*Review Article*

# The Development and the Use of Experimental Animal Models to Study the Underlying Mechanisms of CA Formation

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Cerebral aneurysms (CAs) have a high prevalence and can cause a lethal subarachnoid hemorrhage. Currently, CAs can only be treated with invasive surgical procedures. To unravel the underlying mechanisms of CA formation and to develop new therapeutic drugs for CAs, animal models of CA have been established, modified, and analyzed. Experimental findings from these models have clarified some of the potential mechanisms of CA formation, especially the relationship between hemodynamic stress and chronic inflammation. Increased hemodynamic stress acting at the site of bifurcation of cerebral arteries triggers an inflammatory response mediated by various proinflammatory molecules in arterial walls, inducing pathological changes in the models similar to those observed in the walls of human CAs. Findings from animal studies have provided new insights into CA formation and may contribute to the development of new therapeutic drugs for CAs.

## 1. Introduction

Vascular diseases represent an important problem due to their potential severity and increasing prevalence. Many series of studies, especially those on atherosclerosis, have contributed to reduce the mortality rate of vascular diseases and to improve the patients' quality life [1]. Unfortunately, it is not a case in subarachnoid hemorrhage (SAH), which is a potentially lethal disease with a mortality rate of up to 50% and is responsible for more than 30,000 patient deaths per year in the United States [2, 3]. Furthermore, SAH can cause a considerable cognitive impairment that results in restricted social activity, even in patients who recover well and successfully return to their daily lives [4]. Therefore, the prevention of SAH is a socially important issue. A cerebral aneurysm (CA) is the primary cause of spontaneous SAH and can be found in approximately 1%–5% of the general population [3, 5–7]. Currently, surgical procedures such as microsurgical clipping and endovascular coiling are the only therapeutic modalities thought to prevent the rupture of pre-existing CAs [6]. However, because of the inescapable risk of complications, surgical treatment is recommended only for a selected group of patients with an estimated high risk of rupture. This means that many patients with CAs are followed without any effective treatment, while managing potential risk factors for rupture [5, 8]. Given the severity of SAH after the rupture of CAs, there is a strong demand for the development of a medical treatment for CA.

In the present paper, we review the current knowledge of the underlying mechanisms of CA formation, mainly derived from animal models and discuss the development, clinical relevance, usefulness, and future potential of animal models of CA.

## 2. Findings and Limitations of Human Studies

There is considerable interest in elucidating the underlying mechanisms of CA formation in order to develop less invasive medical treatments. For this purpose, many human studies, including the histopathological analysis of surgically dissected CAs or cerebral arteries, gene linkage analysis, and epidemiological analysis, have been performed and

achieved a measure of success. These studies have revealed certain elements that may be important in the pathogenesis of CAs. Here, a CA is characterized as the blooming of cerebral arterial walls, especially at the bifurcation site, that is accompanied by the disruption of the internal elastic lamina and degenerative changes in arterial walls represented by the thinning of the media and the loss of medial smooth muscle cells [9, 10].

Aneurismal SAH has a familial clustering or a difference in race, suggesting the genetic influence. Certainly, gene linkage analyses have identified some of the susceptibility loci or genes that increase the risk for the development and rupture of CAs [11–24]. Most identified genes are pro-inflammatory genes or extracellular matrix-related genes, suggesting that an inflammatory process or the turnover of the extracellular matrix is actively involved in the pathogenesis of CAs.

Epidemiological analyses have identified some risk factors for the enlargement or rupture of CAs, most notably hypertension [8, 25, 26], which increases the hemodynamic stress at the bifurcation site of cerebral arteries and potentially contributes to the formation of CAs through the induction of mechanical damage in the arterial wall [9]. These studies provided epidemiological support for a hypothesis derived from the computational simulation of blood flow at a prospective CA formation site which suggest that hemodynamic stress triggers CA formation [27–30].

Histopathological studies of human CA tissues have implicated the involvement of inflammatory processes in the pathogenesis of CA. The increased expressions of pro-inflammatory factors such as collagenolytic matrix metalloproteinases (MMPs) [31–33], vascular cell adhesion molecule-1 (VCAM-1) [34], tumor necrosis factor-alpha (TNF-$\alpha$) [35], monocyte chemoattractant protein-1 (MCP-1) [36], and mitogen-activated protein kinases (MAPKs) [37, 38] have been found in human CA walls using immunostaining, Western blot, or PCR analysis. Further, histological studies also revealed the infiltration of macrophages and T cells [34], complement or immunoglobulin deposition and activation [34, 39], and apoptotic cell death in CA walls [40, 41], suggesting the active involvement of inflammation in CA formation.

As described above, studies using human samples have contributed to the understanding of the underlying mechanisms of CA formation; however, these studies also have several important limitations. First, microsurgical dissection of CA may increase the rupture. Second, CA formation is thought to be influenced by the genetic background as in the Japanese and Finish populations which are known to have a significantly higher incidence of CAs than other populations [4]. CAs can also exhibit familial clustering [5, 8, 25]. Taken together, the complexity of this problem may render the analysis of CA formation difficult. Third, we can only evaluate human CA samples at certain time points, and we can not assess sequential changes of CA formation. To overcome these limitations and to more systematically examine the underlying mechanisms of CA formation, animal models of CAs have been demanded and developed.

## 3. Overview of Animal Models of CA

Animal models can reduce the complexity of genetic analysis because of their homogeneous genetics and bring ease of manipulation through the availability of molecular biological tools. Currently, there are 2 major classes of animal models of CA. First are the animal models that are used to evaluate the underlying mechanisms of CA formation, which will be described in detail later on in this review. Second are the models mainly used to determine the technical proficiency of endovascular devices or to assess histopathological changes after endovascular treatment; however, this class is not used to determine the underlying mechanisms of CA formation. These models are surgically induced by creating a venous pouch mainly in the carotid artery of dogs or pigs [42–45].

## 4. Animal Models of CA Induced by Increased Hemodynamics

Several studies attempted to develop an animal model of CA in which the histopathological features of human CA were reproduced, for example, the disruption of the internal elastic lamina and the degeneration of the media, before Hashimoto et al. reported their first rat model of CA [46]. Previous attempts involved the use of various compounds including a nitrogen mustard and cyanoacrylate, in order to degenerate the arterial walls, for example, [47–49], but failed to induce CAs with similar pathological characteristics to human ones.

Hashimoto et al. successfully induced CAs at the bifurcation site of cerebral arteries of rats in 1978 by increasing hemodynamics on the basis of the hypothesis that CA was formed at fragile arterial walls loaded with a high hemodynamic stress [46]. They thoughtfully used the lathyrogen, $\beta$-aminopropionitrile (BAPN), which inhibits the cross-linking of collagen and elastin fibers [50, 51], to weaken arterial walls. The oral administration of BAPN to animals degenerates arterial walls and, as a result, occasionally induces an arterial dissection (angiolathyrism) [52, 53]. To further increase hemodynamic stress with systemic hypertension, they ligated the unilateral common carotid artery, performed a unilateral nephrectomy, administered deoxycorticosterone, and increased salt intake in BAPN-treated rats. CAs were thus spontaneously induced at the bifurcation sites of the cerebral arteries [46]. Histopathological studies of the induced CAs demonstrated that their pathological features were in accordance with those of human CAs [54]. This group also examined the effects of hemodynamic stress on CA formation by comparing the bilateral or unilateral ligation of carotid artery and confirmed that hemodynamic stress greatly influenced CA formation [29].

The CA rat model has since undergone several modifications. Currently, CAs are induced by the unilateral ligation of the common carotid artery with induced hypertension by the unilateral ligation of the renal artery and increased salt intake with or without BAPN treatment (Figure 1). BAPN treatment enhances the incidence of CA formation and the size of the induced CAs [46, 55]; however, it also disturbs normal collagen synthesis and the turnover
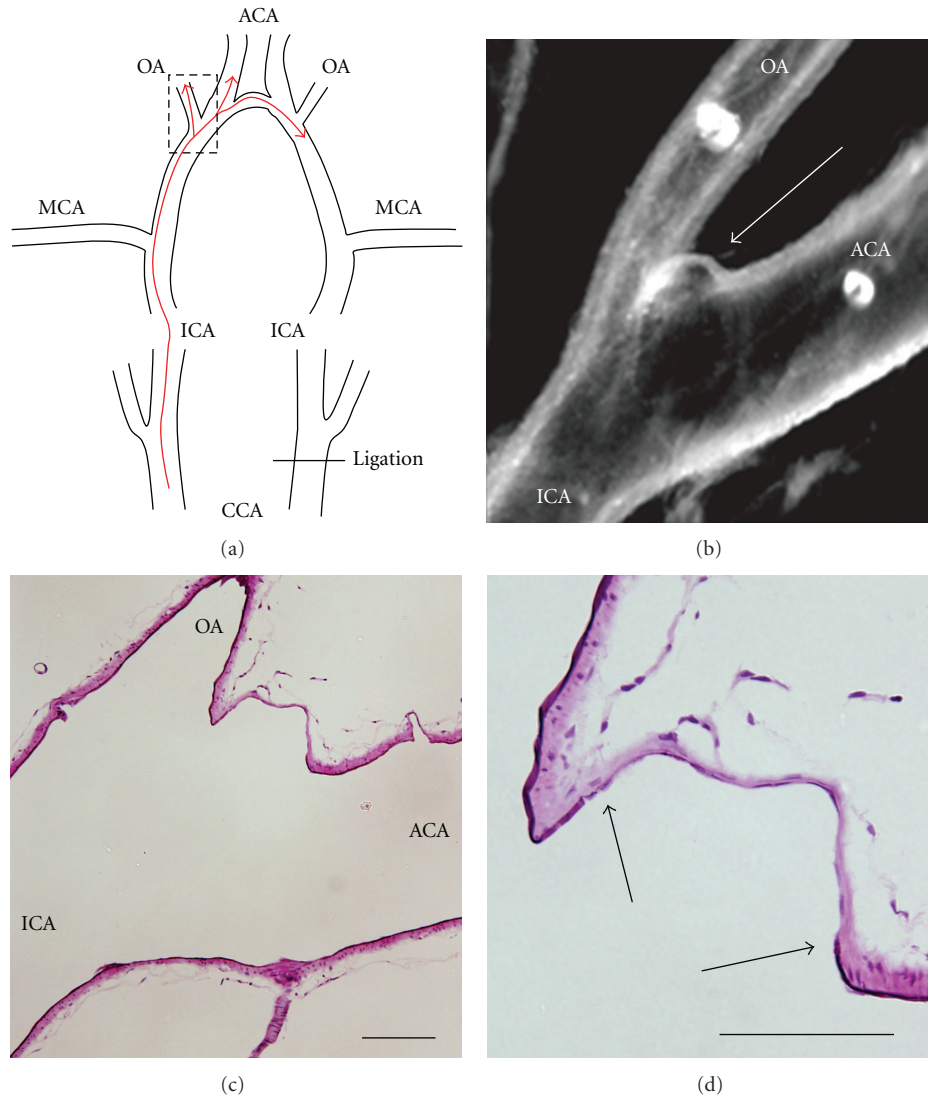
(a)

(b)

(c)

(d)

FIGURE 1: Cerebral aneurysm (CA) formation in the rat model. (a) The method for CA induction. As illustrated, the unilateral common carotid artery (CCA) is ligated to induce a compensatory increase in cerebral blood flow in the contralateral internal carotid artery (ICA). As a result of increased hemodynamics, a CA is induced at the anterior cerebral artery-(ACA-) olfactory artery (OA) bifurcation (indicated by the boxed region). MCA: middle cerebral artery. (b) Macroscopic image of the dissected ACA-OA bifurcation indicated as the boxed region in (a). Note that a CA is induced at this bifurcation (arrow). (c, d) Histopathological examination of induced CA by Elastica van Gieson staining. Higher magnified image of CA walls is shown in (d). Note that the disruption of the internal elastic lamina (arrow) and the degeneration of the media, which are histopathological features of human CA walls, are observed. Bar: 50 $\mu$m.

of the extracellular matrix. Further, Nagata et al. have also demonstrated that BAPN treatment and salt overloading have a synergistic effect on CA formation [56].

A mouse model of CA was successfully established in 2002 by the unilateral ligation of the carotid artery and induced hypertension [57]. The histopathological examination of murine CAs by electron microscopy shows the disrupted internal elastic lamina and degenerative changes in the media, as observed in human CAs [57]. As mice are more resistant to induced hypertension and vascular inflammation, more time is needed to induce CAs and their incidence is less than in the rat model [57, 58]. Technical advancements in molecular biology have enabled

the generation of genetically modified mice. Increased availability of molecular biological tools in this species allows us to genetically analyze the underlying mechanisms of CA formation using various gene-deficient mice. These mice are particularly useful to analyze the contribution of particular genes to disease pathogenesis.

Hashimoto et al. have also successfully induced CAs in monkeys (*Macaca fascicularis*) by the ligation of the common carotid artery and systemic hypertension with BAPN treatment [59]. Histopathological studies revealed that the CAs induced in primates had similar characteristics as in human CAs [60]. The usage of the primate model is limited due to ethical concerns; however, since rats and mice

Animal model of cerebral aneurysm

Aneurysm formation

By venous pouch

Dog or pig *2

By increased hemodynamics

Formation of new bifurcation

Ligation of CCA + induced hypertension *1

Dog/carotid artery *3

Unilateral CCA

Bilateral CCA

Male

Female

Rabbit *8
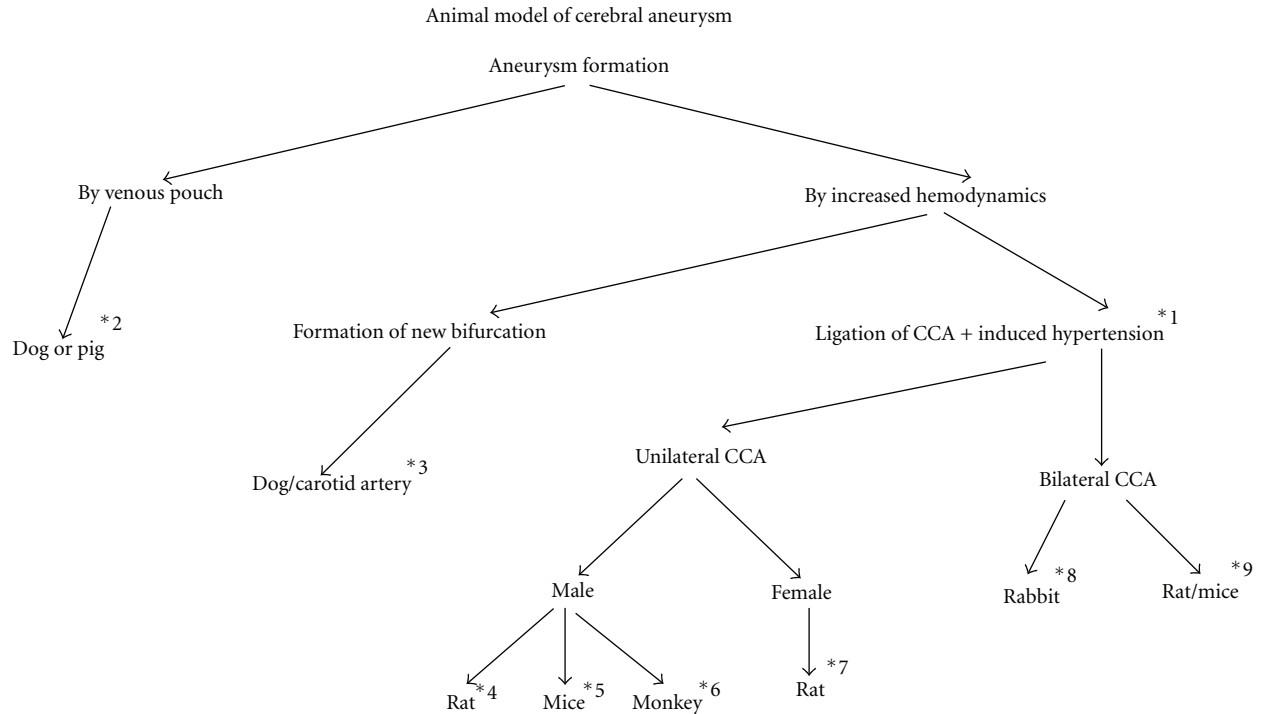
Rat/mice *9

Rat *4    Mice *5    Monkey *6

Rat *7

FIGURE 2: Brief summary of animal models of CA used in recent experimental studies. A brief summary of animal models used in recent experiments is shown. The particularities, advantages, and disadvantages of each model are as follows. *1: Induced hypertension can be achieved by several methods such as the ligation of the renal artery, high salt diet intake, deoxycorticosterone treatment, and angiotensin II injection. *2: This model is mainly used for the development of endovascular devices and not for the analysis of the molecular mechanisms of CA formation. *3: The new bifurcation is created at the carotid artery by side-to-end ligation. This model is suitable for the analysis of hemodynamics-induced CAs, but the hemodynamic stress is greater than in the intracranial arteries where the CAs are formed. *4: CAs can be induced with a high frequency and with a low risk, but they seldom rupture. BAPN treatment enlarges the size of the induced CAs. *5: BAPN intake or local elastase injection is essential for the induction of CAs. Lipopolysaccharide can also enhance CA formation and huge CAs can sometimes be observed. *6: It takes over 1 year to induce CAs, but their incidence is high. *7: It is necessary to perform bilateral oophorectomy to effectively induce CAs. *8: Large CAs are frequently induced in the posterior circulation. This model has the potential to be used in studies linking hemodynamics and molecular expression. *9: Bilateral CCA ligation results in high mortality, but can induce large CAs in the posterior circulation. CCA: common carotid artery.

are more resistant to arterial inflammation than primates and monkeys and humans are closely related species, a monkey model may still be necessary in some situations.

Several other groups have also applied the induced hypertension/lathyrism model [30, 52, 61–66]. We have mainly used male rats or mice as CA models to exclude the influence of sex hormones. Jamous et al. recently induced CAs in female rats through carotid ligation, induced hypertension, and bilateral oophorectomy [63]. The sex hormone estrogen has a protective effect on endothelial cell function and may therefore influence CA formation [67]. Indeed, they demonstrated that bilateral oophorectomy increased the size of the induced CAs by decreasing the levels of estrogen [63]. Furthermore, they examined the protective effect of estrogen on CA formation by applying hormone replacement therapy to their rat model and confirmed that hormone replacement therapy could attenuate the increased formation of CAs by bilateral oophorectomy [62].

Gao et al. induced CAs in New Zealand white rabbits by increasing hemodynamic stress through the bilateral ligation of the carotid arteries [61]. He and his colleagues selected

rabbits because the arterial diameter of rats and mice is too small to reproducibly perform a hydrokinetic analysis of hemodynamics during CA formation. They demonstrated that increased hemodynamic stress triggered CA formation and that the induction of CAs was well correlated with the increase of blood flow in the basilar artery.

Meng et al., who was the corresponding author of Gao's paper, further reported the correlation of hemodynamic stress with CA formation using a canine model [30]. They induced CAs by surgically creating a new bifurcation site using the carotid artery of dogs and measured the hemodynamic stress in situ. As a result, the high wall shear stress and high wall shear stress gradient induced pathological changes resembling human CA, for example, the disruption of the internal elastic lamina and the loss of medial smooth muscle cells [30]. The canine models were used to unravel the correlation of hemodynamic stress with CA formation using a different concept than our models, which are designed to study the molecular basis of CA formation.

We and other researchers have modified the present CA models and tried to develop novel models that are designed
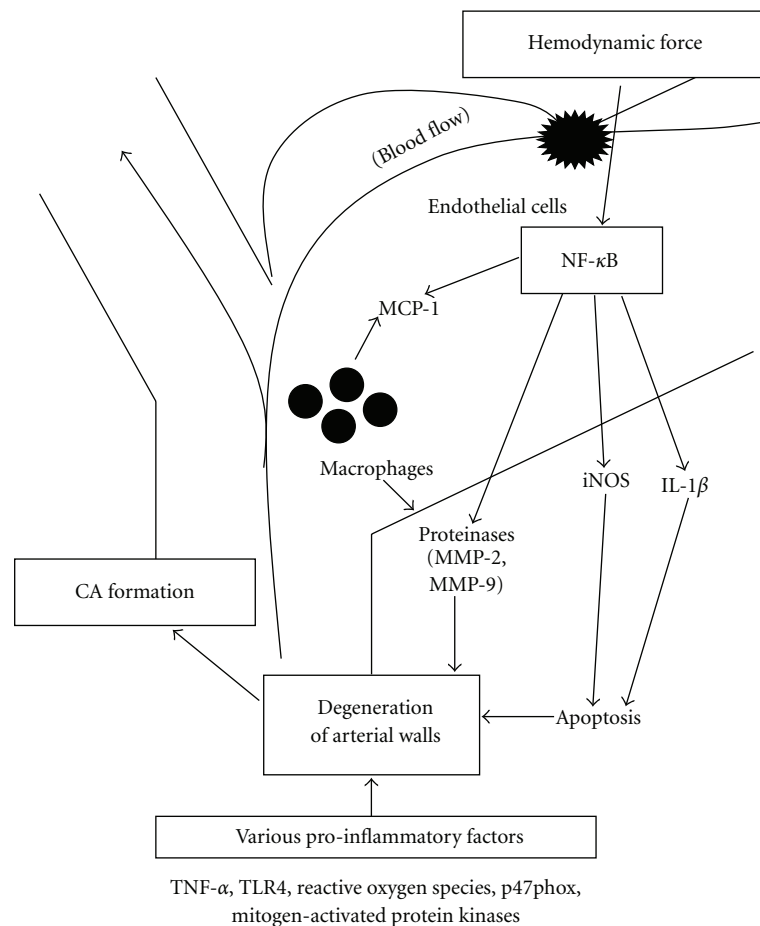
FIGURE 3: Proposed mechanisms of CA formation from human and animal studies. Proposed mechanisms of CA formation from human and animal studies are summarized and illustrated.

to answer a question (Figure 2). In the near future, we hope that more desirable models of CAs will be developed to reveal the mechanisms of CA formation in more detail.

## 5. Exploratory Pathophysiology of CAs from Animal Studies

Animal models of CA have provided us with insights into the underlying mechanisms of CA formation, and we can propose a hypothesis for the molecular basis of CA formation from the experimental findings of animal models (Figure 3). Here, we will summarize the experimental findings of CA formation.

On the basis of the finding that inflammatory cells, especially macrophages, are observed in CA walls in humans [34], the infiltration of inflammatory cells in CA walls was assessed using a rat model. The primary inflammatory cells in rat CA walls are macrophages, in good agreement with observations in human CA walls [68, 69], and their number gradually increases during CA formation, suggesting that macrophage-mediated inflammation may contribute to CA formation [68]. Macrophages secrete various tissue-destructive proteinases and cytokines, which can degenerate the components of the extracellular matrix of arterial walls,

especially collagen and elastin, and are hypothesized to contribute to CA formation, especially the enlargement of CAs through the weakening of CA walls. Indeed, macrophages secrete collagenolytic proteinases, MMP-2 and MMP-9 in CA walls of rats [68, 70], and enhanced collagenolytic activity is detected in CA walls of rat models by *in situ* zymography [68, 69] or gelatin zymography [71–74]. Consistent with these observations, the oral administration of MMP inhibitors to rat models or a deficiency of MMP-9 results in the decreased formation of CAs [68, 69]. Another group of proteinases, cysteine cathepsins, are also upregulated in rat CA walls and their activities are significantly elevated in comparison with those in control arterial walls [75]. A specific inhibitor of cathepsins effectively suppresses CA formation [75]. These results suggest that proteinases actively participate in the pathogenesis of CA and promote CA formation.

Macrophages are recruited to inflammatory sites by chemoattractants, for example, MCP-1 [76, 77]. In CA walls of rat models, the expression of MCP-1 is upregulated in intimal endothelial cells at the early stage of CA formation [58] and in whole arterial walls, including infiltrating inflammatory cells, at the late stage [58, 70]. These findings are in accord with previous human studies in which the expression of MCP-1 mRNA was confirmed in human

CA specimens by *in situ* hybridization [36]. Further, in MCP-1-deficient mice, in which macrophage infiltration of CA walls is abolished, CA formation is inhibited with the suppression of inflammation [58]. The upregulation of various pro-inflammatory molecules in human CA walls has been reported and gene microarray data also support these observations [17, 78].

We identified the upregulation of pro-inflammatory genes during CA formation in CA walls of rat models using microarray analysis and adaptor-tagged competitive-PCR analysis [79, 80]. Most of the upregulated genes can be categorized as proteinases, cytokines, adhesion molecules, reactive oxygen species, members of the apoptotic cascade, and complements, suggesting that the inflammatory response in arterial walls plays a crucial role in CA formation [79].

The genetic contribution to CA formation has also been examined using animal models. In rats, the upregulation of reactive oxygen species-producing enzymes such as p47phox [81], superoxide-related genes such as NOX4 or Rac1 [70], cytokines such as interleukin-1$\beta$ (IL-1$\beta$) [82], and inducible nitric oxide synthase (iNOS) [83] is confirmed in CA walls. However, contradictory results for the contribution of the renin-angiotensin system (RAS) in CA walls have been reported. Tada et al. reported in the induced CA walls of female rat models that the expression of angiotensin converting enzyme (ACE) was upregulated as determined by RT-PCR analysis, and the final product of RAS, angiotensin II production, was also increased in CA walls as determined by immunostaining [70]. On the contrary, our group found that angiotensin II receptor type 1 (AT1R) was not induced in CA walls of male rats by immunostaining and, consistently, the administration of an AT1R blocker (ARB) failed to inhibit CA formation [84]. In human CA walls, Ohkuma et al. reported the decreased expression of ACE and AT1R by RT-PCR analysis and immunostaining [85]. It is not clear why these differences occur and future studies should address this issue.

In mice, the role of a particular gene on CA formation can be assessed more clearly by applying gene-deficient mice to the models. Mice deficient in MMP-2 or -9 [69], tissue inhibitor of MMP (TIMP)-1 or -2 [73], MCP-1 [58], p47phox [55], toll-like receptor-4 (TLR-4) [86], NF-$\kappa$B p50 subunit [87], IL-1$\beta$ [82], apolipoprotein E (ApoE) [88], or iNOS [89] have been applied to CA models revealing the involvement of each gene in the pathogenesis of CAs. In summary, MMP-9, MCP-1, p47phox, TLR-4, NF-$\kappa$B p65 subunit, IL-1$\beta$, and iNOS promote CA formation, while TIMP-1 and TIMP-2 suppresses CA formation.

These experimental results suggest that chronic inflammation in arterial walls plays the important role in CA formation. We have proposed that the transcription factor NF-$\kappa$B is a critical mediator due to its transcriptional regulation of various pro-inflammatory genes in CA walls including MMPs, iNOS, IL-1$\beta$, and MCP-1, which have been shown to be involved in the pathogenesis of CA [58, 68, 82, 83, 87, 89]. NF-$\kappa$B is phosphorylated and activated first in the endothelial cells of CA walls at the early stage of CA formation and then throughout CA walls at the late stage

[88]. We have hypothesized that NF-$\kappa$B activation in the endothelial cell layer is due to hemodynamic stress, which is thought to be a trigger for CA formation [27, 29, 90–94]. This hypothesis is in line with the experimental findings that NF-$\kappa$B is activated in endothelial cells by hemodynamic stress in vitro [95] and that high hemodynamic stress induces the expression of MMP-2, -9, iNOS, and IL-1$\beta$ in CA walls created in the carotid arteries of a canine model [96]. The inhibition of NF-$\kappa$B transcriptional activity by decoy oligodeoxynucleotides [97] or a deficiency in the p50 subunit of NF-$\kappa$B results in the remarkable inhibition of CA formation by the suppression of pro-inflammatory gene expression and macrophage infiltration in CA walls, suggesting the critical role of NF-$\kappa$B activation in CA formation [88].

## 6. Limitations of the Existing CA Models and the Necessity for Further Models

As described in the previous sections, animal models of CA have been used to demonstrate some of the important mechanisms of CA formation and identified therapeutic targets for the treatment of human CAs (Figure 3); however, there is a fundamental problem to be addressed in animal models. It is beyond question that the rupture of CAs and the subsequent SAH is a devastating event and should be prevented; therefore, the prevention of CA rupture is a critical target. For this reason, animal models of CAs are needed where CAs have a high likelihood of spontaneous rupture. Unfortunately, there are no established models with this feature. In our rat models, the rupture rate is only 3% during 3 months after CA induction. We have preliminarily examined several compounds and modified the procedures to induce CAs; however, we failed to establish a rat model with a high incidence of rupture and have never observed the spontaneous rupture of CAs in mice. Recently, Nuki et al. reported that they stereotaxically injected an elastase into the basal cistern in combination with the continuous infusion of angiotensin II to induce CAs in mice [69]. In their report, these induced CAs in murine models spontaneously ruptured, although the exact incidence of rupture was not made clear [69]. Therefore, it is essential that an animal model is developed in which CAs spontaneously and frequently rupture.

## 7. Future Perspectives: From the Results of Animal Studies to Human Treatment

Extensive studies using animal models of CAs are, of course, designed to unravel the underlying mechanisms of CA formation and to establish new therapeutic drugs for unruptured CAs in humans. As described in the previous sections, we have identified NF-$\kappa$B as one of the factors closely related to CA formation and a potential therapeutic target [87, 98, 99], therefore, we have examined the preventive effects of several drugs with anti-NF-$\kappa$B activity on the enlargement of CAs induced in a rat model [71, 72, 74, 81, 84]. Among several candidate drugs, the class of statins, a powerful cholesterol-lowering drug, have been

found to effectively prevent the enlargement of CAs induced in rats [71, 74]. The oral administration of statin to rats significantly suppresses the expression of pro-inflammatory genes in CA walls [74] through its anti-NF-$\kappa$B effect well known as a pleiotropic effect [100]. As a result, the chronic inflammation in CA walls, transcriptionally regulated by NF-$\kappa$B, is inhibited. These results, combined with experimental findings indicating that chronic inflammation contributes to CA formation, suggest that statin can suppress the enlargement of CAs. In present models, we can not assess the rupture of CAs because of their low incidence of spontaneous rupture; however, statin effectively prevents the degenerative changes of CA walls, suggesting a preventive effect of statin on the rupture of CAs. Furthermore, we and others have independently demonstrated that 3 different kinds of statins prevent the formation and enlargement of CAs induced in rat models, indicating that the preventive effect of statins on the enlargement of CAs is due to their class effect [71, 74, 101]. These results suggest the therapeutic potential of statins as drugs for CAs in humans. Based on these experimental findings, a case-control study to examine the preventive effect of statins on the rupture of human CAs is currently in progress. Other candidates as therapeutic drugs for CA treatment, for example, Ibudilast or a phosphodiesterase-4 inhibitor, have been examined using rat CA models with focus on their anti-inflammatory effects [66, 70, 102].

## 8. Conclusions

SAH caused by the rupture of a pre-existing CA is a potentially devastating and socially restricting event. To unravel the underlying mechanisms of CA formation and to develop a new class of therapeutic drugs to prevent rupture, animal models of CAs have been established. Experimental results from animal models and findings from human specimens have revealed some of the important mechanisms underlying CA formation. Increased hemodynamic stress at the bifurcation site of the cerebral arteries is considered to play a crucial role in CA formation by inducing inflammatory responses in arterial walls. Inflammation in cerebral arterial walls triggered by hemodynamic stress is considered to disrupt the internal elastic lamina and degenerate the media. As a result of the increased hemodynamic stress and inflammatory responses in cerebral arteries, CA is induced. Through recent experimental findings, we have identified NF-$\kappa$B as a potential therapeutic target for CA. The inhibition of NF-$\kappa$B activity in animal models, significantly suppress CA formation, suggesting that anti-NF-$\kappa$B drugs can potentially be therapeutic drugs for CAs. In the future, there is a hope that, through increasing use and extensive studies by animal models of CAs, the elucidation of the underlying mechanisms of CA formation allows the pharmacological prevention of SAH.

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