TGFbeta signalopathies as a paradigm for translation medicine

Marfan syndrome (MFS) is a disorder that affects different organ systems, such as the heart, aorta, eyes and the skeleton. Typically MFS patients present with tall stature, hands with long fingers, chest deformity. One of its most severe symptoms is the aneurysm of the aorta, a widening of the main artery in the body. This dilation can lead to ruptures in the aortic wall, which in many cases will be deadly. The cause of Marfan syndrome was discovered in 1991 when researchers identified the gene *FBN1* as the culprit. This gene encodes for fibrillin-1, an important component of fibrils, which are essential for the strength the extra-cellular matrix of the aortic wall . MFS patients have a mutation or error in the DNA code of the fibrillin-1 gene that leads to decreased amount of fibrillin-1 or fibrillin-1 with abnormal structure. Historically, researchers hypothesized that mutations lead to a structural deficiency of the aortic wall that in turn causes a weakening of the aortic wall that makes the aortic wall more vulnerable to dissection. More recently, it was discovered that the weakening of the wall is not only caused by the FBN1 mutations directly, but is also is the consequence of the dysregulation of a cellular process, called the TGFbeta pathway. The key role of this pathway has been confirmed by research on related aortic aneurysm syndromes, such as Loeys-Dietz syndrome and Shprintzen-Goldberg syndrome. All these disorders are caused by errors in genes that encode for components of the TGFbeta pathway. A remarkable fact is that evidence shows that the TGFbeta pathway signalling, despite the apparent loss-of-function nature of the identified mutations.

These insights have created new hope for innovative treatment strategies. Beta-blockers, such as atenolol and propranolol have long been the golden standard medication as they reduce stress on the aortic wall, but opposing results in different studies have led to doubts about its efficacy. More promising is the use of angiotensin receptor blockers such as losartan, which have a direct effect on the affected TGFbeta pathway. In Marfan mouse models, these drugs cause a slowing down of the aorta widening and improve the architecture of the aortic wall. In humans, losartan treatment was equally effective as high dose of atenolol in a cohort of severely affected MFS patients. At present, a number of different treatment strategies affecting different parts of the TGFb pathway are also being studied in mice. Intriguingly, the first steps to personalised treatment have also been taken when researchers showed a different response to losartan depending on the type of mutation in the patient. In conclusion, more research is needed to bring the best therapies to the right patients. When the diameter of the aorta reaches a certain threshold (eg. in Marfan patients 5 cm), surgical intervention is still recommended. Overall, new medical treatments and improved surgical procedures have improved life quality of Marfan patients.

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