

# Crucial role of Rho-kinase inhibition during development in arrhythmogenic right ventricular cardiomyopathy in mice

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学位授与番号	11301甲第15440号
URL	<a href="http://hdl.handle.net/10097/58334">http://hdl.handle.net/10097/58334</a>

(書式12)

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学位の種類	博士 (医学)
学位授与年月日	2013年9月25日
学位授与の条件	学位規則第4条第1項
研究科専攻	東北大学大学院医学系研究科 (博士課程) 医科学 専攻
学位論文題目	Crucial role of Rho-kinase inhibition during development in arrhythmogenic right ventricular cardiomyopathy in mice (不整脈原性右室心筋症の発症における胎生期心筋 Rho キナーゼ阻害の重要な役割)
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## 論文内容要旨

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited myocardial disorder characterized by fibrofatty changes, mainly in the right ventricle, ventricular arrhythmias and sudden death. ARVC-causing mutations have been identified mostly in genes encoding the major components of the cardiac desmosome. However, the causative genes are unknown in almost half of ARVC patients and the pathogenic mechanisms have not yet been fully elucidated. Rho-kinase signaling is involved in the regulation of a wide range of fundamental cell functions, all of which are involved in the pathogenesis of cardiovascular diseases. In this study, we explore the role of Rho-kinase inhibition in the cardiovascular system during development. Interestingly, these mice spontaneously develop cardiac dilatation and dysfunction, myocardial fibrofatty changes, ventricular arrhythmias, and sudden premature death; phenotypes recapitulating ARVC in humans. We also demonstrate altered desmosome structure and aberrant Wnt signaling, which has been recently implicated in the pathogenesis of ARVC, in the Rho-kinase-deficient hearts. Thus, this study highlights a novel role of Rho-kinase inhibition in the heart during development in the pathogenesis of ARVC in mice.