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TRANSLATIONAL PERSPECTIVES

When fat meets the engine: implications of dietary rumenic acid on myosin-targeting therapies in heart failure

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Acute heart failure is associated with high morbidity and mortality, along with an increasing incidence of hospital admission worldwide. Traditional therapeutic agents, including phosphodiesterase inhibitors and/or catecholamines, acutely improve myocardial function but at the expense of increases in cardiac oxygen utilization and predisposition to life-threatening arrhythmias via alterations of cellular calcium (Maack *et al.* 2018). Recent treatment strategies via myosin modulation, such as the selective myosin effector omecamtiv mecarbil (Morgan *et al.* 2010), efficiently increase contractile function without impacting upon cellular calcium dynamics or activation of the adrenergic system. In genetic cardiomyopathies, such as hypertrophic cardiomyopathy (HCM), a disease characterized by hypercontractility and myocardial energetic depletion, viable treatment strategies are still lacking. While metabolic drugs, including perhexiline, have been shown to modestly improve the symptoms of patients, those agents are characterized by a pleiotropic action (George *et al.* 2016). The small-molecule myosin deactivator mavacamten reverses the hypercontractility, maladaptive cardiac remodelling, myofibrillar disarray and fibrosis in a mouse model of HCM (Green *et al.* 2016). Because of their selective binding to myosin, myosin-targeting agents may evolve as promising alternatives for treatment of cardiomyopathy and heart failure patients.

In this issue of *The Journal of Physiology*, Pertici and co-workers investigated the impact of the trans fat rumenic acid on actomyosin function (Pertici *et al.* 2021). Low-load experiments with reconstituted motility assays show that rumenic acid (1) increases myosin release rates of phosphate and (2) calcium-sensitivity. Under loaded conditions in demembranated rat trabeculae, rumenic acid (3) decreased force generation. The authors identified similar modulation by rumenic acid on non-muscle myosin, while skeletal and smooth muscle myosin activity was unaffected. Using *in silico* modelling, Pertici and co-workers estimated that rumenic acid binding to cardiac myosin occurs in an allosteric pocket formed by residues from the upper and lower 50K domains and the converter region (Pertici *et al.* 2021). The findings are important for two reasons: (a) mechanistically, this study validates this region of myosin as the hot-spot for *de novo* design of small-molecule therapeutics (e.g. mavacamten, omecamtiv mercabil, etc.), but (b) secondly, and perhaps the most important, Pertici *et al.* speculate that physiological concentrations of rumenic acid ($\leq$5 μM) are likely sufficient to compete against pharmacological myosin modulators for the binding to cardiac myosin (Pertici *et al.* 2021). Hence, the overall success of any future clinical trial using small-molecule myosin modulators will require the close monitoring of dietary intake of rumenic acids (and potentially other acids) of participants during test trials.

Naturally produced trans fats are produced in the rumen of ruminants (biohydrogenation) and are chemically characterized by having the trans double bond typically positioned at the delta (Δ)-11 position (e.g. rumenic acid [C18:2 cis9, trans11]). Natural trans fats differ considerably from their artificial counterparts, which are industrially produced (from partial hydrogenation of vegetable fat), in that industrial-derived trans-fatty acids have their double bonds in the Δ-8,-9/-10,-ll/ and -12 positions (Gunstone, Harwood, & Dijkstra 2007). Past studies showed the trans -9 and -10 positions to be notoriously damaging to the human body, since they appear unable to undergo proper β-oxidation (likely caused by the artificial double bond positioning, a requirement to be recognized by mitochondrial desaturase enzymes). Dietary intake of industrially produced trans fats associates well with several cardiovascular risk factors and comorbidities. However, mechanistic research and information regarding trans-fatty acids produced from natural origin is still lacking. The study from Pertici and co-workers is the first to indicate that physiological concentrations of rumenic acid are sufficient to interfere with cardiac myosin, thereby reducing cellular force generation, and potentially myocardial function (Pertici *et al.* 2021).

During myofilament contraction, myosin transits between three functional states. The (1) actin-bound state, which has a rapid ATP turnover, and two unbound states with very low ATP turnover: (2) the disorder relaxed state (DRX) with about 100-fold less activity than the actin-bound state, and (3) the super-relaxed state (SRX), which exhibits an additional 10-fold decrease in activity compared with the DRX state (Anderson *et al.* 2018). Actin-free myosin motors are in a dynamic DRX:SRX state equilibrium with up to 60% of myosin heads held 'in reserve' in the energy-conserving SRX state. Destabilization of the SRX state and with it increased ATP turnover has been proposed to be causative of HCM. The latter is supported by the positive effects of mavacamten to reverse the HCM phenotype due to its primary effects in stabilizing the SRX state with consequent reduction in energetic load on the myocardium (Anderson *et al.* 2018). Less clear at this point is the mode of action of omecamtiv mecarbil on cardiac myosin. Although commonly described as a myosin activator that acts by increasing the fraction of actin-bound myosin motors with rapid ATP turnover, omecamtiv mecarbil inhibits basal ATP turnover of myosin as well (Malik *et al.* 2011). In combination with X-ray crystallographic data (Planelles-Herrero *et al.* 2017), this provides support for the concept that omecamtiv mecarbil can additionally stabilize an SRX-like state of myosin (Anderson *et al.* 2018). Notably, Pertici *et al.* show that rumenic acid, like mavacamten and omecamtiv, binds to the same region of the myosin motor

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domain thereby modulating the DRX:SRX equilibrium. The authors demonstrate enhanced activation of the DRX state in the presence of physiological concentrations of rumenic acid, indicative for an increase in energetic strain on the myocardium (Pertici *et al*. 2021).

Some questions do remain from the study. Molecular docking experiments estimated that rumenic acid binding occurs at the same region of the myosin motor domain where omecamtiv mecarbil (and mavacamten) interact although this point remains untested. Ideally, future studies should describe the effects of rumenic acid, combined with omecamtiv mecarbil and/or mavacamten, under unloaded and/or loaded conditions. Such studies would provide the valuable mechanistic information required to further develop myosin modulators, and their effects on the DRX:SRX state equilibrium, as a viable therapeutic option for heart failure and genetic cardiomyopathies alike.

In conclusion, this comprehensive landmark study by Pertici and colleagues tackles the important question of how dietary intake of rumenic acid likely impacts myocardial function via modulation of cardiac myosin (Pertici *et al*. 2021). The novel findings of this study pave the way for further preclinical work aiming to translate these insights into much-needed therapeutic strategies.

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Additional information

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