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GLUT10 deficiency leads to oxidative stress and non-canonical αvβ3 integrin-mediated TGFβ signalling associated with extracellular matrix disarray in arterial tortuosity syndrome skin fibroblasts

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Abstract:
Arterial tortuosity syndrome (ATS, OMIM #208050) is a rare autosomal recessive connective tissue disorder characterized by tortuosity and elongation of the large and medium-sized arteries and a propensity towards aneurysm formation and vascular dissection. ATS is caused by mutations in SLC2A10 encoding the facilitative glucose transporter 10 (GLUT10). GLUT10 deficiency leads to the disarray of the extracellular matrix (ECM) and to the activation of the TGFβ pathway, but the pathomechanisms of ATS is still an enigma.
To discern the pathomechanisms underlying the ATS aetiology, we performed gene expression profiling and biochemical studies on skin fibroblasts. Transcriptome analyses revealed the dysregulation of several genes involved in TGFβ signalling and ECM homeostasis as well as the perturbation of specific pathways that control both the cell energy balance and the oxidative stress response. Biochemical and functional studies showed a marked increase in ROS-induced lipid peroxidation sustained by altered PPARγ function, which contributes to the redox imbalance and the compensatory antioxidant activity of ALDH1A1. ATS fibroblasts also showed activation of a non-canonical TGFβ signalling due to TGFBRI disorganization, the upregulation of TGFBRII and connective tissue growth factor, and the activation of the αvβ3 integrin transduction pathway, which involves p125FAK, p60Src, and p38 MAPK. Stable GLUT10 expression in patients' fibroblasts normalized redox homeostasis and PPARγ activity, rescued canonical TGFβ signalling, and induced partial ECM re-organization. These data add insights into the dysregulated biological pathways and definition of the pathomechanisms involved in ATS. This work was supported by the Telethon Foundation (grant number GGP13167).
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