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Gata1 low mice as a model for multi-organ fibrosis

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In previous studies, we have shown that mice carrying the hypomorphic mutation which reduce the expression of the transcription factor GATA1 in Mk , the GATA1low mutation, develop myelofibrosis, a phenotype which resemble primary myelofibrosis, the most severe of the myeloproliferative neoplasms. The phenotype is driven by high levels of TGF-beta and the bone marrow from Gata1low mice, as those from the patients, is characterized by a strong activation of non-canonical TGFβ signaling including high level of expression of the transcription factor c-Jun which regulates myelo-monocytic maturation. More recently, over-expression of c-Jun has been described to be responsible for multi-organ fibrosis in mice [1]. The strong c-Jun signature suggested to us that also Gata1low mice may develop multi-organ fibrosis with age. This hypothesis was tested by histo-pathological analyses of bone marrow, spleen, liver, skin, lungs, heart and kidney of Gata 1low mice and of their wild-type littermates at 1-, 8- and 15-months of age. Cellular organization was detected by hematoxylin-eosin staining while fibrosis was detected by Gomory and Mallory staining. In addition to bone marrow and spleen, fibrosis was detected in skin, lung, heart and kidney but not in liver. At 1-month, fibrosis was detected only in skin and showed a tissue distribution resembling that observed in Scleroderma. At 8-months, fibrosis was detected in bone marrow, lung and heart. In the lung, the alveoli has thickened walls and fibers bundles were observed on the bronchus walls. In the heart, collagen fibers appeared of variable thickness and the cardiomyocytes had abnormal morphology which a strong reduction of intercalar disks. In the kidney, fibrosis was observed at 15-months and was localized in the medullary and nephron region. In conclusion, in addition to myelofibrosis, Gata1low mice may represent models for scleroderma, idiopathic pulmonary fibrosis and heart and kidney fibrosis, depending on age.

References

[1] Werning et al (2017) PNAS 114, 4757.