X	X	X		32	40%	NR	126
Alvarez [24]	1986	J Neruosurg	Rat	X	X				19	42%	NR	112
Kojima [25]	1986	Stroke	Rat	X	X				20	15%	NR	84
Hazama [26]	1986	Am J Pathol	Rat	X	X				22	36%	NR	90
Hashimoto [27]	1987	J Neruosurg	Primate	X	X		X		7	29%	0%	365
Roda [28]	1988	Acta Neurochir Suppl	Rat	X					8	38%	NR	240
Kim [29]	1988	Stroke	Rat	X	X				13	15%	NR	90
Kim [30]	1989	Surg Neurol	Primate	X	X		X		7	86%	NR	365
Yamazoe [31]	1990	Stroke	Rat	X	X		X		19	58%	NR	112
Kang [32]	1990	J Neruosurg	Rat	X	X		X		32	13%	NR	42
Nakatani [33]	1991	J Neruosurg	Rat	X	X		X			NR	NR	90
Kim [34]	1992	Surg Neurol	Primate	X	X				3	67%	NR	180
Nakatani [35]	1993	Acta Neurochir	Rat	X	X		X		12	50%	NR	90
Kim [36]	1993	Acta Neurochir	Rat	X	X				NR	0%	NR	90
Futami [37]	1995	Stroke	Rat	X	X				25	24%	NR	90
Futami [38]	1995	Stroke	Rat	X	X				15	58%	NR	90
Kondo [39]	1997	Stroke	Rat	X	X				35	54%	0%	365
Coutard [40]	1997	Stroke	Rat	X	X				43	26%	NR	405
Kondo [41]	1998	Stroke	Rat	X	X				35	31%	NR	180
Futami [42]	1998	Surg Neurol	Rat	X	X				23	30%	NR	90
Coutard [43]	1999	Int J Exp Pathol	Mouse	X	X				31	19%	3%	360
Fukuda [44]	2000	Circulation	Rat	X	X				8	100%	NR	90
Coutard [45]	2000	Stroke	Rat	X	X				142	30%	16%	NR
Morimoto [46]	2002	Stroke	Mouse	X	X				18	33%	NR	120
Zhang [47]	2003	Chin Med J	Rat					X	20	10%	NR	365
Sadamasa [48]	2003	Stroke	Mouse	X	X		X		24	38%	NR	120
Jamous [49]	2005	J Neurosurg	Rat	X	X				12	60%	NR	60
Jamous [50]	2005	J Neurosurg	Rat	X	X	X			15	53%	0%	90
Jamous [51]	2005	J Neurosurg	Rat	X	X	X			11	18%	0%	90

Table 1 (continued)

First author	Year	Journal abbreviation	Animal	Flow modification	Hypertension	Estrogen manipulation	Connective tissue weakness	Genetics	Number of experimental animals	Aneurysm rate	Rupture rate	Max. Time of evaluation (days)
Kaufmann [52]	2006	Neuroradiology	Rat	X					37	19%	NR	365
Moriwaki [53]	2006	Stroke	Mouse	X	X				8	50%	NR	150
Aoki [54]	2007	Stroke	Rat	X	X		X		21	90%	NR	90
Sadamasa [55]	2007	J Neurosurg	Rat	X	X		X		28	100%	NR	90
Aoki [56]	2007	Stroke	Rat, Mouse	X	X		X		16	19%	NR	150
Abruzzo [57]	2007	Curr Neurovasc Res	Mouse	X					13	31%	NR	690
Jamous [58]	2007	J Neurosurg	Rat	X	X				40	10%	0%	60
Aoki [59]	2008	Circulation	Rat, Mouse	X	X		X		10	30%	NR	90
Aoki [60]	2008	Curr Neurovasc Res	Rat	X	X		X		20	NR	NR	30
Aoki [61]	2008	Stroke	Rat	X	X				10	NR	NR	90
Sibon [62]	2008	J Neurosurg	Rat	X	X				NR	NR	NR	180
Sadamasa [63]	2008	J Vasc Res	Rat	X	X		X		18	NR	NR	90
Aoki [64]	2008	Int J Mol Med	Rat, Mouse	X	X		X		25	16%	NR	150
Gao [65]	2008	Stroke	Rabbit	X					6	NR	NR	84
Aoki [66]	2008	Stroke	Rat	X	X		X		19	90%	NR	90
Aoki [67]	2008	Int J Mol Med	Rat	X	X		X		27	NR	NR	30
Aoki [68]	2009	Stroke	Rat, Mouse	X	X		X		15	20%	NR	90
Aoki [69]	2009	Neurosurgery	Rat	X	X				20	NR	NR	90
Tamura [70]	2009	J Hypertens	Rat	X	X	X			18	25%	NR	90
Aoki [71]	2009	Arterioscler Thromb Vasc Biol	Rat	X	X		X		NR	NR	NR	90
Aoki [72]	2009	Lab Invest	Rat, Mouse	X	X		X		NR	NR	NR	90
Tada [73]	2009	Hypertension	Rat	X	X	X			32	59%	NR	91
Aoki [74]	2009	Int J Mol Med	Rat	X	X		X		NR	NR	NR	30
Nuki [75]	2009	Hypertension	Mouse	X	X		X		44	77%	NR	14
Eldawoody [76]	2009	Brain Res	Rat	X	X	X			32	94%	NR	90
Eldawoody [77]	2010	Neurosci Lett	Rat	X	X	X			16	100%	NR	60
Dai [78]	2010	AJNR Am J Neuroradiol	Rabbit	X					30	0%	NR	231
Kimura [79]	2010	Brain Res	Rat	X	X	X			14	50%	NR	90
Yagi [80]	2010	Neurosurgery	Rat	X	X	X			20	30%	NR	90
Tada [81]	2010	J Hypertens	Rat	X	X	X			14	NR	NR	91
Metaxa [82]	2010	Stroke	Rabbit	X					NR	NR	NR	5
Aoki [83]	2010	J Neurosurg	Rat, Mouse	X	X		X		NR	NR	NR	90
Ishibashi [84]	2010	Curr Neruovasc Res	Rat	X	X		X		NR	NR	NR	30
Aoki [85]	2010	Gene Ther	Rat	X	X		X		NR	NR	NR	90
Meng [86]	2011	J Neurosurg	Rabbit	X					17	NR	NR	189
Kanematsu [87]	2011	Stroke	Mouse	X	X		X		10	60%	NR	21
Kolega [88]	2011	J Vasc Res	Rabbit	X					NR	NR	NR	5
Aoki [89]	2011	Br J Pharmacol	Rat, Mouse	X	X		X		36	61%	NR	150
Aoki [90]	2011	Lab Invest	Rat, Mouse	X	X		X		37	56%	NR	150
Gopal [91]	2011	J Thromb Thrombolysis	Mouse					X	12	33%	NR	45
Tada [92]	2011	Stroke	Rat	X	X	X			19	47%	0%	168
Xu [93]	2011	Neuroscience	Rat	X	X				NR	NR	NR	90
Xu [94]	2011	Neruosci Lett	Rat	X	X				15	20%	NR	90

Table 1 (continued)

First author	Year	Journal abbreviation	Animal	Manipulation					Number of experimental animals	Aneurysm rate	Rupture rate	Max. Time of evaluation (days)
				Flow modification	Hypertension	Estrogen manipulation	Connective tissue weakness	Genetics				
Aoki [95]	2012	Neurosurgery	Rat	X	X		X		29	NR	NR	60
Dolan [96]	2012	Am J Physiol Cell Physiol	Rabbit	X					NR	NR	NR	5
Cai [97]	2012	J Clin Neurosci	Rat	X					15	20%	NR	90
Ishibashi [98]	2012	Neurosurgery	Rat		X		X		20	NR	NR	30
Makino [99]	2012	Stroke	Mouse	X	X		X		8	63%	50%	28
Mandelbaum [100]	2013	PloS One	Rabbit	X					45	100%	0%	180
Dolan [101]	2013	Am J Physiol Cell Physiol	Rabbit	X					NR	100%	0%	150
Ali [102]	2013	J Cereb Blood Flow Metab	Rat	X					24	100%	0%	14
Wada [103]	2013	Transl Stroke Res	Mouse		X		X		34	75%	1%	28
Lee [104]	2013	J Korean Neurosurg Soc	Rat	X	X				NR	NR	NR	90
Li [105]	2014	West Indian Med J	Rabbit	X	X				NR	100%	NR	90
Hosaka [106]	2014	J Neurointerv Surg	Mouse	X	X		X		40	98%	43%	90
Tutino [107]	2014	J Cereb Blood Flow Metab	Rabbit	X					6	100%	NR	180
Tada [108]	2014	Stroke	Mouse		X		X		16	75%	50%	28
Aoki [109]	2014	Acta Neuropathol Comm	Rat, Mouse	X	X		X		37	NR	NR	90
Tada [110]	2014	Hypertension	Mouse		X		X		19	74%	58%	21
Starke [111]	2014	J Neuroinflammation	Mouse		X		X		22	82%	68%	28
Liaw [112]	2014	PLoS One	Rabbit	X					7	100%	NR	5
Tada [113]	2014	Neurosurgery	Mouse		X		X		NR	36%	NR	28
Li [114]	2014	Brain res	Rat	X	X				NR	NR	NR	60
Fukuda [115]	2014	J Pharmacol Sci	Rat, Mouse	X	X		X		24	NR	NR	1
Yokoi [116]	2014	J Neurosurg	Rat	X	X				36	100%	NR	90
Nowicki [117]	2014	Hypertension	Mouse	X	X		X		15	67%	NR	14
Li [118]	2015	Neurochem Res	Rat	X	X				20	NR	NR	60
Zhao [119]	2015	J Clin Neurosci	Rat	X	X		X		12	42%	16%	49
Pena-Silva [120]	2015	Hypertension	Mouse		X		X		14	86%	64%	21
Lee [121]	2015	Circulation	Mouse		X			X	8	60%	NR	28
Makino [122]	2015	J Cereb Blood Flow Metab	Mouse		X		X		10	60%	50%	14
Chu [123]	2015	Stroke	Mouse		X	X	X		17	90%	83%	19
Tutino [124]	2015	Anat Rec	Rabbit	X	X				6	100%	NR	180
Shimada [125]	2015	J Cereb Blood Flow Metab	Mouse		X		X		20	85%	76%	14
Zhang [126]	2015	J Neuropathol Exp Neurol	Mouse	X	X		X		30	NR	NR	NR
Hasan [127]	2015	Hypertension	Mouse		X		X	X	27	81%	59%	21
Shimada [128]	2015	Stroke	Mouse		X		X		39	85%	79%	21
Pena-Silva [129]	2015	Neurosurgery	Mouse		X		X		11	73%	0%	21
Wu [130]	2015	Cell Mol Biol	Rabbit	X					48	27%	NR	28
Wu [131]	2015	Cell Mol Biol	Rabbit	X					NR	NR	NR	NR
Wu [132]	2016	Turk Neurosurg	Rat	X	X				30	90%	NR	180
Jung [133]	2016	J Neuropathol Exp Neurol	Rat	X	X	X			36	78%	14%	150
Tutino [134]	2016	Curr Neruovasc Res	Rat, Rabbit	X					18	50%	NR	7
Chalouhi [135]	2016	Hypertension	Mouse		X		X	X	14	100%	100%	19
Zhu [136]	2016	J Neurointerv Surg	Mouse		X		X		38	21%	13%	28
Sawyer [137]	2016	J Neuroinflammation	Mouse	X			X		NR	NR	100%	14

Table 1 (continued)

First author	Year	Journal abbreviation	Animal	Manipulation					Number of experimental animals	Aneurysm rate	Rupture rate	Max. Time of evaluation (days)
				Flow modification	Hypertension	Estrogen manipulation	Connective tissue weakness	Genetics				
Aoki [138]	2016	Acta Neuropathol Commun	Rat	X	X		X		NR	NR	NR	NR
Lee [139]	2016	J Clin Neurosci	Mouse		X		X		15	100%	100%	NR
Liu [140]	2017	Stem Cells	Mouse		X		X		NR	74%	81%	21
Miyamoto [141]	2017	J Cereb Blood Flow Metab	Rat	X	X	X			21	40%	81%	90
Yamamoto [142]	2017	Br J Pharmacol	Rat, Primate	X	X	X	X		30	57%	NR	364
Miyata [143]	2017	PLoS One	Rat	X	X				15	NR	NR	60
Ikedo [144]	2017	J Am Heart Assoc	Rat	X	X		X		7	NR	NR	28
Aoki [145]	2017	J Stroke Cerebrovasc Dis	Rat	X	X		X		NR	NR	NR	5
Liu [146]	2017	Shock	Mouse		X				NR	70%	75%	20
Aoki [147]	2017	Sci Signal	Rat, Mouse	X	X		X		24	NR	NR	224
Maekawa [148]	2017	J Neuroinflammation	Rat	X	X	X			NR	100%	17%	84
Wu [149]	2017	Am J Trans Res	Rabbit	X					35	NR	NR	NR
Kuwabara [150]	2017	Neurosurgery	Mouse		X		X		11	91%	90%	21
Labeyrie [151]	2017	Stroke	Mouse		X		X		12	100%	67%	28
Starke [152]	2018	Arterioscler Thromb Vasc Biol	Mouse		X		X		25	84%	71%	28
Suzuki [153]	2018	Cerebrovasc Dis	Mouse		X		X		54	67%	81%	21
Hoh [154]	2018	J Am Heart Assoc	Mouse	X	X	X	X		19	65%	NR	NR
Quan [155]	2018	Frontier Pharmacol	Rat	X	X		X		12	58%	29%	35
Kamio [156]	2018	Stroke	Mouse		X		X		22	68%	47%	21
Ikedo [157]	2018	Biochem Biophys Res Commun	Rat	X	X		X		NR	NR	NR	NR
Liu [158]	2018	J Photochem Photobiol B	Rat				X		NR	NR	NR	NR
Li [159]	2018	CNS Neurosci Ther	Rat	X	X				NR	NR	NR	30
Zhang [160]	2018	Biochem Biophys Res Commun	Rat	X	X		X		NR	NR	NR	NR
Hoh [161]	2018	J Neurointerv Surg	Mouse				X		NR	NR	NR	21
Nowicki [162]	2018	J Neurointerv Surg	Mouse		X		X		NR	100%	48%	NR
Zhao [163]	2018	Mol Med Rep	Mouse	X	X		X		25	72%	44%	14
Shikata [164]	2019	Hypertension	Mouse				X		19	80%	NR	NR
Pascale [165]	2019	J Cereb Blood Flow Metab	Mouse		X		X		60	70%	90%	14
Tutino [166]	2019	Cur neurovasc res	Mouse	X					3	0%	NR	80
Rajabzadeh-Oghaz [167]	2019	Proc SPIE Int Soc Opt Eng	Mouse	X					3	0%	NR	80
Miyata [168]	2019	Neurol Med Chir	Rat		X				NR	NR	NR	NR
Wei [169]	2019	Med Sci Monit	Rat	X	X				NR	NR	NR	NR
Suzuki [170]	2019	Stroke	Mouse		X		X		NR	NR	80%	21
Xiao [171]	2019	World Neurosurg	Rat, Rabbit	X	X				NR	NR	NR	NR
Ikedo [172]	2019	World Neurosurg	Rat	X	X		X		11	NR	NR	90
Ma [173]	2019	Mol red rep	Rat	X	X				NR	NR	NR	28
Yamaguchi [174]	2019	J Neurosurg	Rat	X		X			42	NR	14%	84
Lai [175]	2019	Biosci Rep	Rat	X	X				40	NR	NR	90
Wei [176]	2019	Pharmazie	Rat	X	X				9	NR	NR	NR
Shimizu [177]	2019	J Neuropathol Exp Neurol	Rat	X	X	X	X		NR	NR	13%	28

Table 1 (continued)

First author	Year	Journal abbreviation	Animal	Manipulation					Number of experimental animals	Aneurysm rate	Rupture rate	Max. Time of evaluation (days)
				Flow modification	Hypertension	Estrogen manipulation	Connective tissue weakness	Genetics				
Miyata [178]	2019	*J Nuerosurg*	Rat	X	X	X			13	100%	30%	70
Yang [179]	2019	*Pharmacology*	Rat	X	X		X		32	NR	NR	120
Feng [180]	2019	*Clin Sci*	Rat	X	X				NR	NR	0%	28
Fan [181]	2019	*Neuropharmacology*	Rat	X	X				NR	NR	0%	30

Studies are presented chronologically. In cases where 0% was reported as the IA formation rate, the studies were still included because the authors reported aneurysm-like remodeling that was consistent with other, previous reports. Oftentimes, a rate of 0% was reported when the observed lesion did not match strict criteria for defining an IA that the author prescribed. *IA,* intracranial aneurysm; *NR,* not reported

weight) and salt diet (1% in drinking water), and vessel wall weakening by oral administration of BAPN (0.12%) to incite aneurysm formation in the anterior Circle of Willis (CoW) of male Sprague-Dawley rats. This led to consistent lesion formation at the anterior cerebral artery-olfactory artery (ACA-OA) bifurcation. Histopathological studies confirmed that IAs induced by this model share common features with human IAs, including bulge formation, IEL loss, destructive changes in the medial layer, and intimal hyperplasia [14]. This model has since been employed in a large number of follow-up studies, making it one of the most extensively studied IA animal models [54, 56, 59, 64, 66, 67, 71, 72, 74, 83, 85, 89, 90, 95]. It has largely served as the means for the most comprehensive pathobiological research on experimental IAs, which has been led by Tomohiro Aoki from the same group [54, 56, 59, 64, 66, 67, 71, 72, 74, 83, 85, 89, 90, 95]. The combination of manipulations in this rat model also laid the foundation for later efforts that added modifications in different species (e.g., mice), with the goal of increasing aneurysm (and rupture) incidence or elucidating the role of specific proteins and signaling pathways.

Since the incidence of IAs in humans is higher among females [183], Suzuki et al. [22] began investigating the role of estrogen in IA models via feminization of male Sprague-Dawley rats in 1980. Further study on the role of estrogen was continued by Jamous et al. [49–51] from Tokushima University in Japan in 2005. In a series of studies, they built upon the rat model introduced by Hashimoto, but used female rats instead of males, removed BAPN from their diet, and added bilateral oophorectomy (removal of the ovaries). Using these manipulations, they showed that estrogen deficiency increased lesion formation 3-fold (from 20 to 60%) in rats when added to hypertension and CCA ligation [49–51, 73]. Eldewoody et al. [76] from Tohoku University in Japan further fine-tuned this model by optimizing the method of hypertension induction. They found that despite the simplified surgical procedure, posterior renal artery ligation was more effective at inducing IA formation, i.e., led to greater degree and frequency of IA lesions than did posterior and inferior renal artery ligation or the use of spontaneously hypertensive, Dahl salt-sensitive rats.

Given a long-recognized correlation between blood flow and IA pathophysiology in humans—IAs preferentially form at locations of high fluid shear stress[184]—several groups began studying the effect of hemodynamic insult on aneurysm formation in flow-only experimental models [24, 185, 186]. In 1986 Alvarez et al. [24] subjected rats to either left CCA ligation or left CCA ligation coupled with anastomosis of the proximal left CCA to the right CCA, to increase flow in the right CCA. They found that the latter manipulation resulted in much higher flow rates in the right CCA compared with unilateral ligation alone and higher rates of aneurysm formation at downstream locations—the anterior communicating
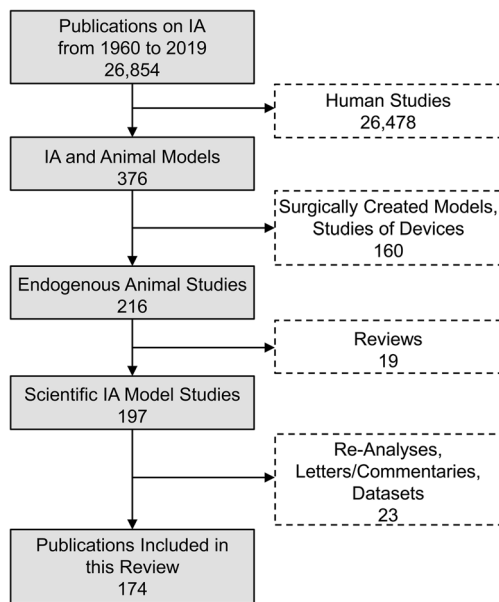
Fig. 1 A flowchart detailing the literature survey that yielded the publications analyzed in this study. In PubMed, we searched for published animal model studies of intracranial aneurysm, excluding those that used surgically created aneurysms (primarily to study medical devices). Furthermore, we manually excluded review articles, as well as other publications (i.e., commentaries on other articles) that did not fit our search criteria

artery and P1 segment of the left posterior cerebral artery—that presumably experience higher flow [24].

The critical role for hemodynamics in IA formation was further explored by Meng et al. [185] at the University at Buffalo in New York. In 2006, this group first observed flow-driven aneurysm-like remodeling in surgically created carotid bifurcations in a canine model (not included in Table 1 as it was not an endogenous model) [187–189]. Using computational fluid dynamics (CFD) simulations of flow at the artificial bifurcation and co-mapping flow topology with histology (hemodynamics-histology co-mapping), they demonstrated that the vascular response to flow (namely IEL loss and groove formation) was associated with increased flow acceleration [190]. Subsequently, the same group built upon Hassler's rabbit model and induced endogenous aneurysmal remodeling at the BT in New Zealand White rabbits after bilateral CCA ligation to increase flow in the BA. The induced remodeling was characterized by IEL loss, medial thinning, and vessel bulging [186]. Using their hemodynamics-histology co-mapping, they showed that the aneurysmal remodeling occurred predominantly in regions where high wall shear stress (WSS) and high positive WSS gradient (WSSG) exceeded a quantitatively defined threshold level [191, 192]. Using this rabbit model, they observed a critical role for smooth muscle cells (SMCs) in IA genesis, finding that SMCs exhibited proinflammatory behavior in response to hemodynamic insult and produced matrix metalloproteinases (MMPs) in the earliest stages of IA development [193]. In 2019, Tutino et al. [166, 167], demonstrated

the feasibility of determining detailed cerebrovascular hemodynamics in mice using CFD and high-resolution 9.4-T MRI, which could permit fine-grained analysis of hemodynamic factors in small animals where a much wider range of molecular tools, such as protein antibodies and genetically engineered animals, are available.

Beginning in the late 1990s, genetic factors that increase IA incidence began to be studied in animal models. Genetic predisposition in the Hashimoto model was first investigated by Coutard et al. [40], who explored the effects of genetic variability as a result of differing strains of rats. Induction of IA formation via unilateral CCA ligation and renal artery ligation in 4 different strains demonstrated that Long Evans rats have over a 5-fold higher IA incidence rate compared with LOU rats and over a 3-fold higher IA incidence compared with Brown Norway rats [40]. Hybrid Brown Norway and Long Evans rats were later shown to have a higher incidence rate (~ 50%) of IA remodeling compared with the original Brown Norway strain (0%), demonstrating that IA incidence could be modulated by genetics [45]. With the rapid evolution of microarray technology in the early 2000s, many began to investigate the RNA expression profiles of endogenously created IAs in animals [48, 89], albeit they did not study the role of inherited genetics [45]. These efforts include microarrays implemented on aneurysmal tissue from the Hashimoto rat model[64] and microRNA arrays in flow- and hypertension-driven rat models [194]. More recently, transgenic knockout (KO) mice have been implemented in several IA models to elucidate the biological mechanisms of key genes/proteins identified in previous animal model studies [72, 111, 121].

At the turn of the century, IA models had been utilized to extensively explore the roles of suspected molecules in IA formation, delineate mechanistic pathways, and develop targets and drugs for reducing IA formation [44, 64, 74]. After the establishment of the rat model in Kyoto, several investigators applied similar manipulations in mice to create aneurysms. In 2009, Nuki et al. [75] reported a new model of IA induction in female C57BL/6J mice, which was distinguished from other endogenous IA models by its aggressive application of elastase (35 mU) and sustained infusion of angiotensin II (500 or 1000 ng/kg/min). They showed that their new model increased the incidence of aneurysm formation by 77%, depending on the dose of elastase and an angiotensin II injection. One variation of this model [75], introduced by Makino et al. [99], was subsequently used to explore aneurysm rupture and resulting subarachnoid hemorrhage. This model used a combination of stereotactic elastase injection, hypertension by unilateral nephrectomy, implantation of a DOCA-salt pellet, and a high-salt diet. These manipulations led to higher rates of IA formation (greater than 60%) and higher rates of aneurysm rupture (greater than 50%) at approximately 1 week after induction. Aneurysms created by this method resembled human IAs in terms of IEL disruption, endothelial cell (EC) loss,
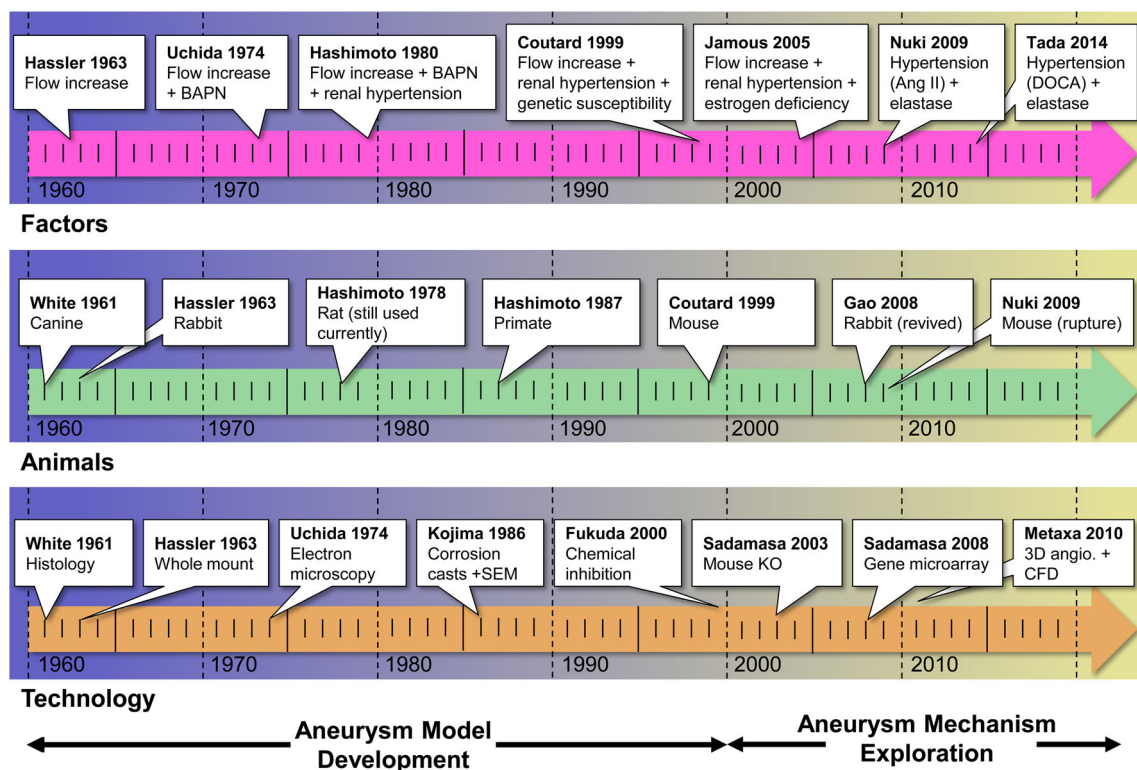
Fig. 2 A timeline of important milestones in IA model development. For the most part, endogenous animal models of IA were developed from 1961 through the early 2000s. At the turn of the century there was an exponential growth in research focused on the pathogenesis of the disease. The top row shows noteworthy studies that utilized new methods to incite IA risk factors. The middle row highlights notable first uses of different animal species (many of which are still in use today, i.e., rats). The bottom row highlights the first use of different analytical technologies in the study of animal models of IA. Ang II, angiotensin II; angio., angiography; BAPN, β-aminopropionitrile; CFD, computational fluid dynamics; DOCA, deoxycorticosterone acetate; IA, intracranial aneurysm; KO, knock-out; SEM, scanning electron microscopy

inflammatory cell infiltration, and SMC hyperplasia. To increase the rate of IA formation and rupture, Hosaka et al. [106] subsequently modified this model to include ligation of the left CCA to increase flow in the CoW, as well as exacerbating hypertension by angiotensin II infusion and 8% NaCl diet (rather than DOCA) in addition to unilateral renal artery ligation, and weakening extracellular matrix (ECM) by adding BAPN to the diet. Since their creation, these models have been also implemented in rats [119, 155, 195], and have been used extensively to explore IA rupture and to test pharmacological treatments that decrease the incidence of IA formation and rupture.

IA induction methods Endogenous animal models of IA have implemented manipulations that mimic risk factors for human IAs [196], such as elevated blood flow, hypertension, and estrogen deficiency in several animal species. Figure 3 illustrates these methods and the frequency at which they appear in the literature. We note that manipulations are most often used in combination; only 32 of the 174 publications (18%) surveyed employed a single manipulation. Figure 4 shows the model-generating manipulations with the numbers of publications that use them, either individually (non-overlapping regions) or combined (overlapping regions).

The abovementioned manipulations have been implemented in 5 types of animals: canines (in < 1% of studies), primates (2%), rabbits (12%), mice (33%), and rats (62%), with rats and mice being used in the vast majority of studies. A total of 7.5% of studies used multiple animal species. In recent years, mice have been increasingly used, likely due to their rapid life cycle, inexpensive housing, and well-established methods for their genetic manipulation that make them ideal candidates for an animal model [166, 170]. New Zealand white rabbits are still used, albeit to a lesser extent, because their cerebral vessels are large enough for imaging by catheter-based digital subtraction angiography, which can enable minimally invasive vessel morphology measurement and CFD analysis [171].

Flow increase Anecdotal observations have strongly implicated hemodynamic insult in IA pathogenesis [197]. Saccular IAs are commonly located at bifurcations and along outer curves of cerebral vessels [190, 192], locations that are exposed to flow impingement and increased wall shear stress (WSS) [192]. Clinical reports have demonstrated de novo IA formation in the human Circle of Willis in contralateral regions where compensatory flow increase occurs following

Fig. 3 Different methods used for IA model creation. A diagram of a rat with annotations of different surgical and chemical manipulations performed to induce IA-associated risk factors. BAPN, β-Aminopropionitrile; DOCA, deoxycorticosterone acetate
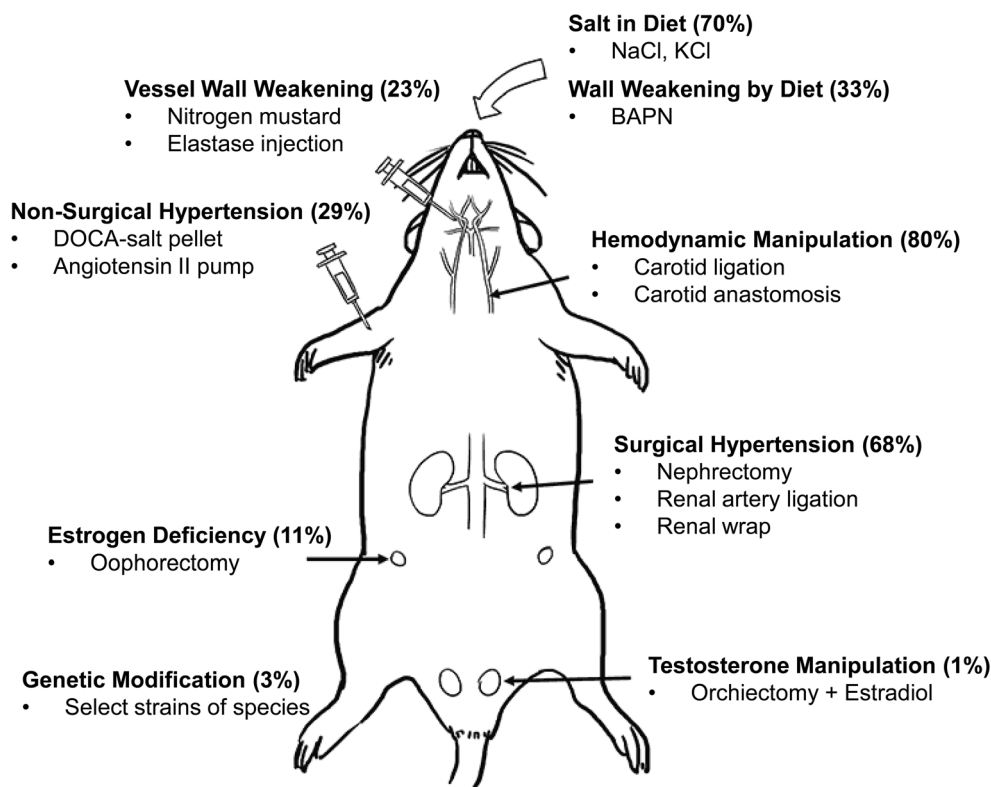
carotid occlusion or ligation [198]. In animal models, cerebral blood flow increase is generally achieved by vessel ligation. Of the 174 publications we surveyed, 137 (79%) used flow increase for aneurysm creation, as indicated by the pink circle in Fig. 4. Out of these, 23 (13%) used flow increase as the sole manipulation. The most frequently performed manipulation to elevate hemodynamic stress has been unilateral common carotid artery (CCA) ligation, which increases blood flow through the contralateral CCA and the basilar artery [116, 118, 168]. This has typically been performed in rodents, where aneurysms are commonly observed at the ACA-OA bifurcation.

Bilateral CCA ligation has also been performed in order to increase flow more drastically through the BA and create more severe hemodynamic insult at the BT [10, 82, 186]. This has been used extensively in rabbits to elucidate the relationship between hemodynamic insult and IA initiation, even without other risk factors. Tutino et al. [124] demonstrated that combining additional risk factors (hypertension and estrogen deficiency) to bilateral CCA ligation increased the observed aneurysmal remodeling at the BT, as well as other locations in the Circle of Willis. While bilateral CCA ligation has been used with great success in rabbits, this manipulation has failed to produce detectable aneurysm initiation at the rat and mouse BT [134, 166]. This may be because the configuration of the rat and mouse Circles of Willis dictates lesser hemodynamic forces at locations around the basilar artery bifurcation where IAs form in the rabbit. Recently, other

flow-only models have been developed in rats [52, 97]. For instance, Cai et al. [97] developed a model that formed aneurysms in the anterior communicating artery following unilateral CCA ligation, and contralateral external carotid artery and
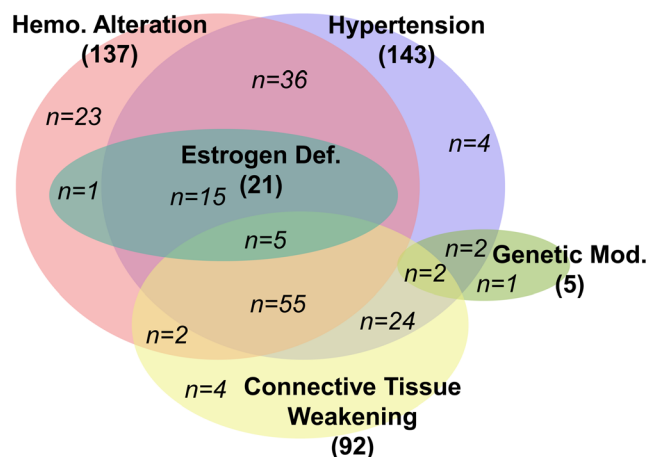
Fig. 4 The different factors induced in endogenous animal models. Each main risk factor (in bold) is represented by one oval (hemodynamic alteration—pink, hypertension—violet, estrogen deficiency—teal, connective tissue weakening—yellow, and genetic modification—green) The overlapping of ovals represents studies in which the respective methods were used in conjunction with each other. The number of studies using each method of IA induction is also indicated (italicization indicates the number for each combination of manipulations). The vast majority of the studies have implemented multi-modal models, with flow increase, hypertension, and connective tissue weakening as the predominant factors used

pterygopalatine artery ligation. Yet, while this model produced large aneurysmal bulges in the anterior communicating arteries, IA incidence was low (< 30%).

Hypertension Hypertension is a major risk factor for IAs in humans, as it is present in 43% of those with IA, compared with 20% of the general population [124]. This may be because increased blood pressure causes greater tensile stress in the vessel wall, leading to arterial remodeling that causes stiffening. Increased stiffness makes the arterial wall less mechanically responsive to changes in blood flow, and thus increases hemodynamic stresses [199], and also disrupts the beneficial production of nitric oxide by endothelial cells in response to flow [200]. Additionally, angiotensin II, a vasoconstrictive hormone involved in the renal initiation of hypertension (it increases Na+ reabsorption), can also cause increased inflammation in the vasculature [201], which could make vessels more susceptible to pathological remodeling.

As shown by the violet circle in Fig. 4, 143 of the 174 surveyed articles (82%) used hypertension in IA model creation. Hypertension is most commonly produced in animal models by surgical means, such as branch ligation of the renal arteries [60, 61], nephrectomy [111, 184], and silk wrapping of the kidneys [13]. All of these manipulations increase salt retention in the bloodstream and elevate systemic blood pressure. Many models combine these surgeries with the addition of salt (in the form of NaCl or KCl, typically at a dose of 1 to 8%) in the animals' diets [29, 73]. Furthermore, hormonal manipulation has also been used to induce hypertension. Here, animals have been given angiotensin II infusions or corticosteroids (such as DOCA at 2.5 mg/100 mg body weight [12]), either alone or in addition to surgery [75]. While studies have shown that hypertension can lead to the formation of micro-aneurysms throughout the cerebral vasculature [12, 13], it has generally not been sufficient to form lesions resembling human IAs on its own. Indeed, all models used in the last 10 years employ hypertension in conjunction with other IA risk factors to induce IAs.

Connective tissue weakening Several studies on human IA tissues collected from autopsy or after resection following aneurysm clipping have found that IA walls tend to have degraded IEL. This is even more pronounced in ruptured aneurysms [202]. Studies have also reported that that aneurysm tissues contain weakened and disorganized collagen matrices, likely because of collagen turnover due to remodeling of the IA tissue [203]. This has typically been attributed to inflammatory cells (macrophages, neutrophils, T/B lymphocytes) infiltrating the IA wall and secreting MMPs and reactive oxygen species (ROS), which are associated with smooth muscle cell turnover and destruction of ECM proteins, like elastin and collagen [204–206].

As indicated by the yellow circle in Fig. 4, 92 of the 174 surveyed publications (53%) incorporated connective tissue

weakening in IA model creation. To mimic degradation, chemical manipulation of the connective tissues has been previously used. This was first described by White et al. [9] in 1961, who injected noxious materials (i.e., hyaluronidase, sodium morrhuate, plasmocid, nitrogen mustard) into the wall of the ICA, which resulted in the formation of berry aneurysms in animals. Since 1974, BAPN has been more commonly used to increase the severity of IA lesions, as it inhibits lysyl oxidase, thus preventing collagen cross-linking and promoting vessel weakening [11, 207]. Early publications by Hashimoto et al. [14, 15], showed that the addition of BAPN (0.12%) to rats' high-salt diet increased the rate of IA incidence. Work by the Kyoto group led by Aoki demonstrated that the addition of BAPN increased IA incidence and IA severity. These findings suggest that this manipulation may therefore simulate aneurysm formation in humans with connective tissue disorders (such as Ehlers-Danlos syndrome [208]). Overall, the combination of connective tissue weakening, hypertension, and flow increase resulted in over a 3-fold increase in IA incidence compared with flow increase plus hypertension or flow increase alone.

More recently, elastase, an enzyme that specifically degrades elastin, has been used to degrade the vessel wall and encourage IA formation. Typically, this has been done by stereotactic injection (typically 25–35 mU) into the basal cistern. To develop a model of IAs that rupture, Nuki et al. [75] combined elastase injection into the basal cistern and osmotic angiotensin II infusion (to simulate hypertension) to create large bulging IAs in the anterior circulation of mice with high frequency (> 70%). This was later followed by modifications, such as those by Makino et al. [99] who used elastase treatment and hypertension via unilateral nephrectomy, DOCA-salt pellet implantation, and 1% NaCl in diet. Such modifications enabled 50–60% of created IAs to rupture within a period of approximately 2 weeks. Tada et al. [108, 110] used this model in a series of studies on the effects of certain pharmacotherapies (e.g., doxycycline) on IA formation and rupture. This approach has since been used extensively to study pharmacological treatments aimed at reducing rupture rates. However, due to its quick, aggressive weakening of the IA wall, there are concerns that the manipulation might mask the true biological mechanisms behind rupture.

Estrogen deficiency The formation of IAs is more prevalent in females [209], particularly in post-menopausal populations [124]. This may be because under normal conditions, estrogen enhances endothelial release of nitric oxide (NO), a vasoprotective molecule that helps regulate vascular tone, dilation, and cell growth, as well as protect vessels from inflammation and injury [210]. Estrogen itself has also been shown to be vasoprotective, as it stimulates the proliferation of endothelial cells, reduces oxidative stress, enhances SMC function, and inhibits MMP-2 and MMP-9. Thus, it has been

hypothesized that the reduction in estrogen levels during menopause may increase the risk for IA formation.

A total of 21 of the 174 surveyed publications (12%) described IA models that incorporated estrogen deficiency and hormonal modulation to augment IA development, as indicated by the teal oval in Fig. 4. However, considering the higher IA incidence in women [1], the majority of investigations opt to use only female animals for experimental IA models although they may not manipulate hormone levels. Early on, the feminization of male rats via removal of the testes and administration of estradiol (1 mg/kg/7 days) was briefly used to test the role of sex on IA formation [23], but did not increase the rate of IA formation. Then, in 2005, Jamous et al. [50] introduced a model to form IAs in rats via unilateral CCA ligation, posterior renal artery ligation, and bilateral oophorectomy. They showed that the incidence of IA formation in this model is three times higher than in rats that were only subjected to unilateral CCA ligation and posterior renal artery ligation (60% vs 20%). In 2014, Tada et al. [113] used oophorectomized mice to show that stimulation of estrogen receptor-β (but not α) protected against IA genesis. Since these studies, estrogen deficiency has been utilized extensively in rat models and added to a flow-only model in rabbits [124], as well as elastase mouse models from Hoh et al. in 2018 [154].

Genetic predisposition Several genetic factors are associated with IAs. In patients with heritable disorders that affect connective tissue, such as Ehlers-Danlos syndrome, Loeys-Dietz syndrome, and Marfan syndrome, the integrity of the vasculature is severely compromised, and IA development occurs at a far greater frequency than in the general population [211]. Even in the absence of any identified heritable syndrome, a family history of IA is associated with higher IA prevalence (10%) and rupture rates (4%), suggesting that other heritable genetic factors may contribute to IA susceptibility [212]. Furthermore, clinical data indicates higher rates of aneurysmal subarachnoid hemorrhage in certain populations, notably the Japanese and the Finnish [213]. Recent genome-wide association studies (GWAS) have identified several important single nucleotide polymorphisms (SNPs) that occur at greater rates in people that have IAs [214–222].

In animal models, only 5 of the 174 surveyed studies (3%) used genetic predisposition in IA model creation, as indicated by the green oval in Fig. 4. To investigate genetic influences on the tendency to develop IAs, researchers have used selective breeding to obtain animals that preferentially develop more severe IA lesions. Established strains, such as Spontaneously Hypertensive Rats (SHR) have been used along with other manipulations to create IAs [47, 76]. Coutard et al. designed an IA-prone rat strain by crossing Long Evans and Norwegian Brown rat strains [45]. After 3 generations of crosses, the IA formation rate following

surgical manipulation increased from 24 to 50%. However, genetic manipulation alone was not sufficient to induce spontaneous aneurysms; at least one other manipulation (such as hypertension) has always been used in conjunction with genetics. More recent studies have begun using genetic knockout mice to study the mechanisms of IA formation [91, 121]. However, these knockouts have been implemented in existing animal models, and thus far have only been used to study the roles of specific molecules in targeted mechanistic pathways, rather than addressing genetic predisposition to aneurysm.

Methods for evaluating experimental IAs

Characterization of experimental IAs has been based not only on aneurysm morphology but also on biological changes in the vascular wall during IA development. A variety of techniques have been used to process specimens in order to assess the morphology and structures of lesions created in animal models. These techniques include tissue (whole-mount) examination, histology, corrosion casting, and scanning electron microscopy (SEM). Their advantages and disadvantages as well as the frequency in the literature are shown in Fig. 5 (for details on which study used each method, see Supplemental Table 1).

Cerebral vessel tissue examination The most basic form of examining aneurysms in experimental models is the inspection of the whole CoW with a dissecting microscope. In all, 68 of the 174 studies we reviewed (40%) used whole-mount specimen examination. Before knowing the location(s) of lesions produced by a given IA model, many investigators opted to inspect the entire cerebral vasculature for morphological changes. For example, this approach enabled Hashimoto et al. [14, 15] to identify common sites of IA formation, namely the ACA-OA bifurcation, in early studies. This examination method has been key in determining where to cut histological sections for further study. While whole tissue examination limits detailed imaging of the IA wall remodeling, as it only reveals the adventitia to a microscope, the collected tissues of IA lesions are often subjected to secondary molecular analyses. Molecular analyses require additional, destructive processing of aneurysmal material, such as physical or chemical breakdown to extract and stabilize biomolecules (primarily proteins or nucleic acids). Extracted materials have been analyzed by gene expression techniques (e.g., PCR [116, 118, 125, 127]) or protein expression methods (e.g., ELISA[173]), which have begun to lead to a greater understanding of the mechanisms behind the pathological remodeling of IA.

Histological sections The majority of studies, 129 of 174 (74%), have used histological sections of the aneurysmal tissue, with or without whole-mount pre-examination. Tissue
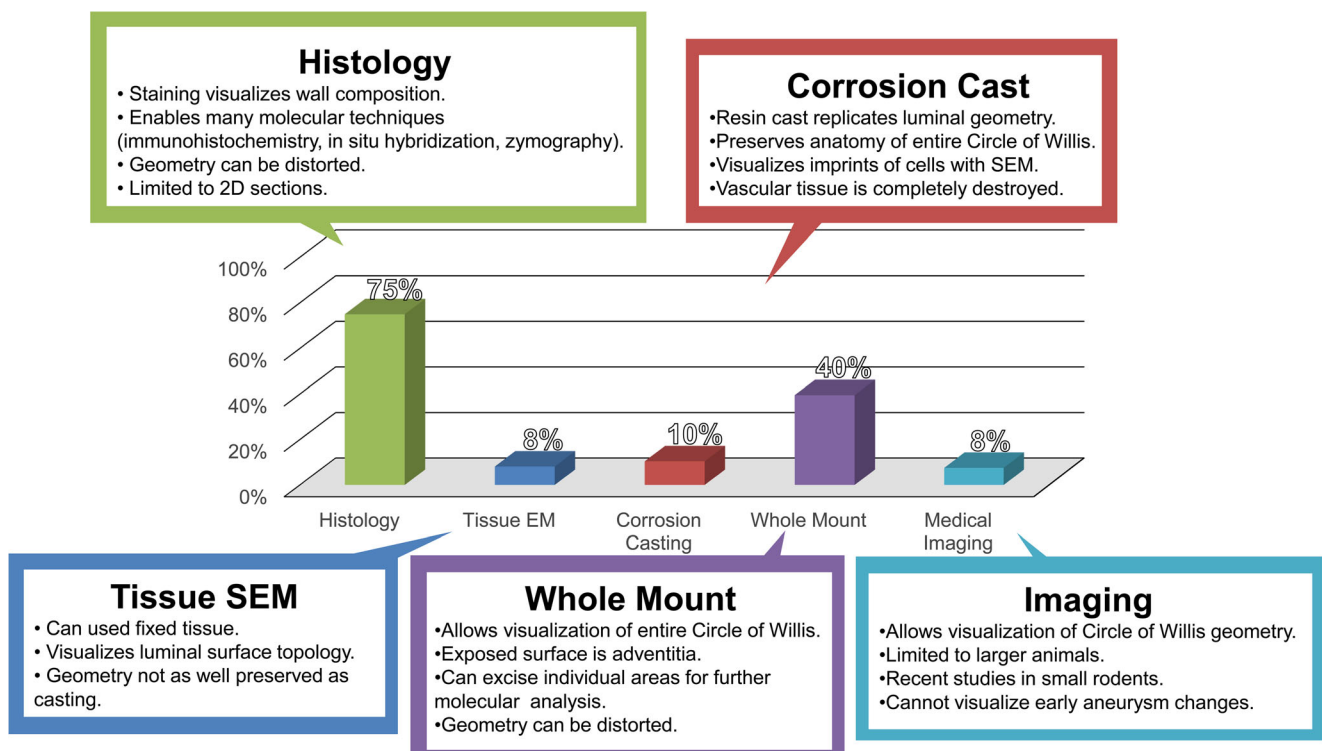
Fig. 5 Aneurysm tissue examination methods in experimental models. A graph indicating percentage each method was used in the literature. Model development studies tended to use corrosion casting and whole mount analysis, while mechanistic studies have strongly favored histology for analysis. SEM, scanning electron microscopy

can be prepared in many ways for histological sectioning, including chemical fixation and embedding in paraffin or being frozen in an optimal cutting temperature compound. It is possible to preserve the vessel geometry more accurately by pressure fixing the vessels with formalin while still in vivo using a perfusion pump or pressure drip. Overall, histological staining can provide cellular information and reveal microscopic lesions that are too small to see with the dissecting microscope. Histological examination allows for visualization of all the vessel layers, and adjacent sections can be stained for different purposes (based on the stain used). Traditional histological analyses using H&E stain have been most frequently used to evaluate aneurysm lesions. Besides revealing overall tissue morphology and cell organization, H&E staining shows the presence of cell nuclei (to determine where cells are present in the wall). Further, Van Giesen staining has been used to visualize elastin, and in aneurysmal lesions, plays a pivotal role in determining if there is a loss of IEL, a hallmark of IA (which will be discussed further below). Trichrome staining additionally has allowed for better demarcation of connective tissues in the vascular wall.

In addition to identifying vessel remodeling present in the arterial wall (which may or may not be obvious when viewed from the vessel's exterior surface), another advantage of histological analysis is that it enables molecular investigation of the tissue by immunohistochemistry or immunofluorescence.

Immunostaining for individual molecules can be done on individual slides to determine the presence and spatial distribution of protein expression [178]. This technique has been widely employed across almost all endogenous animal models and has greatly contributed to the current knowledge of the molecular mechanism of aneurysmal remodeling. For example, in multiple studies, Aoki et al. have used immunostaining to characterize the inflammatory environment of the IA wall, demonstrating increased MCP-1, MMP-9, and NF-kB protein levels [54, 59, 68]. Additional analyses, such as in situ hybridization to reveal expression of specific mRNAs [100], have also been employed in histological sections but to a lesser degree.

Corrosion casting Another method of tissue preparation, which has some of the advantages of both whole-mount specimen and histological sections, is the creation of vascular corrosion casts [134]. This has been performed in 18 of the 174 studies we reviewed (10%). By injecting a polymer that hardens inside the arteries, then chemically removing the artery tissue, a cast is created that accurately preserves the geometry of the vascular lumen. Such casts can capture the geometry of the entire CoW, which makes it easy to study morphological changes across all cerebral vessels. The casts can be quickly analyzed via dissecting microscope with oblique illumination or by SEM for accurate morphological

assessment at high resolutions to reveal large- and small-scale changes. Furthermore, visualization of the endothelial cell imprints is possible under SEM, which can permit the assessment of changes in the endothelial layer [107]. For example, several models employing this technique have found that, early in IA formation, ECs at bifurcations where the aneurysms form change morphology from smooth spindle shapes (aligned with the flow) to amorphous, cobblestone shapes [25]. Unfortunately, the tissue is typically destroyed by the casting process, thus limiting further biological analyses of the vessels from these animals [107].

Scanning electron microscopy A few studies (14 of the 174 surveyed, 8%) have performed SEM on the vascular tissue itself (not on corrosion casts, as discussed above). Tissue SEM allows for visualization of the intima of the vessel and can allow for direct visualization of endothelial cells and gaps in endothelial cells. SEM has primarily been employed in early model development studies to observe en face vascular damage during IA formation at the highest magnification. For SEM, fixed tissue is prepared by taking the desired vessel section and opening it up to expose the intima. The sample is then coated with a thin layer of conductive material (i.e., carbon or gold) to allow visualization of the tissue via the microscope. Tissue used for SEM cannot undergo the same molecular studies as preparations for histological sections, but some studies have used SEM to visualize inflammatory cells on the inner walls of IAs [207]. However, the vast majority of studies employing SEM have used it to analyze corrosion casting of the cerebral arteries after IA induction as described in the previous section.

Cerebrovascular imaging Cerebrovascular imaging, typically by traditional medical imaging modalities, such as digital subtraction angiography or MRI, has been used in a limited number of reported studies, primarily because aneurysmal lesions in animal models are substantially smaller than human IAs. It is not surprising that medical imaging has only been performed in 13 of the 174 reviewed studies (7%). Typically, imaging has been used to confirm the presence of IAs, since it cannot reliably be used to analyze aneurysm morphology in most models where both the animals and the lesions are small. Hashimoto was the first to report in vivo imaging of IAs in rats with 2D angiography [17, 20], but the procedure involved immediate euthanasia of the animal. This was similar to Cai et al. who reported cyclotron imaging of rat aneurysms, but this was also accompanied by the termination of the animal. However, recent efforts with MRI have demonstrated survival IA model imaging. In 2015 Makino et al. reported successful serial imaging of the mouse cerebral vasculature via 3 T MRI in a mouse IA model. More recently, Tutino et al. [166] and Rajabzadeh-Oghaz et al. [167] used non-invasive, survival 9.4-T MRI to track aneurysmal remodeling in mice,

demonstrating the feasibility of longitudinal IA studies using high-resolution MRI in small animals. They also demonstrated the feasibility of generating 3D geometries of the mouse CoW during flow-induced remodeling, which allowed them to perform CFD to study the detailed cerebrovascular hemodynamics. These recent efforts show promise of the ability to longitudinally image aneurysmal lesions that can be visualized at a resolution as low as 50 μm^3.

Characteristics of experimental IAs

It is important to compare experimentally induced IAs to the human aneurysms that the animal models aim to recapitulate. Histopathological evaluation of human IAs has shown that, aside from their bulging appearance, the hallmarks of IA tissue are degradation of the IEL (the main load-bearing element of the vessel wall) and degeneration of the ECM, both of which severely weaken the IA wall [202]. Loss of mural cells, mainly SMCs, is also common, as IAs tend to have thinned or absent medial layers [202, 223, 224], which can lead to anoikis [225]. Inflammatory cells, including macrophages and T lymphocytes, can contribute to aneurysm degeneration via production of MMPs and the release of ROS. These cells are present in aneurysms at a much higher rate (~50%) than in healthy vasculature [223] and have been shown to be more numerous in ruptured IAs [202]. Common characteristics of experimental aneurysms are detailed in Fig. 6 (for details on what study reported each characteristic, see Supplemental Table 1). Unlike human IAs, aneurysmal lesions induced in animal models tend to be small with shallow/wide necks. This may be because animal IA models are created within a relatively short time window (a few days to a few months) via a limited number of manipulations, and thus may only recapitulate certain aspects of the human disease. Nonetheless, key features of human IAs are typically investigated in animal models as noted below.

Bulging Bulging is the ultimate defining characteristic of aneurysms, and as such, is commonly used to denote the IA presentation. Of the 174 studies surveyed here, 129 (74%) noted bulging in experimental IA models. Unlike human IAs, however, bulges observed in animal models tend to be microscopic, often only visible after histological processing and imaging. These bulges are measured either by maximal lesion diameter, length along the bulge, or dome height to neck ratio [136, 144]. Aneurysmal bulges in animal models tend to have a larger neck and less rounded shape than human IAs. Using animals sacrificed at different end points, Meng et al. [86] inferred progressive development of a BT aneurysm due to flow increase in the bilateral CCA ligation rabbit model. The longest time-point was six months after flow increase manipulation, at which time the aneurysm was a wide-necked, thin-walled bulge that was pointed, but not rounded, and
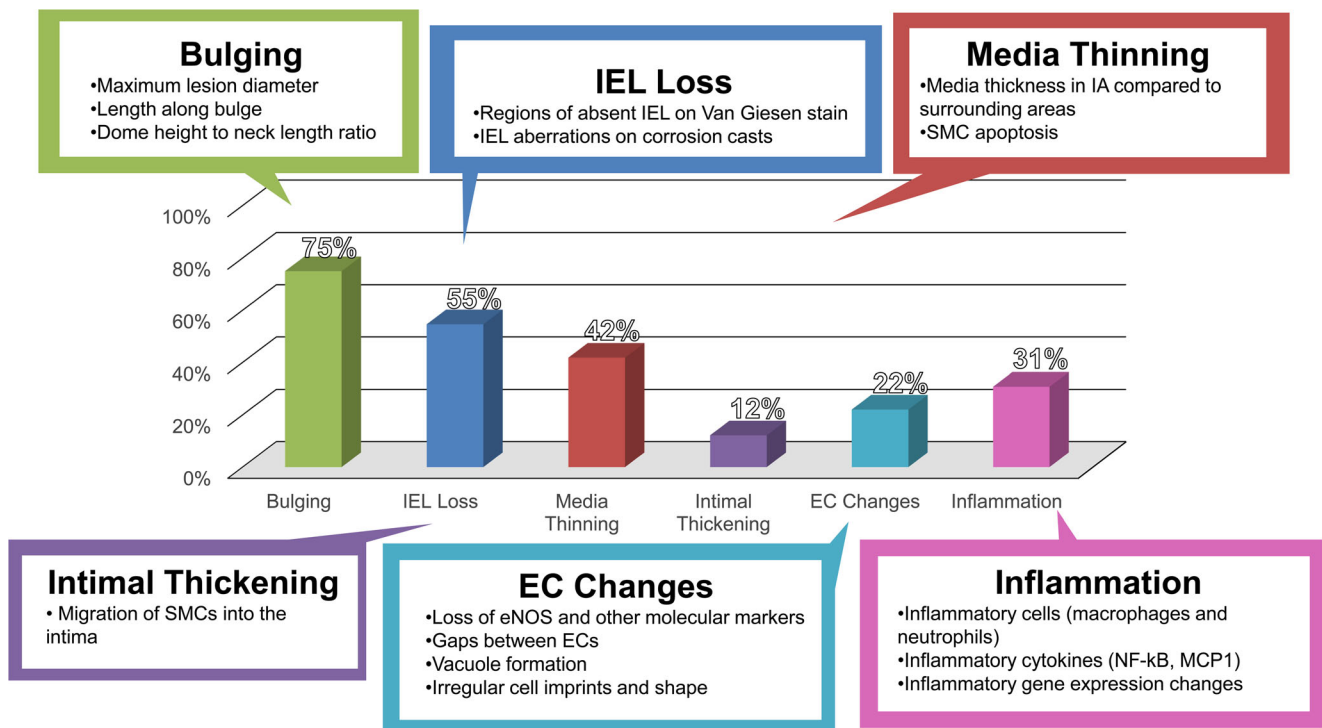
Fig. 6 Features observed in endogenously created animal aneurysms. A graph indicating the percentage that each feature was observed in the literature. The three most common IA features are bulging, IEL loss, and medial thinning. EC, endothelial cell; IEL, internal elastic lamina; SMC, smooth muscle cell

exhibited complete loss of media and IEL. Many models that have used combinations of flow increase, hypertension, and estrogen deficiency have created aneurysmal lesions such as these. Recent models of IA formation and rupture that induce aneurysms by multiple risk factors and injection of elastase have shown prominent bulging, berry IAs that have diameters larger than the parent artery, as one would see in humans.

IEL destruction Vessel wall remodeling during IA formation has most notably been shown by the loss of the IEL (as well as medial thinning) and can be seen in the absence of discernable bulging [86]. Typically, the IEL (or its absence) is detected by Van Giesen staining on histological sections, and its loss is the most commonly used marker of IA development other than bulging. Of the 174 publications we studied, 94 (54%) indicated IEL loss associated with IA formation. Many studies have even used IEL loss to define the formation of the aneurysmal lesion. Indeed, IEL loss appears to be one of the first morphological changes during aneurysm development in animal models [82, 88]. This highlights one important strength of the developed models: the ability to reveal early stages of aneurysm genesis and development that are not readily observable in humans (where most studied IAs are terminal). Indeed, even 5 days after hemodynamic driven IA induction, Tutino et al. [107] found IEL fenestrations or raised circular lesions on the corrosion cast surface representing indentations

in the vessel due to IEL loss or focal weakening of the IEL or matrix degradation, in locations that develop aneurysms.

Smooth muscle cell loss In human aneurysms, SMCs undergo phenotypic modulation from a contractile to a proinflammatory phenotype [226]. This is often accompanied by increased SMC turnover and apoptosis that increases as the vessel wall degenerates [227]. Studies of human IA tissues have shown that ruptured IAs have widespread SMC apoptosis with few remaining SMCs, while unruptured IAs still had some thinned SMC layers [228]. Indeed, a loss of media is noted in many IA models either by comparing the thickness of the media in the lesion to the thickness in the adjacent wall, or by investigating surrogate markers, such as apoptosis of SMCs. In all, 72 of the 174 studies we investigated also observed SMC loss associated with experimental IAs. The loss of SMCs is interpreted as evidence of a weakened wall that is susceptible to rupture. In many models, SMC loss and media thinning are commonly observed together with IEL loss on histology [88]. Several studies have even created scores to grade aneurysmal development, which combine the degree of SMC loss and media thinning, along with bulging, e.g., the Aneurysm Development Score [86].

Endothelial changes The endothelium is responsible for sensing shear forces of flow and communicating with the blood,

and as such is critical in the initiation of IAs [229]. EC changes were noted in 38 of the 174 studies investigated as part of this review. Typically, investigators have looked at the loss of endothelial nitric oxide synthase production, gaps between endothelial cells, or endothelium irregularities, typical markers of endothelial dysfunction [230]. Early tissue SEM studies demonstrated degeneration of ECs at locations of IA formation [31], while later corrosion casting experiments by Jamous et al. [49] found that early EC morphology changes were related to changes in hemodynamic shear stress and blood flow patterns. Tutino et al. [107] also showed EC irregularities, deviations from healthy, spindle-shaped, flow-aligned ECs in locations that form IAs in the Meng rabbit model. A rough and irregular endothelial surface has conventionally been interpreted as a sign of EC dysfunction. Dolan et al. further demonstrated altered EC gene expression in these locations [101].

Intimal thickening Intimal thickening (or intimal hyperplasia) is the process by which the intimal layer becomes enriched with vascular SMCs and proteoglycan-rich ECM components and is typically associated with atherosclerosis [231]. In humans, many IAs are seen with atherosclerotic changes occurring in the sac [232, 233], and individuals with atherosclerosis are at greatly increased risk of IA formation [234]. Migration of smooth muscle cells or inflammatory cells into the intima of the vessel, which causes thickening of the intima (as observed in humans) has been reported in a number of animal studies. Intimal thickening is commonly observed in OA-ACA aneurysms formed in response to unilateral CCA ligation, renal artery ligation, and salt diet in rats (i.e. the Hashimoto rat model). This feature was observed in experimental aneurysms in 21 of the 171 studies we surveyed here, which mostly included the OA-ACA IAs of the Hashimoto model.

Inflammatory changes Inflammation plays a key role in IA pathophysiology. The natural history of the disease is characterized by an escalating inflammatory response, which accompanies the progressive degradation of the aneurysm wall [235–237]. This process is thought to begin with risk-factor (including elevated blood flow) induced pro-inflammatory responses in ECs and SMCs that lead to local production of MMPs and the initial formation of an aneurysmal sac. Once formed, the IA sac creates a hemodynamic environment characterized by slower recirculating flow that is conducive to leukocyte infiltration into the wall. In the IA tissue, inflammatory cells, such as macrophages and neutrophils, extensively produce MMPs and ROS (via expression of myeloperoxidase) which further degenerate the aneurysm, advancing its growth and rupture [227]. Our knowledge of the presence of inflammation in human IAs has largely been informed by early histological studies [202, 223, 224]. However, recent gene expression studies of IA tissues have demonstrated increased inflammatory processes and production of inflammatory cytokines/chemoattractants in the walls of humans IAs [238, 239].

Inflammatory cells, primarily macrophages, have been observed infiltrating aneurysmal lesions in animal models. Beginning in the late 2000s and owing to the wide acceptance of inflammation as a main driver in IA natural history, many investigators have begun to directly study inflammation in experimental IA models. In addition to purely inflammatory cell staining, immunostaining for inflammatory cytokines is common in many studies [59, 68]. Inflammation has been uncovered to be among the first responses to IA risk factors, such as increased hemodynamics. Meng et al. demonstrated that during IA formation pro-inflammatory SMCs produce MMPs [100]. Furthermore, the inflammatory pathways involving NF-kB, MCP-1, TNF, and MMP were thoroughly investigated over several studies by Aoki et al. [54, 59, 68, 109]. More recent gene profiling studies and qPCR-based investigations have also been used to study inflammatory gene expression in experimental IA tissues [174]. In all, 53 out of 174 studies (30%) specifically denoted inflammatory changes associated with experimental IAs.

Discussion

The pathogenesis and natural history of human IAs is a complex process that remains widely unknown. In order to study this disease and uncover pathobiological mechanisms, endogenous animal models of IA have been implemented over the past 60 years and have enabled investigations of the pathophysiological, cellular, and molecular biology of IA. Most models have implemented multiple manipulations mimicking aspects of the human disease, largely to maximize the rates of aneurysm development. The majority of these were implemented in rats and mice, used histology to study lesion pathobiology, and defined IA remodeling by IEL loss, bulge formation, and medial thinning. While there was a wide range of aneurysm induction techniques, the most common models included hemodynamic stress, hypertension, and connective tissue weakening (typically by elastase injection).

Endogenous IA models were largely developed between the years 1961 and the early 2000s, starting with relatively large animals (e.g., canines, rabbits, and primates) and quickly moving to rodents (i.e. rats and mice) due to their versatility and low cost. Since the turn of the century, several models have been extensively used to study the mechanisms of IA, leading to discoveries about the physical and molecular mechanisms behind IA formation and rupture. The most common models have been the Hashimoto model (rat—unilateral CCA ligation, unilateral nephrectomy, DOCA, salt diet, and BAPN) [14]—or modifications thereof (such as that published by

Nagata et al. [20] and Aoki et al. [56], rat—unilateral CCA ligation, bilateral renal artery ligation, salt diet, and BAPN), to study the molecular biology of aneurysmal tissue, the Jamous model [50] (rat—unilateral CCA ligation, renal artery ligation, oophorectomy) to study the influence of added risk factors, namely estrogen deficiency, the Meng model [82] (rabbit—bilateral CCA ligation) to study the role of hemodynamics in IA genesis, and the Nuki [75]/Makino [99] model (mouse—elastase injection with either Angiotensin II pump or unilateral nephrectomy and DOCA salt diet, respectively), which has been most recently used to study IA rupture. These models of IA have been very successful at emulating many histological and geometric properties of human IAs. In particular, multimodal models where many etiological factors are employed have shown particularly impressive bulge formation in addition to IEL damage, wall thinning, and apoptosis [40, 45, 177]. On the other hand, other studies with genetic and chemical manipulations have teased out the beginnings of the mechanisms that may lie behind IA formation in humans [47].

Over the last 20 years, the use of these models, in conjunction with new technology, such as high-resolution imaging, microarray technology, and genetic knockouts has led to the identification of several key molecular pathways involved in IA formation and rupture [63, 67, 72, 111, 121]. One of the most important successes of the endogenous IA models is that they allow the study of early pathological events that precipitate IA formation, which is impossible in humans. Kolega et al. [88] used the rabbit bilateral CCA ligation model to investigate mechanisms of IA formation as early as 2 days after aneurysm induction. They observed the earliest changes in aneurysm genesis reported to date, namely loss of the IEL and degradation of the medial layer, and correlated these changes with changes in smooth muscle differentiation and local expression of matrix proteases.

Despite these successes, there remain many opportunities for improvement that would help further elucidate mechanisms of aneurysm formation and progression. While they share some features with human IAs, aneurysms in animals may have significant pathophysiological differences, since several factors in the development of human IAs have not been incorporated into endogenous animal models. A number of risk factors that influence IA development in humans have only just begun to be explored in animal models. For example, a predominant risk factor for IAs in humans is cigarette smoking [240, 241], possibly through toxic effects on the vasculature, including increased oxidative stress in the vasculature, damage to the endothelium, and stimulation of the production of pro-inflammatory cytokines [242]. Starke et al. [152] recently explored the role of NOX1-mediated SMC phenotype switching in IA formation in mice that were exposed to cigarette smoke and found that smoke exposure brings about oxidative stress-induced SMC phenotypic modulation during IA formation.

Other risk factors have yet to be studied. Older age, for example, is strongly correlated with IA development [243], as it is associated with stiffening of the vasculature and decreasing EC responses to vasodilatory factors [244], which make blood vessels less adaptive to changes in blood flow [245]. While comparisons have been made between different age animals [10], no group to date has explored animals at an age with documented vascular changes consistent with human old age. The addition of more risk factors into animal models of IA will likely give rise to studies to determine mechanisms behind different induced factors. Animal models can contribute to understanding how factors interact in inciting IA, by varying the manipulations in order to disentangle the contributions of individual factors to the observed traits or pathways. Indeed, several groups have already reported such studies, broadly finding that adding extra risk factors leads to increased rates of aneurysmal development. Throughout their work, Hashimoto et al. added manipulations to their rat IA model, demonstrating that tissue weakening (via BAPN), hypertension, and flow increase increased the formation rate of aneurysmal lesions by more than 300% compared with rats subjected to hypertension and flow increase alone [14, 15]. Jamous et al. [50] also showed that adding estrogen deficiency via bilateral oophorectomy to the Hashimoto model increased IA lesion formation from 20 to 60%. More recently, Tutino et al. [124] investigated IA formation in the rabbit CoW after flow manipulation alone and in combination with risk factors (hypertension and estrogen deficiency) and reported increased IA formation and a greater degree of IEL damage in the model with combined risk factors. Nevertheless, work is still needed to determine how and to what extent individual risk factors contribute differently to IA formation and development.

In addition to combining and exploring the contribution of aneurysm risk factors to IA formation, animal models could elucidate what factors influence progression of the disease, i.e. growth and rupture. One of the most important advancements in IA animal models to emerge in recent years has been the creation of IA rupture models, which hold the promise of revealing how and why an IA progresses towards rupturing [110, 120, 122, 128]. With a reported rupture rate of ~ 50%, their success has been facilitated by the addition of direct injection of elastase to hypertension and hemodynamic manipulation. Compared with other endogenous models, connective tissue weakening brought on by the injection of elastase is the major differentiator that leads to the creation of larger IAs that proceed to rupture. Thus, the observed biological responses in models that include elastase may reflect that of human IAs in patients with connective tissue disorders. For example, Ehlers-Danlos syndrome, a hereditary disease that is associated with higher rates of IA formation and rupture, results in part from SNPs in exonic regions of collagen [246, 247]. Such rupture models have been used to study the effects of certain pharmaceutical drugs on IA formation and rupture

[108, 110]. Still, as the fast delivery of a massive bolus of elastase likely does not occur in humans during IA formation (rather proteases and elastases are released over time by inflammatory cells [248]), these models may better simulate end-stage rupture-prone IAs, rather than the true growth and rupture phenomenon. Furthermore, the massive destruction of elastin that is induced throughout the cerebral vessels causes side-wall IAs that may, in some cases, reflect dissecting aneurysms. The disruption of the IEL may cause blood leakage into the medial layer and ballooning of the artery that may rupture through the adventitia, and could thus produce lesions/ruptures similar to those reported in animal studies of elastase-induced IAs. Future endogenous IA models that incorporate the effect of collagen degradation using more physiological methods are needed.

Conclusions

We believe that future studies aimed at longitudinally assessing IA pathobiology in models that incorporate aneurysm growth will likely have the largest impact on our understanding of the disease. Investigations using the latest developments in vascular imaging may permit the tracking of the entire course of the disease on an individualized basis, as well as the tracking of disease reversal in response to hemodynamic or pharmacological interventions. Putatively, once an aneurysm is established in a growth/rupture model, the success of a treatment can be monitored via imaging, to see if the IA stops growing or even decreases in size. This would enable longitudinal and non-destructive analysis of IA development in an individual before and after IA initiation, which would be uniquely possible in animals. The major limitation of current methods that use tissue examination for assessment is that they are only useable as endpoint assessments. In contrast, intravascular imaging of the IA wall (i.e. via optical coherence tomography[249]) or live cell imaging would allow for longitudinal studies of the IA that can continue even after bulge visualization. Recently Miyata et al. [168] reported real-time in vivo imaging of IAs in transgenic rats with GFP-stained ECs and were able to visualize aneurysm wall movement. However, the procedure was unable to be repeated serially. Future efforts to merge imaging and pathobiology analyses like this could enable longitudinal assessment of biological pathways in IA and would be highly valuable in investigating IA natural history.

Declarations

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