



The level of hepatic ABCC6 expression determines the severity of calcification after cardiac injury

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Résumé en anglais

Because vascular or cardiac mineralization is inversely correlated with morbidity and long-term survival, we investigated the role of ABCC6 in the calcification response to cardiac injury in mice. By using two models of infarction, nonischemic cryoinjury and the pathologically relevant coronary artery ligation, we confirmed a large propensity to acute cardiac mineralization in *Abcc6*^{-/-} mice. Furthermore, when the expression of ABCC6 was reduced to approximately 38% of wild-type levels in *Abcc6*^{+/-} mice, no calcium deposits in injured cardiac tissue were observed. In addition, we used a gene therapy approach to deliver a functional human ABCC6 via hydrodynamic tail vein injection to approximately 13% of mouse hepatocytes, significantly reducing the calcification response to cardiac cryoinjury. We observed that the level and distribution of known regulators of mineralization, such as osteopontin and matrix Gla protein, but not osteocalcin, were concomitant to the level of hepatic expression of human and mouse ABCC6. We notably found that undercarboxylated matrix Gla protein precisely colocalized within areas of mineralization, whereas osteopontin was more diffusely distributed in the area of injury, suggesting a prominent association for matrix Gla protein and osteopontin in ABCC6-related dystrophic cardiac calcification. This study showed that the expression of ABCC6 in liver is an important determinant of calcification in cardiac tissues in response to injuries and is associated with changes in the expression patterns of regulators of mineralization.

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