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Original article

Transverse tubular network structures in the genesis of intracellular calcium alternans and triggered activity in cardiac cells

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ABSTRACT

Rationale: The major role of a transverse-tubular (TT) network in a cardiac cell is to facilitate effective excitation-contraction coupling and signaling. The TT network structures are heterogeneous within a single cell, and vary between different types of cells and species. They are also remodeled in cardiac diseases. However, how different TT network structures predispose cardiac cells to arrhythmogenesis remains to be revealed.
Objective: To systematically investigate the roles of TT network structure and the underlying mechanisms in the genesis of intracellular calcium (Ca^{2+}) alternans and triggered activity (TA).
Methods and results: Based on recent experimental observations, different TT network structures, including uniformly and non-uniformly random TT distributions, were modeled in a cardiac cell model consisting of a three-dimensional network of Ca^{2+} release units (CRUs). Our simulations showed that both Ca^{2+} alternans and Ca^{2+} wave-mediated TA were promoted when the fraction of orphaned CRUs was in an intermediate range, but suppressed in cells exhibiting either well-organized TT networks or low TT densities. Ca^{2+} alternans and TA could be promoted by low TT densities when the cells were small or the CRU coupling was strong. Both alternans and TA occurred more easily in uniformly random TT networks than in non-uniformly random TT networks. Subcellular spatially discordant Ca^{2+} alternans was promoted by non-uniformly random TT networks but suppressed by increasing CRU coupling strength. These mechanistic insights provide a holistic understanding of the effects of TT network structure on the susceptibility to arrhythmogenesis.
Conclusions: The TT network plays important roles in promoting Ca^{2+} alternans and TA, and different TT network structures may predispose cardiac cells differently to arrhythmogenesis.

1. Introduction

Transverse tubules (TTs) are sarcolemma membrane invaginations of skeletal and cardiac muscle cells. The TTs also branch into axial tubules (ATs), forming a TT network inside the cell [1–3]. The major role of a TT network in a cardiac myocyte is to facilitate effective excitation-contraction (E-C) coupling and signal transduction [4–6]. The TT network structure is very heterogeneous within a cardiac cell and also varies across different types of the heart cells [4,7,8], which may undergo remodeling in diseases, such as ischemia and heart failure [2,9–16]. For example, a normal ventricular myocyte (VM) consists of a well-structured high-density TT network (Fig. 1A) [1,2], which are remodeled in hypertension and heart failure to have a reduced TT density due to TT disruption [2,10–15]. The remodeled TT networks become more heterogeneous, which include patchy (Fig. 1B) [2,11] and sheet-like (Fig. 1C) [15] structures. Unlike those in VMs, the TT networks in atrial myocytes (AMs) are usually much less dense than those in VMs (Fig. 1D) [3]. Studies also have shown that the TT networks in AMs are very heterogeneous between regions in the same heart [17–20] and between species [21]. Some AMs exhibit well-organized TT structures, similar to those in VMs, while other AMs exhibit sparse TT networks such as the one shown in Fig. 1D, and some AMs even completely lack TTs. Purkinje cells (P-cells) are largely free of TTs [7,22,23]. TTs are also largely absent in myocytes in early development, in cultured myocytes, and in stem-cell derived cardiac myocytes [4,24–27].

Under normal conditions, different types of cardiac cells exhibit different types of TT network structures, which may reflect their fitness for E-C coupling and signaling in the heart. For example, the main role of a P-cell is to facilitate fast conduction, and thus lacking a TT network is an advantage since a smaller membrane capacitance or surface-to-volume ratio results in a faster conduction. On the other hand, the main

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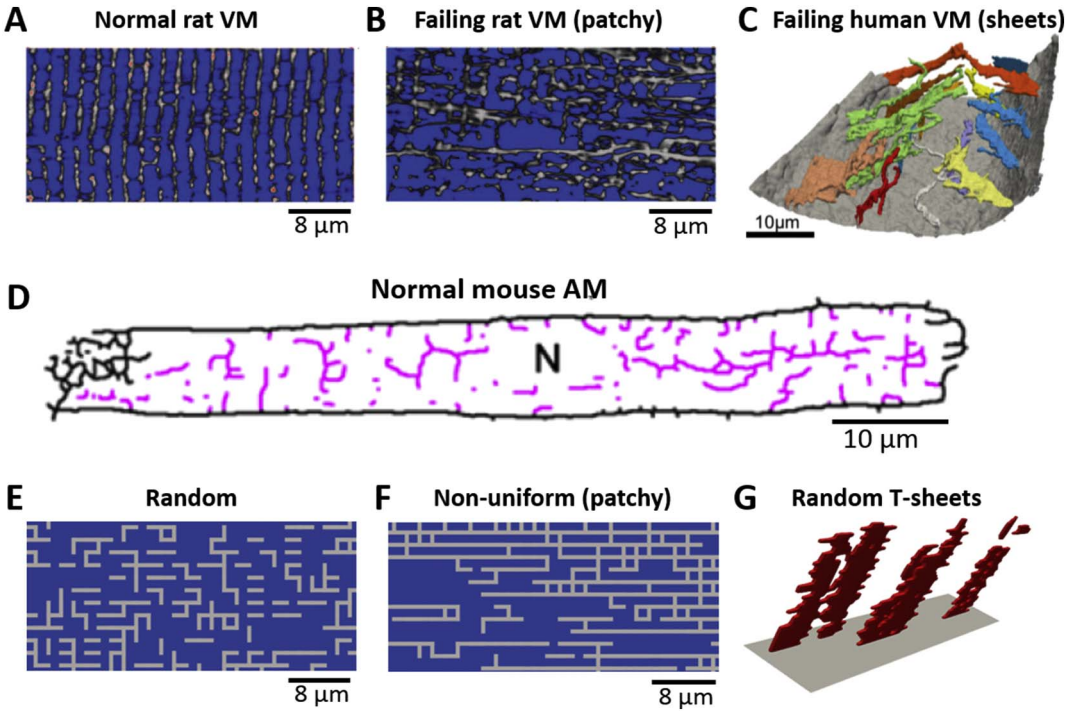

Fig. 1. TT network structures observed in VMs and AMs and computer generated TT network structures. A. TT network structure in a normal rat VM (Song et al. [2]). B. TT network in a failing rat VM (Song et al. [2]). C. Sheet-like TT structure in a failing human VM (Seidel et al. [15]). D. TT network in a normal mouse AM (Brandenburg et al. [3]). E. A computer generated uniformly random TT network. F. A computer generated non-uniformly random TT network (AT-to-TT ratio = ~3). G. A computer generated sheet-like TT structure.

role of a VM is to facilitate robust contraction, and a dense TT network is needed for synchronous calcium (Ca^{2+}) release. If the TT network is uniformly dense, the efficacy of E-C coupling and signaling does not depend on cell size since the Ca^{2+}-dependent ion channels, such as L-type Ca^{2+} channels (LCCs) and Na^{+}-Ca^{2+} exchange (NCX), are distributed everywhere inside cells. However, when the TT network becomes sparse and heterogeneous, the efficacy will depend on cell size. For example, in the absence of a TT network, a smaller cell can have a better E-C coupling efficacy since it is easier for the LCCs on the sarcolemmal membrane to trigger a more synchronous whole-cell Ca^{2+} release. The TT network structure may also correlate with RyR cluster density (or spacing) in a cell since ryanodine receptor (RyR) clusters tend to colocalize with LCC clusters. For example, the average RyR cluster distance in normal VMs is larger than in AMs [28], and much larger than in sino-atrial nodal (SAN) cells [29]. A closer RyR cluster spacing promotes Ca^{2+} waves and Ca^{2+} oscillations [29–32], which facilitates Ca^{2+} clocks for normal SAN function but is arrhythmogenic in VMs. While different TT network structures may be optimized for their needs in normal cardiac functions, these differences may also predispose the cardiac cells differently to arrhythmogenesis under cardiac diseases. Moreover, remodeling of the TT network in cardiac diseases may further potentiate arrhythmogenesis, such as TT disruption in heart failure promoting intracellular Ca^{2+} alternans [33]. However, the roles of TT network structures and the underlying arrhythmogenic mechanisms remain to be elucidated [34].

In this study, we investigate the roles of TT network structures in the genesis of intracellular Ca^{2+} alternans and Ca^{2+}-wave mediated triggered activity (TA) using computational modeling. A three-dimensional (3D) cell model consisting of a network of Ca^{2+} release units (CRUs) was used [35–37]. Different TT network structures were simulated, including uniformly random structures (Fig. 1E), patchy structures (Fig. 1F), hollow structures (Figs. 4B and S3), and sheet-like structures (Fig. 1G). A CRU that does not associate with a TT (and thus without a LCC cluster) is called an orphaned CRU (OCRU) [2]. We showed that both Ca^{2+} alternans and Ca^{2+} wave-mediated TA were promoted when the fraction of OCRUs was in an intermediate range, but suppressed in cells with well-organized TT networks (low OCRU ratios) or low TT densities (high OCRU ratios). Ca^{2+} alternans and TA could be promoted by low TT densities when the cells are small or the CRU coupling is strong. Both alternans and TA occurred more easily in uniformly random than in non-uniformly random TT networks under the same OCRU ratio. Subcellular spatially discordant Ca^{2+} alternans was promoted by non-uniform TT networks but suppressed by increasing CRU coupling strength. These mechanistic insights provide a holistic understanding of how TT networks affect the susceptibility to arrhythmogenesis.

2. Methods

2.1. Cell model

The cell model consisted of an action potential (AP) model with detailed spatiotemporal Ca^{2+} cycling described by a 3D network of CRUs, which was detailed in our previous studies [35–37] and briefly described in *Supplemental Information*. The parameter changes used to induce Ca^{2+} alternans and TA were shown in Tables S1 and S2, respectively. The control size of the cell was $L_x \times L_y \times L_z = 64 \times 32 \times 16$ CRUs. We used $L_x = 64$ CRUs and $L_y = 32$ CRUs but varied L_z to study the effects of cell size. The LCC cluster size, i.e., the number of LCCs (n_{LCC}) in each CRU, was 6, but was varied to investigate the effects of LCC cluster size on alternans and TA.

2.2. TT network model

The main role of the TT network in a cardiac cell is to allow ion channels to distribute spatially inside the cell volume. Since our focus in this study was Ca^{2+} cycling dynamics, we distributed the LCC clusters and NCX (or LCC-NCX clusters) spatially according to the TT network structure. That is, whenever a CRU is associated with a sarcolemmal or tubular membrane, it has a LCC-NCX cluster. A CRU without a LCC-NCX cluster is called an OCRU [2]. The CRUs in the outermost layer which are proximal to the sarcolemmal membrane were always coupled to