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Disrupting KATP channels diminishes the estrogen-mediated protection in female mutant mice during ischemia-reperfusion

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Estrogen has been shown to modulate female protection against ischemia-reperfusion (I-R) stress. Composed by a Kir6.2 pore and an SUR2 regulatory subunit, cardiac ATP-sensitive potassium channels (KATP) remain quiescent under normal physiological conditions but they are activated by stress stimuli. It remains unclear whether KATP is a regulatory target of estrogen in the female-specific stress signaling pathway. In this study, we employed knockout mice in which SUR2 is disrupted (SUR2KO) to characterize their I-R response using an *in vivo* occlusion model. Echocardiographic results indicated that SUR2KO females were pre-disposed to cardiac dysfunction at baseline. These mice were more susceptible to I-R stress by having bigger infarcts than WT controls. The observation was confirmed using ovariectomized mice implanted with 17β-estradiol (E2) or placebo pellets (0.1 μg/g/day, 21-day release), where the estrogen-mediated protection was diminished in KO hearts post IR. Expression studies showed that SUR2 protein level, but not RNA level, was up-regulated in WT-IR mice relative to untreated controls, possibly via post-translational modifications. Our antibodies further detected differentially glycosylated SUR2 species after PNGase-F treatment, suggesting that SUR2 is modified by N-glycosylation. We subsequently showed that E2 could increase level of complex-glycosylated SUR2. Comparative proteomic profiling identified 41 differentially altered hits between KO-IR and WT-IR mice encompassing those related to estrogen biosynthesis and N-glycosylation. Our data suggest that KATP is likely a downstream regulatory target of estrogen and it is indispensable in female stress signaling. Increasing SUR2 expression by N-glycosylation mediated by estrogen may be effective to enhance KATP activity in I-R.

Biography

Nian-Qing (Nan) Shi has completed her Ph.D. in Microbiology in 2000 from The University of Wisconsin-Madison. After she finished an industrial post-doctoral training in mitochondrial redox regulation with Tate and Lyle, she returned to academia to investigate the molecular composition and structure/function of a mitochondrial ATP-sensitive potassium (mitoKATP) channel in cardioprotection. Her team identified and cloned the cardiac mitoKATP channel, which had been pursuing by the field since 1991. In her recent studies, she started exploring the roles of HCN2 channels in congenital heart diseases. She serves as editorial members for 3 journals and reviewers for several major cardiac journals.

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