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RESEARCH NEWS

cMyBPC phosphorylation alters response to heart failure drug

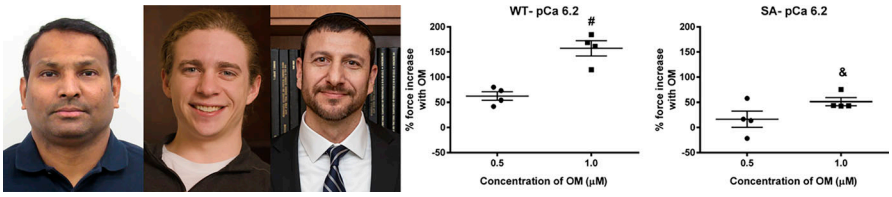
Ben Short

***JGP* study shows that the phosphorylation state of cMyBPC modulates the ability of omecamtiv mecarbil to enhance myocardial force generation.**

The small molecule omecamtiv mecarbil (OM) is a cardiac-specific myosin activator that is currently undergoing clinical trials for the treatment of heart failure with reduced ejection fraction. In this issue of *JGP*, Mamidi et al. demonstrate that OM's ability to increase cardiac force production is altered by the phosphorylation state of cardiac myosin-binding protein C (cMyBPC), a target of β-adrenergic signaling that is often dysregulated in late-stage heart failure patients (1).

OM enhances myocardial force generation by increasing the number of strongly bound myosin cross-bridges (2), partly by slowing ADP release and cross-bridge detachment (3). Though the drug has progressed to phase 3 clinical trials, little is known about how its effects may be influenced by pathophysiological changes in other sarcomeric proteins, such as cMyBPC, that regulate myosin cross-bridges and force production.

During exercise or other physiological stresses, adrenaline stimulates the phosphorylation of cMyBPC by PKA, thereby accelerating cross-bridge kinetics and myocardial contractility to meet the increased demand for cardiac output (4). In late-stage heart failure patients, however, β-adrenergic signaling is dysregulated and cMyBPC phosphorylation is greatly reduced. "We wanted to test how the phosphorylation state of cMyBPC would effect OM treatment," explains Julian Stelzer, a professor at Case Western Reserve University.



(Left to right) Ranganath Mamidi, Joshua Holmes, Julian Stelzer, and colleagues reveal that the effects of the heart failure drug OM are modulated by the phosphorylation state of the contractile protein cMyBPC. For example, OM's ability to increase force generation is significantly blunted in mouse myocardial preparations expressing phosphoablated (SA) rather than WT cMyBPC due to changes in myosin cross-bridge kinetics.

Stelzer's team, including cofirst authors Ranganath Mamidi and Joshua Holmes, prepared myocardial tissue from both WT mice and mice expressing a cMyBPC mutant that lacks the three main PKA phosphorylation sites. The researchers treated the preparations with OM and found that the ablation of cMyBPC phosphorylation significantly blunted OM's ability to increase force production (1).

Dephosphorylated cMyBPC is thought to stabilize the super-relaxed state of myosin, in which the head domains are folded back toward the filament backbone and are less available to form active cross-bridges (5). Stelzer and colleagues have previously shown that ablating cMyBPC phosphorylation slows cross-bridge kinetics (6).

"This is exacerbated by the addition of OM," Stelzer says. "It creates an even slower system that limits cross-bridge recruitment, and those that are recruited can't really be detached." This may reduce the effectiveness of OM in end-stage heart failure patients with low levels of cMyBPC phosphorylation.

In contrast, phosphorylation of cMyBPC by PKA usually accelerates myosin cross-bridge kinetics. However, when Stelzer and colleagues treated their myocardial preparations with both PKA and OM, mimicking the scenario of an early-stage heart failure patient exercising or experiencing stress, the effects of the drug dominated the effects of the kinase.

"OM did not allow any acceleration and, in fact, slowed cross-bridge kinetics even further, completely negating the effect of PKA on contractility," Stelzer says. This could mean that early-stage patients on OM are unable to increase their cardiac output during exercise, elevating the risk of ischemia.

New iterations of OM are already being explored as potential next-generation treatments for heart failure. Stelzer says that it will be important to investigate how

bshort@rockefeller.edu

This work is part of a special collection on myofilament function and disease.

these drugs interact with cMyBPC and other components of the contractile machinery. In the meantime, Stelzer's laboratory is focused on developing novel therapeutic approaches involving the direct manipulation of cMyBPC phosphorylation.

References

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