

A Short Commentary on Potential Role of the IFN-γ/mini-TrpRS Signaling Axis in Abdominal Aortic Aneurysm

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Abstract

Aneurysms demonstrate vascular smooth muscle cells (VSMC) phenotypic modulation characterized by the prevailing of synthetic over contractile properties. We have shown previously the ability of interferon-gamma (IFN- γ) to switch VSMC from contractile to synthetic phenotype via upregulating the truncated form of tryptophanyl-tRNA synthetase (mini-TrpRS) *in vitro*. Here we discuss a possible role of the IFN- γ /mini-TrpRS signalling axis in the pathology of human abdominal aortic aneurysm (AAA).

Keywords: Mini tryptophanyl-tRNA synthetase; Interferon-gamma; Abdominal aortic aneurysm

The Background

Abdominal aortic aneurysm (AAA) is a common cause of chronic morbidity in the elderly population associated with more than 90% mortality when it ruptures [1]. Aneurysm rupture is mainly attributed to the weakening of the aortic wall associated with the loss of stabilizing structures and smooth muscle cell contractility [2]. Vascular smooth muscle cells (VSMC) are the predominant cell-type within the thickest layer of the aortic wall that regulates pulse pressure and force distribution due to their contractile properties and linkage with the extracellular matrix [3]. Dysregulated positive remodelling of the artery wall characterizing AAA involves the dedifferentiation of VSMC [4]. Although phenotypic modulation of VSMC between their quiescent contractile and active synthetic phenotype is a fundamental property of these cells in regulating the aortic wall integrity, mechanisms leading to dysregulation of this basic cell phenomenon in AAA pathophysiology is poorly understood.

Several traditional risk factors have been linked to AAA, including smoking, ageing, hypertension, hypercholesterolemia, and family history [5]; however, there is clear evidence that inflammatory pathways are principal and common pathogenic mediators in the course of AAA [6] under the stimuli of traditional risk factors. The proinflammatory cytokine interferon (IFN)- γ is a classic representative of inflammatory mediators that are expressed at high levels in AAA [7]. Biological effects of IFN- γ on VSMC contributing to vascular remodelling have been described [8-10], requiring a shift from a quiescent contractile phenotype to an activated synthetic phenotype. In a recent study, we identified a novel indirect molecular mechanism by which IFN- γ elicits VSMC phenotypic modulation that opens a promising non-immunomodulatory treatment option for patients with AAA [11].

The Problem: Impaired VSMC contractility is a novel concept to explain the occurrence and progression of AAA [2]. Innovations in controlling the phenotypic modulation of VSMC would lead to asignificant improvement in the clinical management of AAA.

The Rationale and Solution: Interferon-gamma (IFN- γ), a pleiotropic cytokine critical for innate and adaptive immunity, stimulates an inflammatory response in VSMCs requiring a shift from a quiescent contractile phenotype to an activated synthetic phenotype [10]. IFN- γ controls cellular processes through transcriptional regulation of its dependent genes. For instance, IFN- γ immediately causes transcriptional stimulation of mini-tryptophanyl-tRNA synthetase (mini-TrpRS) that represents the truncated form of the cytoplasmic full-length TrpRS enzyme [12,13]. Interestingly, mini-TrpRS is the only aminoacyl-tRNA synthetase that is transcriptionally inducible by IFN- γ [14-20]. The biological significance of this phenomenon lies in the fact that mini-TrpRS exerts potent signalling actions outside its canonical role in protein synthesis in which mini-TrpRS enzymatically attaches its cognate amino acid tryptophan (Trp) onto the transfer ribonucleic acid tRNA^{Trp}. In our experiments, a characteristic epithelioid (synthetic) phenotype of VSMCs activated with IFN- γ [8] corresponded with the remarkable up-regulation of mini-TrpRS [21]. Importantly, we discovered that blockade of mini-TrpRS with D-tryptophan, acting as a decoy substrate to prevent mini-TrpRS signalling, caused a phenotypic switch to a spindle-shaped (contractile) VSMC morphology

in the presence of IFN- γ in vitro, identifying mini-TrpRS to be essential for a mechanism by which IFN- γ indirectly controls phenotypic modulation of VSMC [11]. An important question, whether the IFN-y/mini-TrpRS signalling axis would be involved in remodelling and weakening of aortic wall at a point in AAA progression in patients, is posed. This hypothesis is holding for data where elevated levels of IFN-y predict an increased rate of AAA expansion [7], wherein AAA diameter is a strong predictor of rupture [22]. Mini-TrpRS signalling inevitably occurs in the context of more complex regulation mediated by IFN-y with the ability to execute specific outcomes depending on the pathological environment and the cell type involved. Thus, a direct blockade of mini-TrpRS with its cognate amino acid D-tryptophan would preserve a quiescent contractile phenotype of VSMC, therefore limit impaired contractility of VSMC in the course of AAA and hold promising non-immunomodulatory treatment option for patients with AAA. In this context, in animal models, D-tryptophan is readily cleared from plasma, and there is no appreciable conversion of D-tryptophan to metabolically active L-tryptophan [23]. D-tryptophan is an enantiomer of L-tryptophan, where the only difference between these two forms of tryptophan is the orientation of the molecule. The essential amino acid L-tryptophan is found in most human proteins and must be resourced from the diet. Ltryptophan is also a precursor to the neurotransmitter serotonin, the hormone melatonin and vitamin B3 [24]. The therapeutic use of L-tryptophan has previously focused on mood-affective disorders with doses up to 6 g/day being considered safe and generally free of side effects [25]. D-tryptophan, unlike L-tryptophan, is not a constituent of human proteins and has no metabolic or biological functions attributable to L-tryptophan. Consequently, side effects such as unintended stimulation of serotonin production in the brain [23] or other metabolic functions of the Ltryptophan [25] would be expected to be negligible in treated AAA patients. The proposed model for the treatment of AAA using D-tryptophan is shown in Figure 1. Studies investigating IFN-γ/mini-TrpRS signalling and suggested intervention with D-tryptophan in AAA is planned for future work.

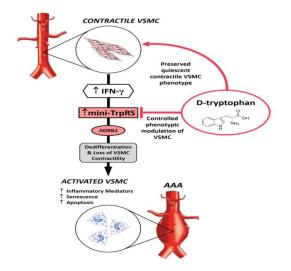


Figure 1: Proposed AAA therapy based on D-tryptophan. Interferon- γ (IFN- γ) is chronically elevated in AAA. This inevitably up-regulates mini-TrpRS that promotes de-differentiation and loss of VSMC contractility.

Intervention with D-tryptophan would prevent the dedifferentiation of VSMC controlling phenotypic modulation of these cells in the course of AAA, thus regulating AAA expansion. *ADRB2*, β 2-adrenoceptor.

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Author Contributions

Conceptualization, E.B. and C.S.M.; Writing – Original Draft Preparation, E.B. and C.S.M.; Writing – Review & Editing, R.B.V., U.H.M., and V.V.; Visualization, C.S.M.; Funding Acquisition, R.B.V. and U.H.M.

Conflicts of Interest

The authors declare no conflict of interest.

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