Identification of drug targets related to the induction of ventricular tachyarrhythmia through systems chemical biology approach

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Ventricular tachyarrhythmia (VT) such as Torsade de Pointes is one of the most serious adverse drug reactions which often leads to death. In vitro assessment of interaction of lead compounds with HERG potassium channel as a main known reason of VT induction is obligatory test during the drug development. However, experimental and clinical data reveal that inhibition of ion channels is not the only possible mechanism of VT induction. Therefore, identification of other protein drug targets contributing to the induction of VT is necessary.

We have developed a systems chemical biology approach for search of VT-related protein targets

1 Creation of three datasets of drug structures with different VT-causing drugs from CredibleMeds [1] and common negative control from SIDER [2]

Set 1: 40 drugs with known risk of Torsade de Pointes
Set 2: 57 drugs with possible risk of Torsade de Pointes
Set 3: 27 drugs with conditional risk of Torsade de Pointes + 577 drugs as common negative control

5 Discrete modeling of cardiomyocyte regulatory network behavior

Cardiomyocyte regulatory network (CRN). CRN was created based on general and heart-specific signaling and regulatory pathways with a specific emphasis on identified VT-related pathways and processes. Pathways and corresponding reactions between proteins were retrieved from KEGG, freely available pathway map of MetaCore™ and PROTEOME™/BIOSOFT GmbH. CRN contains 1026 nodes (proteins and genes) and 2952 directed edges (divided on two types: activation and inhibition).

Algorithm of discrete dichotomic modeling. This algorithm allows performing simulation of large regulatory networks behavior. Each node of dichotomic network model can be in two states: 1 (active) or 0 (inactive). The state of each node is calculated at each step of modeling as \( S(t+1) = S(t) \cdot [1 - \delta(t)] \), where \( S(t) = 1 \) is a current state of node, \( S(0) \) is a states of upstream nodes at previous step of modeling, \( \delta \) is weights of inputs edges: 1 (activation) or -1 (inhibition).

Parameter \( \alpha \) may be used for more accurate adjustment of the model according to the known data on regulatory processes. Initial state in CRN dichotomic model corresponds to 60 housekeeping genes presenting in network and was considered as \( S(0) = 1 \).

Key events. Dichotomic modeling allows identifying nodes of network whose inhibition can lead to a selected key event. The selected key events correspond to the activation/inactivation of a fragment of network or distinct nodes. We found in literature 26 proteins which inhibition can lead to VT in mouse models. We selected inactivation of each of 36 proteins in CRN dichotomic model as key events and searched for other CRN proteins, whose inhibition can lead to these key events, by simulation of CRN behavior.

We identified 97 protein nodes whose inhibition can lead to the inactivation of 26 “key event” nodes (26 and 97 = 119 nodes in total). Most of 119 nodes with corresponding genes (except only one protein) form a single connected component in CRN (in figure proteins are ellipses, genes are diamonds, activating edges have green color, inhibiting edges have red color). This component besides 26 proteins (nodes in figure colored in blue), which have known relationships to VT in mouse models, also contains 32 potential VT-related target proteins (nodes in figure have dark blue border) which can be revealed by Mann-Whitney analysis of predicted drug target interactions for at least one dataset of drug structures (11 of 32 targets were revealed for at least two datasets from three ones).

We have performed Gene Ontology and KEGG pathways enrichment analysis using Cytoscape plug-in of Cytoscape [4]. Pathways and processes with Benjamini-Hochberg corrected p-value = 0.05 were selected. Subsequent literature analysis on these processes allows identifying processes that are related to drug-induced VT etiology. We manually annotated 203 potential VT-related targets associated with these processes and found that 104 of 203 proteins participate in them.

Can we identify additional VT-related protein targets?

Examples of potential VT-related protein targets from high confidence category

**Target name** | **Gene** | **Brief description**
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Advanced glycosylation and product-specific receptor (AGER) | AGSR | Enhances redistribution of connexin 43 that may be associated with increased risk of arrhythmias in diabetes.
AMP-activated protein kinase | PRKAA1 | Provides link between cardiac metabolism and arrhythmias.
Cannabinoid CB1 and CB2 receptors | CBR1/2 | Activation may possess pro- or antiarrhythmic effect.
Hepatocyte growth factor receptor | MET | HGF gene therapy has an antiarrhythmic effect after myocardial ischemia.
Histamine H2 receptor | HRA2 | Modulates arrhythmogenic potential of histamine.
Kappa opioid receptor | DOR1K | Agonist possesses pro- or antiarrhythmic effect which depends from concentration.
Nociceptin receptor | OPRL1 | Nociceptin has antiarrhythmic properties.
Phosphoinositide 3-kinase IA class | PIK3CD | Knockout causes prolongation of QT interval in ECG.
Protein tyrosine kinase 2 beta | PTK2B | Knockout increases risk of VT
Serine/threonine-protein kinase PAK 1 | PAK1 | Knockout increases risk of arrhythmias during ischemia through enhanced reactive oxygen species production Participates in pathways which are important for arrhythmogenesis.
Serotonin 5-HT1A receptor | HTR1A | Knockout causes suppression of arrhythmias.

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[1] https://www.crediblemeds.org