Saverio Gentile, J Clin Exp Cardiology 2013, 4:4
http://dx.doi.org/10.4172/2155-9880.S1.011

OMICS Group Conferences
Accelerating Scientific Discovery

3rd International Conference on
Clinical & Experimental Cardiology

April 15-17, 2013 Hilton Chicago/Northbrook, USA

Cardiac ion channels phosphorylopathy: A link between genomic variations and heart arrhythmia

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Ion channels play a fundamental role in generating and controlling electrical signals and contraction of the heart. Mutations that inhibit or up-regulate ion channels activities can dramatically interfere with normal heart function leading to unpredictable organ failure, and therefore poor quality of life or even death. However, the molecular mechanism linking these mutations to inherited cardiac disiseases still is very elusive.

Phosphorylation exerts significant effects on the biophysical mechanisms of ion channels ranging from variations in current kinetics to changes in ion channel trafficking.

We found that disease-associated mutations on different ion channels can create or disrupt phosphorylation sites which in turn strongly affect ion channel function. We call these events "Ion Channels Phosphorylopathies".

In summary here we show:

1) A mutation on the L-type calcium channel Cav1.2 associated with the cardiac arrhythmia creates a consensus site for CAMKII. Aberrant phosphorylation at this site leads to an abnormal Cav1.2 activity.
2) A frequent mutation of the voltage gated potassium channel hERG1-associated with the Long-QT2 syndrome creates a consensus sites for the specific protein kinases PKB. Aberrant phosphorylation at this site affects the thyroid hormone (T3)-dependent regulation of on Kv11.1 channel activity.
3) Another distinct Long-QT2-associated mutation on hERG channel disrupts a PKCα-dependent phosphorylation. Inhibition of phosphorylation at this PKC site leads to abnormal regulation of Kv11.1 activity.

Understanding Phosphorylopathies offers the opportunity to find a mechanism linking genomic variations to human heart disease and it is crucial in the process of designing an effective pharmacological strategy.

Biography

Saverio Gentile has completed his Ph.D. from the Neuroscience Laboratory of the Stazione Zoologica "A. Dohrn" Naples, Italy and Universita' Degli Studi Della Calabria, Italy. In 2003, he moved to the laboratory of Neurobiology at the from National Institute of Environmental Health Sciences (NIEHS/NIH), NC, and USA to study regulation of ion channels activity and later he joined the Cardiology Department at Duke University. He is now Assistant Professor in the Department of Molecular Pharmacology at Loyola University Chicago. His research is focusing on hormonal regulation of ion channel activity. He has published several papers in reputed journals.

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