Downregulation of stanniocalcin 1 is responsible for sorafenib-induced cardiotoxicity

Sorafenib is associated with adverse cardiac effects, including left ventricular dysfunction. However, the precise mechanism remains unclear. Here, we aimed to establish the genes responsible for this cardiotoxicity using zebrafish and human cardiomyocytes. Fluorescent cardiac imaging using pigmentless zebrafish with green fluorescent protein hearts revealed that the ventricular dimensions of the longitudinal axis with sorafenib were significantly shorter than those of the control group. Transcriptome analysis of their hearts revealed that stanniocalcin 1 (stcl) was downregulated by sorafenib. stcl knockdown in zebrafish revealed that reduction of stcl decreased the longitudinal dimensions of zebrafish ventricles, similar to that which occurs during sorafenib treatment. STCl downregulation and cytotoxicity were also seen in human cardiomyocytes exposed to sorafenib. To clarify the molecular function of stcl in sorafenib-induced cardiotoxicity, we focused on oxidative stress in cardiomyocytes treated with sorafenib. Reactive oxygen species (ROS) production significantly increased in both species of human cardiomyocytes and zebrafish exposed to sorafenib and STC1 knockdown compared with the controls. Finally, we found that forced expression of stcl normalized impairment, decreasing the longitudinal dimensions in zebrafish treated with sorafenib. Our study demonstrated that STC1 plays a protective role against ventricular dysfunction and ROS overproduction, which are induced by sorafenib treatment. We discovered for the first time that STC1 downregulation is responsible for sorafenib-induced cardiotoxicity through activated ROS generation.