Two Chinese Patients with Loeys-Dietz Syndrome due to TGFBR2 Mutations

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Background: We previously reported 6 patients with Marfan-like phenotype due to transforming growth factor b-receptor 2 (TGFBR2) mutations (Am J Med Genet Part A 149A:1452-1459). Loeys-Dietz syndrome (LDS) is a recently described autosomal dominant connective tissue disorder characterized by facial dysmorphism, cleft palate, aortic dilatation, blood vessel tortuosity and a high risk of aortic dissection. It is caused by mutations in the TGFBR1 and 2 genes. Two of the 6 patients reported in 2009 were re-assessed and confirmed to have phenotypic features of LDS.

Clinical information: K.T.H. and T.W.S. (Patient 4 and 5 in AJMG 149A:1452-1459) both presented with asymptomatic murmur and marfanoid features in their childhood. In addition they have unique craniofacial features including craniosynostosis, hypertelorism and bifid uvula. They did not fulfill the Ghent or modified Ghent criteria. Both have significant progressive aortic root dilatation requiring surgical replacement in adolescence. K.T.H. had a missense mutation c.1069G>A/p.G357R in TGFBR2 gene while T.W.S. also had a missense mutation c.973A>C/p.T325P in the same gene.

Conclusion: The arterial involvement of LDS is more extensive and the propensity to rupture is higher when compared to Marfan syndrome. A third of LDS patients can presented with aortic dissection or death before 19 years of age. The youngest age of presentation was 6 months and aortic dissection can occur when the aortic root is <4 cm. LDS patients are also prone to cerebral/abdominal arterial dissection and cervical spine instabilities. It is important to recognize LDS as a differential diagnosis of Marfan-like phenotypes so that accurate genetic counseling, lifelong surveillance and timely surgical intervention can be offered.

Astragaloside IV Enhanced Haematopoiesis via the EGFR-MEK-EKR1/2 Signalling Pathway

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Background: *Radix Astragali*, a major component of Danggui Buxue Tang (DBT) decoctions, is extensively used in Chinese medicine and is known to promote haematopoiesis *in vivo* and *in vitro*. Astragaloside IV (AS-IV) is one of the major compounds of *Radix Astragali*. As the major compound involved in DBT, whether it is responsible for the haematopoiesis enhancement of DBT remains unknown. Therefore, we investigated the function of AS-IV by an *in vitro* haemotopoiesis model and explored the possible underlying cell signaling mechanism.

Design and methods: Murine colony forming units (CFU) assays were used to determine the effects of AS-IV on haematopoiesis *in vitro*. K562 cells were used as a haematopoietic cell model *in vitro* to explore the possible molecular mechanisms underlying AS-IV's activity. Phosphorylation of EKR1/2 (pEKR1/2) quantification were analyzed by flow cytometry, which included: 1) a control group; 2) AS-IV treatment group; 3) inhibitor groups with PD98059 or Gefinitib; 4) and a combination treatment group of the corresponding inhibitor and AS-IV. Meanwhile, cells proliferation was analyzed using ^{3}H-Thymidine radioactive assay and the examinations of cells' survival percentage were analyzed by Annexin V/PI staining using flow cytometry. The pEKR1/2, tEKR1/2, Bcl-2 and Bax expression were analyzed by western blot.

Results: AS-IV promoted the formation of bone marrow colony forming units (CFUs) in erythrocytes, granulocytes, monocytes *in vitro*. AS-IV also significantly enhanced CFU-megakaryocytes (MK) formation. However, CFU-MK formation was significantly reduced by PD98059, suggesting that ERK1/2 activating process was one of the main pathways of AS-IV action. In K562 cells, AS-IV also promoted cell proliferation, prolonged S-phase (DNA synthesis) and prevented cells from apoptosis. The impact of EFGR inhibitor Gefinitib on the ERK1/2 phosphorylation process was further investigated. We demonstrated that AS-IV acted via the EGFR-ERK1/2 signalling pathway, which up-regulated the anti-apoptotic protein Bcl-2 expression through the ERK1/2 phosphorylation.

Conclusion: We found that astragaloside IV promoted haematopoiesis *in vitro* and this is possibly in part via activation of the EGFR-EKR1/2 signaling pathway.