

The role of EMMPRIN in Marfan syndrome-related thoracic aortic aneurysms: A commentary

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Commentary

The authors of this study investigated the pathogenesis of thoracic aortic aneurysms (TAAs) in patients with Marfan Syndrome (MFS). The prevailing hypothesis attributes TAAs to the aberrant remodeling of the extracellular matrix, driven by matrix metalloproteinases (MMPs), which progressively degrade the vessel wall [1,2]. The extracellular MMP inducer (EMMPRIN) stimulates MMP production, suggesting that EMMPRIN may play a critical role in the pathogenesis of TAAs. EMMPRIN is present in both tissue and circulation, and its release is dependent on Membrane Type-1 matrix metalloproteinases (MT1-MMP) [3,4]. Elevated levels of both markers are observed in TAA tissues [5-7], and in various TAA pathologies, EMMPRIN is also elevated in circulation [8-13]. Conversely, decreased circulating EMMPRIN levels are noted in aortic ectasia among MFS patients [8], indicating that the pathological role of EMMPRIN requires further exploration.

To investigate this topic, the authors obtained MFS TAA tissue and plasma samples, along with control samples of healthy human plasma. Plasma and tissue markers were measured in all samples. Healthy aortic fibroblasts were cultured and modified to investigate MT1-MMP localization within the cell. Using these modified fibroblasts, the authors examined and measured the plasma and tissue markers, followed by comprehensive data analysis. The authors determined a paradoxical elevation of EMMPRIN in the tissue, but a reduction in the plasma of MFS TAA samples compared to controls. This finding contrasts with other TAA pathologies, where EMMPRIN levels are typically elevated in both tissue and plasma [8-13]. This result aligns with previous research indicating that elevated EMMPRIN levels in MFS TAA tissue have detrimental effects on TAA pathology [7]. Clinically, these findings suggest that plasma EMMPRIN level measurements could aid in assessing the severity of TAAs in MFS patients. Such measurements, when used alongside current imaging techniques, could inform surgical intervention decisions [14,15].

This study underscores the unique pathologies of different TAA etiologies, revealing a more complex disease process than previously understood. Therapeutics targeting EMMPRIN have been suggested as a potential means to mitigate disease progression [7], but further research is needed. A deeper understanding of MT1-MMP and EMMPRIN may lead to novel therapies for MFS TAA, but each TAA etiology requires individual investigation to develop targeted treatments. MT1-MMP's expression across various tissue types suggests that its role is tissue and cell-type dependent [16]. This research explored how molecular function changes with cellular localization, emphasizing the need to comprehend the enzyme's localization in aneurysm disease. The study demonstrated that MT1-MMP predominantly localizes on the cell surface in MFS TAA tissues, yet its internalization is necessary for EMMPRIN release into the plasma [17-19]. Given EMMPRIN's tissue buildup's degenerative properties and its likely role in MFS TAA pathogenesis [7], understanding this localization pathway is crucial.

Understanding the localization pathway of MT1-MMP could lead to therapeutic interventions for MFS TAAs. As mentioned earlier, internalization of MT1-MMP is essential for EMMPRIN release [17-19], and controlling molecular localization within cells could influence function. In MFS TAA pathogenesis, managing MT1-MMP localization and thus tissue EMMPRIN levels could reduce aortic tissue degeneration. This study advances the knowledge of TAA in MFS patients, demonstrating that plasma EMMPRIN level measurements can assist in clinical decision-making for TAA management. The critical role of MT1-MMP localization in TAA pathogenesis in MFS patients is also highlighted, calling for further research into therapeutic techniques targeting this pathway. Recognizing the uniqueness of each TAA etiology is essential, as a single treatment is unlikely to be effective for all pathologies. Research into these distinct pathways and treatment possibilities would enhance clinical knowledge on TAA management. Overall, this study significantly enhances the understanding of EMMPRIN's effects in MFS TAA and underscores the need for further research on the MT1-MMP localization pathway to identify potential treatment targets.

References

- Jones JA, Beck C, Barbour JR, Zavadzkas JA, Mukherjee R, Spinale FG, et al. Alterations in aortic cellular constituents during thoracic aortic aneurysm development: myofibroblast-mediated vascular remodeling. *Am J Pathol.* 2009 Oct;175(4):1746-56.
- Lindsey ML, Mann DL, Entman ML, Spinale FG. Extracellular matrix remodeling following myocardial injury. *Ann Med.* 2003;35(5):316-26.
- Sidhu SS, Mengistab AT, Tauscher AN, LaVail J, Basbaum C. The microvesicle as a vehicle for EMMPRIN in tumor-stromal interactions. *Oncogene.* 2004 Jan 29;23(4):956-63.
- Egawa N, Koshikawa N, Tomari T, Nabeshima K, Isobe T, Seiki M. Membrane type 1 matrix metalloproteinase (MT1-MMP/MMP-14) cleaves and releases a 22-kDa extracellular matrix metalloproteinase inducer (EMMPRIN) fragment from tumor cells. *J Biol Chem.* 2006 Dec 8;281(49):37576-85.
- Ikonomidis JS, Nadeau EK, Akerman AW, Stroud RE, Mukherjee R, Jones JA. Regulation of membrane type-1 matrix metalloproteinase activity and intracellular localization in clinical thoracic aortic aneurysms. *J Thorac Cardiovasc Surg.* 2017 Mar;153(3):537-46.
- Jones JA, Ruddy JM, Bouges S, Zavadzkas JA, Brinsa TA, Stroud RE, et al. Alterations in membrane type-1 matrix metalloproteinase abundance after the induction of thoracic aortic aneurysm in a murine model. *Am J Physiol Heart Circ Physiol.* 2010 Jul;299(1):H114-24.
- Perrucci GL, Rurali E, Corliano M, Balzo M, Piccoli M, Moschetta D, et al. Cyclophilin A/EMMPRIN Axis Is Involved in Pro-Fibrotic Processes Associated with Thoracic Aortic Aneurysm of Marfan Syndrome Patients. *Cells.* 2020 Jan 8;9(1):154.
- Rurali E, Perrucci GL, Gaetano R, Pini A, Moschetta D, Gentilini D, et al. Soluble EMMPRIN levels discriminate aortic ectasia in Marfan syndrome patients. *Theranostics.* 2019 Apr 12;9(8):2224-34.
- Ni K, Wang C, Carnino JM, Jin Y. The Evolving Role of Caveolin-1: A Critical Regulator of Extracellular Vesicles. *Med Sci (Basel).* 2020 Nov 4;8(4):46.
- Lin W, Xiong J, Jiang Y, Liu H, Bian J, Wang J, et al. Fibrillin-1 mutation contributes to Marfan syndrome by inhibiting Cav1.2-mediated cell proliferation in vascular smooth muscle cells. *Channels (Austin).* 2023 Dec;17(1):2192377.
- Diehl JN, Ray A, Collins LB, Peterson A, Alexander KC, Boutros JG, et al. A standardized method for plasma extracellular vesicle isolation and size distribution analysis. *PLoS One.* 2023 Apr 28;18(4):e0284875.
- Akerman AW, Collins EN, Peterson AR, Collins LB, Harrison JK, DeVaughn A, et al. miR-133a Replacement Attenuates Thoracic Aortic Aneurysm in Mice. *J Am Heart Assoc.* 2021 Aug 17;10(16):e019862.
- Itoh Y, Takamura A, Ito N, Maru Y, Suenaga N, et al. Homophilic complex formation of MT1-MMP facilitates proMMP-2 activation on the cell surface and promotes tumor cell invasion. *EMBO J.* 2001 Sep 3;20(17):4782-93.
- Rozado J, Martin M, Pascual I, Hernandez-Vaquero D, Moris C. Comparing American, European and Asian practice guidelines for aortic diseases. *J Thorac Dis.* 2017 May;9(Suppl 6):S551-60.
- Elefteriades JA, Farkas EA. Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. *J Am Coll Cardiol.* 2010 Mar 2;55(9):841-57.
- Xia XD, Alabi A, Wang M, Gu HM, Yang RZ, Wang GQ, et al. Membrane-type I matrix metalloproteinase (MT1-MMP), lipid metabolism, and therapeutic implications. *J Mol Cell Biol.* 2021 Oct 21;13(7):513-526.
- Manso AM, Elsherif L, Kang SM, Ross RS. Integrins, membrane-type matrix metalloproteinases and ADAMs: potential implications for cardiac remodeling. *Cardiovasc Res.* 2006 Feb 15;69(3):574-84.
- Strongin AY, Collier I, Bannikov G, Marmer BL, Grant GA, Goldberg GL. Mechanism of cell surface activation of 72-kDa type IV collagenase. Isolation of the activated form of the membrane metalloprotease. *J Biol Chem.* 1995 Mar 10;270(10):5331-8.
- Wang Z, Juttermann R, Soloway PD. TIMP-2 is required for efficient activation of proMMP-2 in vivo. *J Biol Chem.* 2000 Aug 25;275(34):26411-5.