Mapping the Heart

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Some of the receptors on the surface of cardiac muscle cells (cardiomyocytes) mediate the response of these cells to catecholamines by causing the production of the common second messenger cyclic adenosine monophosphate (cAMP). An example of such receptors are the \( \beta_1 \)- and \( \beta_2 \)-adrenergic receptors (\( \beta \)ARs) that are heterotrimeric guanine nucleotide-binding protein (G protein)-coupled receptors. Selective stimulation of these two receptor subtypes leads to distinct physiological and pathophysiological responses, but their precise location on the surface of cardiomyocytes has not been correlated with these responses. In an ingenious combination of techniques, Viacheslav Nikolaev, Alexey Moshkov, Alexander Lyon, Michele Miragoli, Pavel Novak, Helen Paur, Martin Lohse, Yuri Korchev, Sian Harding, and Julia Gorelik have mapped the function of these receptors for the first time [1]. (See Figure 1.)

The key was to combine a fluorescence resonance energy transfer (FRET)-based cAMP sensor with scanning ion conductance microscopy (SICM). The FRET sensor gave functional data that was correlated spatially with SICM. SICM is a specialized version of scanning probe microscopy in which a nano-pipette is used to visualize the three-dimensional surface topography of living cells. The resolution is equal to the inner diameter of the pipette (in the range of 50 to 100 nm). Nikolaev et al. imaged structural features of cardiomyocytes such as Z-grooves, cell crests located between the grooves, and the opening of transverse (T)-tubules on the surface; they correlated...
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Next, Nikolaev et al. studied whether βAR localization was altered in a rat model of chronic heart failure induced by myocardial infarction. Extensive experiments suggested that the redistribution of the β2AR-cAMP from the T-tubules to the cell crest in failing cardiomyocytes results in uncoupling of the β2ARs from the normal compartmentation of β2AR-cAMP signaling. Thus, in failing cells, activation of the β2ARs leads to cell-wide cAMP signal propagation patterns similar to the patterns observed for the β1ARs. Thereby the normally cardioprotective properties of the β2AR response may acquire characteristics of the β1AR response, contributing to the heart failure phenotype.

Nikolaev et al. have combined two techniques to functionally localize β1- and β2ARs on cardiomyocytes and reveal mechanisms leading to abnormal cAMP compartmentation in heart failure. These findings provide a deeper understanding of this common cardiac disease and facilitate the development of new therapeutic strategies. Furthermore, they have demonstrated the usefulness of combining techniques that provide both functional and spatial information that can have significant biological and clinical implications [2].

References


[2] The author gratefully acknowledges Dr. Julia Gorelik for reviewing this article.

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