Cerebral Arteriovenous Malformations (AVMs): Causes, Treatment and Research

Abstract
This work describes an overview of brain arteriovenous malformations (AVMs) causes, current treatment methods, and the research conducted in this field to better understand the biology and pathophysiology of these vessels, and to develop novel therapies, especially for a subset of AVMs that are not treatable with current treatment methods.

Keywords: Brain AVMs, pathophysiology, endothelial cells, proteomics

Brain AVMs
Brain AVM is a tangle of abnormal blood vessels (arteries and veins) (Figure 1), this abnormal collection causes blood to flow quickly and directly from the arteries to the veins, therefore, AVM vessels have a higher rate of bleeding compared to normal vessels. Ruptured AVMs are the main cause of haemorrhagic stroke in children and adults [1]. The cause of brain AVMs remain unclear; some researchers believe that it may be caused by a rupture of blood vessels during foetal development while others suggest that they develop postnatally, undergoing a growth during childhood or early adulthood, this growth may be caused by venous hypertension or by shear stress that trigger growth factor expression by endothelial cells lining the AVM fistula [2]. AVMs are not inherited, with the exception of hereditary hemorrhagic telangiectasia (HHT) condition. AVM is not a cancer and does not spread to other parts of the body [3]. Brain AVM can occur in any region, and range in size from 3-6 cm. According to Spetzler-Martin AVM grading system, they are graded from (I-V), based on their size, location and treatment risk [4]. One third of AVMs are high grade (IV-V), 90% of those are not treatable, and 25% of grade (III) AVMs are not treatable without high risk [5].

Figure 1: AVM vessels (right), unlike normal vessels (left), they lack the capillaries that deliver oxygen slowly through their walls to the surrounding brain tissue.

Treatment Methods
Treatment of AVM is important to prevent bleeding (haemorrhage). The risk of bleeding is 4% per year; each haemorrhage carries a high risk of permanent disability or death [6,7]. Treatment will also relieve the symptoms associated with AVM, such as headaches, seizures and increasing paralysis. Current treatment options are; surgery, embolization, and stereotactic radiosurgery. Small AVMs that are located on the surface of the brain are suitable for surgical removal, however the risks of surgery is high with large AVMs and the AVMs that are located in the deep parts of the brain [4]. Embolization is performed under X-ray direction. A small catheter is inserted through the artery in the groin and navigated to the brain arteries [5,8], (Figure 2). This procedure itself is not usually a cure; often combined with other treatments such as radiosurgery or surgery [8]. Stereotactic radiosurgery is suitable for small AVMs; with this method a focused x-ray beam or gamma-rays are delivered to the AVM such that a high dose is concentrated on the AVM with...
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Research

To develop novel therapies for currently untreatable AVMs, researchers have been studying the genetics, pathophysiology and the molecular process of AVM vessels. Animal models have also been developed to better understand the biological and hemodynamic characteristics of human brain AVMs, such as the swine model developed by Massoud TF [9], the sheep model by Qian Z et al. [10], the dog model by Pietila T et al. [11] 2000 and the rat model by Morgan M et al. [12] and Yassari R et al. [13]. To develop gene therapy, genetic studies suggested that HHT are caused by mutations in either endoglin (ENG) gene or activin receptor-like kinase 1 (ACVRL1) gene, both are associated with TGFβ/BMP signalling. Mutation in the co-receptor ENG is associated with HHT1, while HHT2 is associated with mutations in the signalling receptor ACVRL1 [14].

Endothelial cells lining the AVM vessels and their response to irradiation have also been studied [15-17] and thrombosis was stimulated in the animal model of AVM after irradiation using non-Ligand targeting agents [18-20], however this approach had limitations. To develop a ligand-based vascular targeting therapy, subsequent studies proposed that radiosurgery alter AVM endothelial surface molecules that allow discrimination from normal endothelial cells. These molecules then can be used for a Ligand-directed vascular treatment to stimulate rapid thrombosis (occlusion) in AVM vessels. To identify potential targets for the AVM molecular therapy, proteomics studies have been conducted in the past few years to identify protein targets on the surface of AVM endothelium post radiosurgery. These target proteins will be employed for the Ligand-directed treatment to promote rapid thrombosis in AVM vessels [21-23]. This is especially important for patients who currently have to wait 2-3y after radiosurgery for their AVM to be completely occluded. To achieve this goal, in vitro and in vivo biotinylation methodologies were developed by Simonian M et al. [21], and employed to label membrane proteins in the murine cerebral endothelial cell culture and in the animal model of AVM post irradiation [21]. Membrane proteins were then identified using quantitative proteomics techniques, iTRAQ and MSE and data analysis software’s such as ProteinPilot and ProteinLynx Global Server (PLGS). Example of identified potential proteins targets were, PECAM-1, cadherin-5, PDI, integrin alpha-5, and integrin beta-1 [21-23]. The target proteins identified are currently being investigated in the animal vascular targeting trials, and will further be investigated in human targeting trials in the future [23].

Conclusion

New effective treatments are needed for currently untreatable AVMs. Proteomics plays an important role in medical research, because of the link between proteins, genes and diseases; hence, identifying unique protein expression associated with diseases is a very important and promising area in the field of clinical proteomics, and in developing targeted therapies for brain AVMs. Bioinformatics tools are also necessary to analyse and interpret the biological datasets.

References

1. Achrol A, Guzman R, Varga M, Adler J, Steinberg G, et al. (2009) Pathogenesis and radiobiology of brain arteriovenous malformations: implications for risk stratification in natural history and post treatment course. Neurosurg Focus 26(5): 1-7.
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2. Jeffree R, Stodley MA (2009) Postnatal Development of Arteriovenous Malformations. Pediatr Neurosurg 45: 296-304.

3. Govani FS, Shovlin CL (2009) "Hereditary haemorrhagic telangiectasia: a clinical and scientific review". Eur J Hum Genet 17 (7): 860-871.

4. Spetzler RF, Martin NA (1986) A proposed grading system for arteriovenous malformations. J Neurosurg 65 (4): 476-483.

5. Han PP, Ponce FA, Spetzler RF (2003) Intention-to-treat analysis of Spetzler-Martin grades IV and V arteriovenous malformations: natural history and treatment paradigm. J Neurosurg 98 (1): 3-7.

6. Brown RD Jr, Wiebers DO, Forbes G, O’Fallon WM, Piepgras DG, et al. (1988) The natural history of unruptured intracranial arteriovenous malformations. J Neurosurg 68 (3): 352-357.

7. Halim AX, Johnston SC, Singh V, McCulloch CE, Bennett JP, et al. (2008) The natural history of unruptured intracranial arteriovenous malformations. J Neurosurg 98 (1): 3-7.

8. Jayaraman M (2008) Embolization of Brain Arteriovenous Malformations for Cure: Because We Could or Because We Should? Commentary, AJNR Am J Neuroradiol 30: 107 - 108.

9. Massoud TF, Ji C, Vifneila F, Guglielmi G, Robert J, et al. (1994) An experimental arteriovenous malformation model in swine: anatomic basis and construction technique. AJNR Am J Neuroradiol 15: 1537-1545.

10. Qian Z, Clement S, Maynar M, Usón-Garallo J, Lima-Rodrigues MA, (1999) A simplified arteriovenous malformation model in sheep: feasibility study. AJNR Am J Neuroradiol 20(5): 765-770.

11. Pietilä TA, Zabramski JM, Thellier-Janko A, Duveneck K, Richard WD, et al. (2000) Animal model for cerebral arteriovenous malformation. Acta Neurochir 142(11): 1231-1240.

12. Morgan MK, Johnston I, Besser M, Baines D (1989) Cerebral arteriovenous malformations, steal, and the hypertensive breakthrough threshold. J Neurosurg 66(4): 563-567.

13. Yassari R, Sayama T, Jahromi BS, Ahara Y, Stodley M, et al. (2004) Angiographic, hemodynamic and histological characterization of an arteriovenous fistula in rats. Acta Neurochir (Wien) 146(5): 495-504.

14. Hashimoto T, Lam T, Boudreau NJ, Bollen AW, Lawton MT, et al. (2001) Abnormal balance in the angiotensin-tie2 system in human brain arteriovenous malformations. Circ Res 89(2): 111-113.

15. Tu J, Stodley MA, Morgan MK, Storer KP (2005) Ultrastructural characteristics of hemorrhagic, nonhemorrhagic, and recurrent cavernous malformations. J Neurosurg 103(5): 903-909.

16. Tu J, Stodley MA, Morgan MK, Storer KP (2006) Ultrastructure of perinidal capillaries in cerebral arteriovenous malformations. Neurosurgery 58(5): 961-970.

17. Tu J, Stodley MA, Morgan MK, Storer KP, Sme R (2009) Different responses of cavernous malformations and arteriovenous malformations to radiosurgery. J Clin Neurosci 17: 945-949.

18. Storer KP, Tu J, Karunanyaka A, Morgan MK, Stodley MA (2007) Thrombolytic molecule expression in cerebral vascular malformations. J Clin Neurosci 14(10): 975-980.

19. Storer K, Tu J, Karunanyaka A, Sme R, Short R, et al. (2007) Coadministration of low-dose lipopolysaccharides and soluble tissue factor induces thrombosis after radiosurgery in an animal arteriovenous malformation model. Neurosurgery 61(3): 604-610.

20. Storer K, Tu J, Stodley MA, Sme R (2010) Expression of adhesion molecules after radiosurgery in an animal model of arteriovenous malformation. Neurosurgery. 67(4): 976-983.

21. Simonian M, Molloy MP, Stodley MA (2012) In vitro and in vivo biotinylation of endothelial cell surface proteins in the pursuit of targets for vascular therapeutics for brain AVMs. Metabolomics Journal (1): 007.

22. Simonian M, Ogorzalek Loo RR, Loo JA, Stodley MA, Molloy MP (2014) Proteomics Detection of Endothelial Cell Surface Proteins Following Irradiation as Potential Targets for Brain Arteriovenous Malformations Molecular Therapy. MOJ Proteomics & Bioinformatics 1(1).

23. Simonian M, Ogorzalek Loo RR, Rannulu N, Loo JA, Molloy MP, et al. (2015) Identification of protein targets for brain arteriovenous malformations (AVMs) molecular therapies. J Proteome Research.

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