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A Concept of a Nonneuronal Cardiac Cholinergic System

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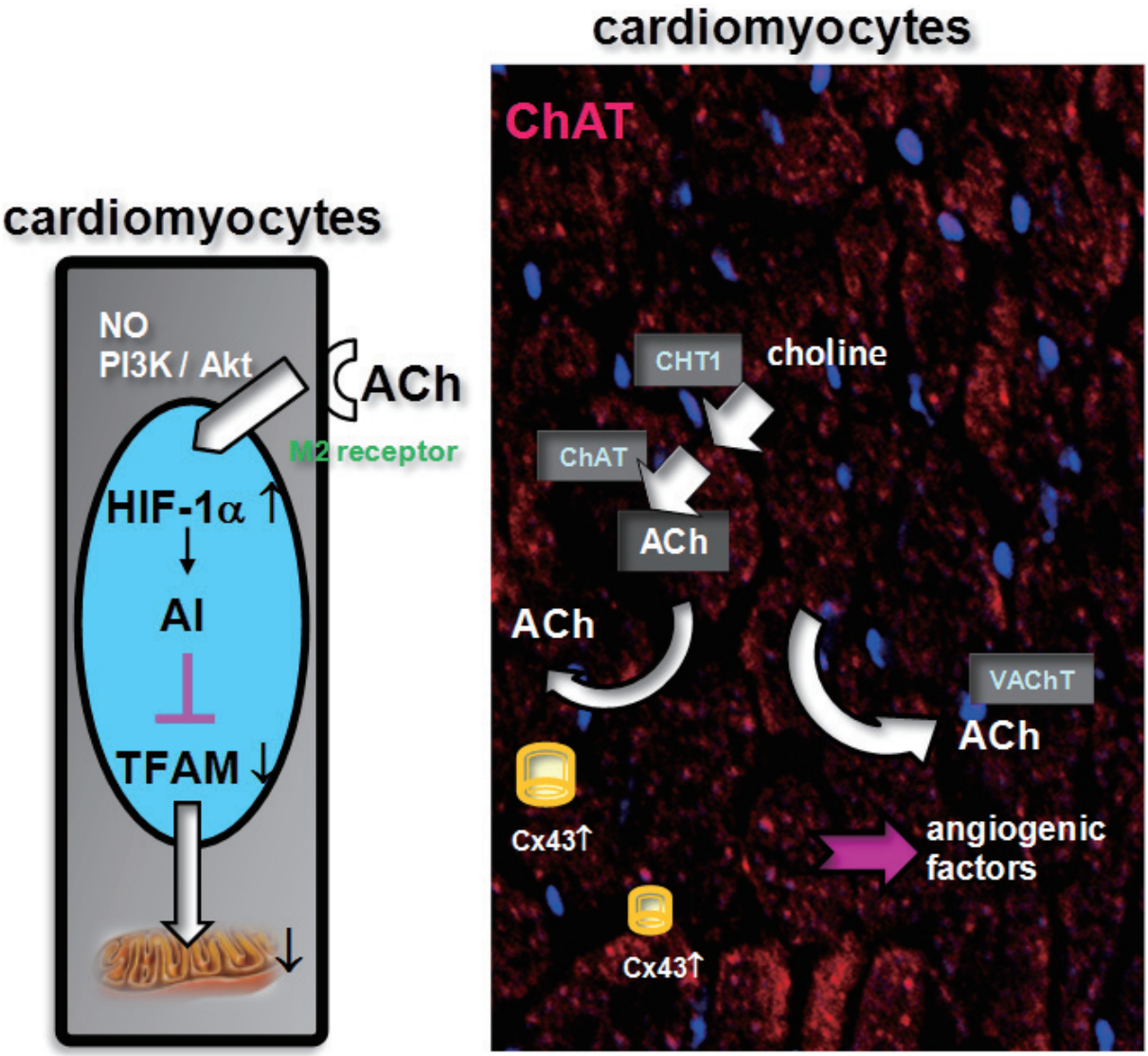

Fig. 1

The cholinergic system has been recently recognized to be composed of both a classical cholinergic system and a nonneuronal cholinergic system. The nonneuronal cholinergic system, in which cells can synthesize acetylcholine to regulate neighboring cells in autocrine fashion or paracrine fashion or both, has been reported to play crucial roles in modulating locally tissue-specific physiological functions[1]. On the basis of several cell types already reported to express system components, we have also recently identified cardiomyocytes as possessing this system[2]**(Fig. 1)**. The predicted functions of this system in cardiomyocytes are as follows. 1) The

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system is indispensable for maintaining the structure of the gap junction[3]. 2) This system negatively regulates cellular metabolism, resulting in sustaining ATP contents through the suppression of consumption[2,3], 3) This system enhances glucose uptake into cells, leading to efficient glucose metabolism and resistance to a poor nutritional environment[4], 4) This system is involved in acceleration of angiogenesis targeting vascular endothelial cells and skeletal satellite cells[5,6]. 5) This system salvages cardiac function during ischemia and the recovery phase[7]. We are now investigating 1) an interventional modality to activate this system with drugs or physiotherapy and 2) sex differences in regulation of this system, especially in the female heart, which predominantly activates this system.

Conflict of Interest: The author declares that there is no conflict of interest.

Fig. 1 Images of the nonneuronal cardiac cholinergic system The right panel shows a transverse section of the murine heart expressing choline acetyltransferase (ChAT) immunoreactivities (red dots). Each cardiomyocyte synthesizes acetylcholine (ACh) with intrinsic ChAT and incorporated choline through a choline transporter (CHT1). Synthesized ACh is stored in vesicular ACh transporter (VAChT), partly secreted into the extracellular space in a nonquantal manner, and plays its specific role in neighboring cells in a paracrine fashion. The system is responsible for maintaining connexin 43 (Cx43) protein, expression of angiogenic factors through hypoxia-inducible factor (HIF) 1α, and negatively regulating mitochondrial function through apoptosis inhibitor (AI)-induced downregulation of mitochondrial transcription factor A (TFAM).

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