Development of Therapeutic Drugs Targeting Somatic Mutations Specific to Intracranial Aneurysms

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Intracranial aneurysms (IAs) are a prevalent condition characterized by bulging of the cerebral blood vessel wall, affecting approximately 5% of the Japanese population. Rupture of these aneurysms can lead to life-threatening subarachnoid hemorrhage. Currently, there are no pharmaceutical treatments available for IAs; existing options are limited to surgical intervention or endovascular catheter procedures. In particular, giant fusiform and dolichoectatic aneurysms of the basilar trunk and vertebrobasilar junction (BTVBJ-GFDA) pose significant treatment challenges. Without intervention, 91% of patients succumb within 5.5 years due to rupture, brainstem infarction, or brainstem dysfunction, while the remaining 9% face severe sequelae (Nakatomi et al., 2020). Even with surgical intervention, only 65–73% of patients regain independence, while 3–15% experience poor outcomes, and mortality rates remain high at 20–24% (Kodama et al., 1982). These statistics underscore the urgent need for new therapeutic approaches.

Our research team aims to develop pharmacological therapies for IAs through the following strategies:

1. Identifying somatic mutations associated with IAs and creating a comprehensive database to support drug discovery and clinical applications.
2. Investigating the mechanisms by which somatic mutations drive aneurysm formation and progression.
3. Exploring potential drugs that inhibit aneurysm growth mediated by somatic mutations.

The development of IAs is influenced by various factors, including age, sex, alcohol consumption, and hereditary genetic predispositions. Familial IAs, however, account for only 10% of cases (Zhou et al., 2018). In recent years, sporadic somatic mutations in abnormal vascular tissues have been identified and are increasingly recognized for their potential role in aneurysm formation and progression (Nikolaev et al., 2018; Karasozen et al., 2019; Shima et al., 2023).

In our recent study, mutations in platelet-derived growth factor receptor β (PDGFRβ) were identified in 6 of 11 fusiform aneurysm cases (54%) and in 2 of 3 giant saccular aneurysm cases (Shima et al., 2023). As the correlation between somatic mutations and the IA types becomes more evident, we have begun to consider frequent somatic mutations, such as PDGFRβ and AHNAK, as promising targets for pharmacological therapy. To advance this work, we aim to expand the somatic mutation database by analyzing a larger number of cases. Additionally, we strive to elucidate the mechanisms by which mutations in PDGFRβ and AHNAK contribute to aneurysm formation and progression. Finally, we seek to identify novel drugs capable of inhibiting the signaling pathways activated by these mutations.