Abstract: 2S

Acetylation of myofilament proteins modulate diastolic function

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Diastolic function of the heart is impaired with age. While these age-related changes are multi-factorial, studies have demonstrated that diastolic dysfunction due to various etiologies is associated with prolonged sarcomeric relaxation. We hypothesize that differential post-translational modifications of the sarcomeric proteins contribute to altered sarcomeric function and thereby contribute to diastolic dysfunction. Seminal studies have unequivocally demonstrated that phosphorylation of specific residues of sarcomeric proteins induce functional modifications. Phosphorylation is well known to occur in response to stimuli leading to dynamic functional changes. Less is known about regulation of sarcomeric function through acetylation. Work by Jeong et al demonstrated for the first time that increasing acetylation using an acetyltransferase decreased the duration of sarcomeric relaxation. Moreover, aged female mice demonstrate prolonged sarcomere relaxation that is rescued by treatment with a histone deacetylase inhibitor. It is becoming clear that acetylation modifications of sarcomeric proteins impact function. The goal of these studies is to understand regulation of sarcomeric acetylation and how specific sarcomeric protein function is impacted by acetylation of individual proteins.

Based on the fact that ex vivo acetylation of myofibrils with p300 decreases the duration of relaxation, we hypothesized that relaxation of myofibrils isolated from mice lacking histone deacetylase 6 (HDAC6) would have faster relaxation. However, we found that rather than altering relaxation, lack of HDAC6 increased myofibril passive stiffness. This was recapitulated in isolated rat ventricular myocytes treated with a specific HDAC6 inhibitor. Conversely, HDAC6 overexpression in ventricular myocytes and ex vivo treatment of myofibrils with recombinant HDAC6 decreased passive stiffness. HDAC6 modulation of passive stiffness was attenuated in mice lacking PEVK region of titin. Moreover, HDAC6 colocalizes at the z-disc and several sarcomeric proteins are deacetylated by HDAC6. These findings suggest that reversible acetylation regulates titin compliance and reveals a novel role for HDAC6 in regulation of sarcomeric function.

In line with our previous work demonstrating that acetylation of a single lysine residue of cardiac troponin I leads to faster relaxation and decreased calcium sensitivity and differential functional responses to selective inhibition of various HDACs, it is clear that acetylation is an emerging modification that can regulate myofilament function. Our preliminary data suggest that aging hearts may have decreased acetylation at specific lysine residues and that this may be regulated in a sex-dependent mechanism. These studies suggest that differential acetylation of sarcomeric proteins may contribute to dysfunction associated with aging. Importantly these findings indicate that regulating acetylation may be potential unique intervention to influence myofilament function.