

Yong-Xiao Wang, M.D., Ph.D.

Expression and Function of FK506 binding Protein 12.6 in Pulmonary Artery Smooth Muscle

Yong-Xiao Wang
Center for Cardiovascular Sciences, Albany Medical College,
Albany, NY12208

It is well known that FK506 binding protein 12 and 12.6 (FKBP12 and FKBP12.6) is physically associated with and biologically stabilizes skeletal and cardiac muscle ryanodine receptors (RyR1 and RyR2), respectively. In this study, we sought to examine their expression and function in smooth muscle cells (SMCs). Our data indicate that both FKBP12 and 12.6 mRNAs were present in pulmonary arteries. FKBP12.6, but not FKBP12 protein, was detected in isolated sarcoplasmic reticulum (SR) membrane preparations from pulmonary arteries. FKBP12.6-GST fusion protein pulled down RyR2, but not RyR1 and RyR3 in isolated SR, whereas FKBP12-GST fusion protein was without effect. Neither FKBP12-GST nor FKBP12.6-GST fusion protein was associated with any subtype of inositol 1,4,5-triphosphate receptors. Removal of FKBP12.6 by FK506 exposure induced intracellular Ca^{2+} release in pulmonary artery SMCs. Similarly, removal of FKBP12.6 by gene deletion increased the activity of RyRs. Chemical and genetic removal of FKBP12.6 both could enhance hypoxia-induced increase in $[Ca^{2+}]_i$ in pulmonary artery SMCs and vasoconstriction in pulmonary arteries. The hypoxic responses were blocked by chemical and genetic inhibition of mitochondrial reactive oxygen species (ROS) generation and mimicked by exogenous ROS. Hypoxic stimulation could disassociate FKBP12.6 with RyRs, manifesting a significant decrease in the amount of FKBP12.6 in isolated SR membrane. Similarly, ROS exposure removed FKBP12.6 from RyRs as well. Taken together, we for the first time provide molecular, genetic and functional evidence that FKBP12.6 is expressed, binds to, and inhibits RyR2 in SMCs. Furthermore, we also demonstrate that hypoxia increases the generation of mitochondrial ROS, which may disassociate FKBP12.6 with RyR2, contributing to hypoxic responses in pulmonary artery SMCs.