Strait Circulation Journal
海峽循環學雜誌

Mini Review

Role of Endothelial to Mesenchymal Transition in Arteriovenous Fistula Dysfunction

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Accepted 1 April 2023; Volume: 5; Issue: 2; Pages: 1-3; DOI: 10.6907/SCJ.202304_5(2).0001
Citation: str.circ.j., 2023, 5, 2, 1, 1-3

1. Review

Arteriovenous fistula (AVF) is the preferred method of vascular access for hemodialysis patients due to its superior patency and lower rates of infection and thrombosis compared to other types of access. However, AVF maturation failure remains a significant clinical problem, with a reported non-maturation rate of up to 50% and failure rates up to 60% [1,2]. Neointima hyperplasia (NH) causes narrowing of the venous outflow and may eventually lead to stenosis or thrombosis. It is more likely to develop at sites where arteriovenous anastomosis occurs, mainly due to the disturbed flow pattern characterized by low shear stress amplitudes, a high oscillatory shear index, and a steep temporal/spatial shear stress gradient. Despite this, the molecular mechanisms that link disturbed flow, endothelial dysfunction, and intimal hyperplasia are not fully comprehended yet. These processes predominantly occur on the venous side of the anastomotic region, where endothelial cells experience high non-physiological blood flow gradients and instability [3,4]. Endothelial-to-mesenchymal transition (EndoMT) has been proposed as a potential mechanism contributing to AVF dysfunction. EndoMT is a process by which endothelial cells undergo a transformation into mesenchymal-like cells with increased migratory and invasive properties [5]. The transition by which endothelial cells lose their characteristic features and acquire a mesenchymal phenotype. EndoMT plays a significant role in vascular development and repair, and it has been implicated in the pathogenesis of various cardiovascular diseases (CVD), such as atherosclerosis, valve diseases, fibrosis, and pulmonary arterial hypertension (PAH) [6] and vascular diseases, including AVF dysfunction [7]. During the early stages of AVF maturation, there is an increase in endothelial cell proliferation and migration, followed by the remodeling of the venous and arterial walls [8]. The remodeling process involves the activation of smooth muscle cells and the deposition of extracellular matrix components, which facilitate the formation of the AVF. EndoMT has been shown to play a role in this process. EndoMT is induced by various stimuli, including inflammation [9], mechanical stress [10], and growth factors, and it is characterized by the loss of endothelial cell markers and the acquisition of mesenchymal markers [11]. Endothelial-to-mesenchymal transition associated with AVF creation and inhibition reduces NH in AVF. EndoMT is also associated with the expression of fibronectin which can lead to tissue fibrosis and transforming growth factor beta 1 (TGF-β1), that involved in vascular remodeling. EndoMT is induced in response to oxidative stress, a common feature of AVF dysfunction [12–14]. The endothelial transition is increased in the venous endothelium of AVF compared to native veins, which is associated with the development of intimal hyperplasia, a major cause of AVF dysfunction. Additionally, inhibiting EndoMT using a specific inhibitor may reduce intimal hyperplasia and improve AVF patency.

Besides, the high and unstable blood flow gradients in the venous side of the anastomotic region can lead to hemodynamic changes, which in turn can cause vascular remodeling and intimal

hyperplasia. This can lead to thr vessel thickening of the venous wall, a process also known as arterialization, due to fluid wall shear stress (WSS) and elevated blood pressure. The process is accompanied by an increase in vessel diameter and a return to physiological stress levels within a month, likely due to the effect of laminar shear stress (LSS) on endothelial cells. Low shear stress induces dedifferentiation of endothelial cells. Despite this, the endothelial cells near the anastomosis are still exposed to fast and large WSS gradients, reverse blood flow, and velocity fluctuations, which can contribute to fast outward remodeling [15,16]. Several studies showed that the occurrence of NH is attributed to multiple pathways in vascular biology, such as inflammation, uremia, hypoxia, shear stress, and thrombosis. These pathways are believed to operate together through related cytokine signal cascades causing vessel remodeling which affects the endothelial layer and stimulates the endothelial transition.

The molecular mechanisms underlying EndoMT involve several signaling pathways and transcription factors. These include the TGF-β pathway, Notch signaling, and the Wnt pathway. TGF-β is a potent inducer of EndoMT and activates various intracellular signaling pathways, including the Smad pathway, which triggers the expression of transcription factors such as Snail, Slug, and Twist [5]. These transcription factors, in turn, repress the expression of endothelial markers and induce the expression of mesenchymal markers, leading to the acquisition of mesenchymal characteristics. Notch signaling is another critical regulator of EndoMT. The Notch pathway is involved in cell fate decisions, proliferation, and differentiation, and is activated by the interaction between Notch receptors and their ligands [17]. In the context of EndoMT, Notch signaling induces the expression of Snail and Slug, leading to the downregulation of endothelial markers and upregulation of mesenchymal markers. Finally, the Wnt pathway also plays a role in EndoMT. The activation of the Wnt pathway leads to the stabilization of β-catenin, which translocates to the nucleus and activates the expression of target genes, including Snail and Slug [18]. This leads to the downregulation of endothelial markers and the upregulation of mesenchymal markers.

CD44 expression is upregulated during EndoMT, and its overexpression has been shown to enhance the EndoMT process. CD44 interacts with various extracellular matrix proteins, including osteopontin (OPN), and fibronectin, which are involved in the regulation of cell adhesion, migration, and differentiation. CD44 can also activate various signaling pathways that are involved in EndoMT, including the TGF-β and Wnt pathways. CD44 has been shown to interact with TGF-β receptors and enhance the TGF-β signaling pathway, leading to the activation of transcription factors that promote the EndoMT process. CD44 can also activate the Wnt signaling pathway by interacting with Wnt ligands, leading to the stabilization of β-catenin and the induction of EndoMT-related genes [19].

Moreover, CD44 also regulates the expression of various EndoMT-related genes, such as Snail, Slug, and Twist, by binding to their promoters and enhancing their transcription. CD44 can also interact with various signaling molecules, such as Akt and ERK, which are involved in cell survival and proliferation, and contribute to the EndoMT process. OPN and CD44 is upregulated in endothelial cells exposed to disturbed flow. This upregulation is associated with the induction of EndoMT. Inhibition of the OPN/CD44 axis has been shown to prevent EndoMT in vitro and in vivo [7].

The molecular mechanisms of EndoMT involve the activation of various signaling pathways and transcription factors, which ultimately lead to the acquisition of mesenchymal characteristics by endothelial cells in a state of injury.

It is essential to consider these factors when evaluating and treating AVF stenosis, as they can significantly impact the success of the treatment. Understanding the underlying causes of arteriovenous stenosis and neointima formation in general and endothelial-to-mesenchymal transition, in particular, can help to develop a new therapy, find a novel pharmacological target and reduce the incidence of complications of dialysis arteriovenous fistulas patients.

Conflicts of Interest:
The authors declare no conflict of interest.

References

1. Ma, S.; Duan, S.; Liu, Y.; Wang, H. Intimal hyperplasia of arteriovenous fistula. *Annals of Vascular Surgery* **2022**.
2. Al-Jaishi, A.A.; Oliver, M.J.; Thomas, S.M.; Lok, C.E.; Zhang, J.C.; Garg, A.X.; Kosa, S.D.; Quinn, R.R.; Moist, L.M. Patency rates of the arteriovenous fistula for hemodialysis: a systematic review and meta-analysis. *American Journal of Kidney Diseases* **2014**, *63*, 464–478.
3. Vazquez-Padron, R.I.; Duque, J.C.; Tabbara, M.; Salman, L.H.; Martinez, L. Intimal hyperplasia and arteriovenous fistula failure: looking beyond size differences. *Kidney360* **2021**, *2*, 1360.
4. Remuzzi, A.; Bozzetto, M.; Brambilla, P. Is shear stress the key factor for AVF maturation? *The journal of vascular access* **2017**, *18*, S10–S14.
5. Platel, V.; Faure, S.; Corre, I.; Clere, N. Endothelial-to-mesenchymal transition (EndoMT): roles in tumorigenesis, metastatic extravasation and therapy resistance. *Journal of oncology* **2019**, *2019*.
6. Peng, Q.; Shan, D.; Cui, K.; Li, K.; Zhu, B.; Wu, H.; Wang, B.; Wong, S.; Norton, V.; Dong, Y.; others. The role of endothelial-to-mesenchymal transition in cardiovascular disease. *Cells* **2022**, *11*, 1834.
7. Chang, C.J.; Lai, Y.J.; Tung, Y.C.; Wu, L.S.; Hsu, L.A.; Tseng, C.N.; Chang, G.J.; Yang, K.C.; Yeh, Y.H. Osteopontin mediation of disturbed flow-induced endothelial mesenchymal transition through CD44 is a novel mechanism of neointimal hyperplasia in arteriovenous fistulae for hemodialysis access. *Kidney International* **2023**.
8. Siddiqui, M.A.; Ashraff, S.; Santos, D.; Carline, T. An overview of AVF maturation and endothelial dysfunction in an advanced renal failure. *Renal Replacement Therapy* **2017**, *3*, 1–6.
9. Rieder, F.; Kessler, S.P.; West, G.A.; Bhilocha, S.; de la Motte, C.; Sadler, T.M.; Gopalan, B.; Stylianou, E.; Fiocchi, C. Inflammation-induced endothelial-to-mesenchymal transition: a novel mechanism of intestinal fibrosis. *The American journal of pathology* **2011**, *179*, 2660–2673.
10. Islam, S.; Boström, K.I.; Di Carlo, D.; Simmons, C.A.; Tintut, Y.; Yao, Y.; Hsu, J.J. The mechanobiology of endothelial-to-mesenchymal transition in cardiovascular disease. *Frontiers in Physiology* **2021**, p. 1409.
11. Choi, K.J.; Nam, J.K.; Kim, J.H.; Choi, S.H.; Lee, Y.J. Endothelial-to-mesenchymal transition in anticancer therapy and normal tissue damage. *Experimental & molecular medicine* **2020**, *52*, 781–792.
12. Xiong, J.; Kawagishi, H.; Yan, Y.; Liu, J.; Wells, Q.S.; Edmunds, L.R.; Fergusson, M.M.; Yu, Z.X.; Rovira, I.I.; Brittain, E.L.; others. A metabolic basis for endothelial-to-mesenchymal transition. *Molecular cell* **2018**, *69*, 689–698.
13. Valero-Muñoz, M.; Oh, A.; Faudoa, E.; Bretón-Romero, R.; El Adili, F.; Bujor, A.; Sam, F. Endothelial-mesenchymal transition in heart failure with a preserved ejection fraction: insights into the cardiorenal syndrome. *Circulation: Heart Failure* **2021**, *14*, e008372.
14. Song, Y.; Jia, H.; Hua, Y.; Wu, C.; Li, S.; Li, K.; Liang, Z.; Wang, Y. The Molecular Mechanism of Aerobic Exercise Improving Vascular Remodeling in Hypertension. *Frontiers in Physiology* **2022**, p. 99.
15. Mahmoud, M.M.; Serbanovic-Canic, J.; Feng, S.; Souilhol, C.; Xing, R.; Hsiao, S.; Mammoto, A.; Chen, J.; Ariaans, M.; Francis, S.E.; others. Shear stress induces endothelial-to-mesenchymal transition via the transcription factor Snail. *Scientific reports* **2017**, *7*, 3375.
16. Li, A.; Tan, L.; Zhang, S.; Tao, J.; Wang, Z.; Wei, D. Low shear stress-induced endothelial mesenchymal transformation via the down-regulation of TET2. *Biochemical and Biophysical Research Communications* **2021**, *545*, 20–26.
17. Liang, M.; Guo, Q.; Huang, F.; Han, G.; Song, K.; Luo, J.; Cheng, H.; Hu, H.; Peden, E.K.; Chen, C.; others. Notch signaling in bone marrow–derived FSP-1 cells initiates neointima formation in arteriovenous fistulas. *Kidney international* **2019**, *95*, 1347–1358.
18. Aisagbonhi, O.; Rai, M.; Ryzhov, S.; Atria, N.; Feoktistov, I.; Hatzopoulos, A.K. Experimental myocardial infarction triggers canonical Wnt signaling and endothelial-to-mesenchymal transition. *Disease models & mechanisms* **2011**, *4*, 469–483.
19. Chen, C.; Zhao, S.; Karnad, A.; Freeman, J.W. The biology and role of CD44 in cancer progression: therapeutic implications. *Journal of hematology & oncology* **2018**, *11*, 1–23.