reduced infarct size in ischaemic rat hearts, confirming that chloramphenicol acts predominantly through CYPs in this model.

Perhaps the most significant finding of the study was that both chloramphenicol and sulphaphenazole protect heart tissue when administered after — as well as before — blood flow is interrupted. This experimental paradigm more accurately reflects the clinical situation of patients presenting to hospital after suffering a heart attack. As such, these data provide hope that exploitation of the CYP-inhibitory activity of various approved agents — such as some members of the statin family of cholesterol-lowering drugs — might improve treatment outcome for the millions of people that live through this devastating experience each year.

Suzanne Farley

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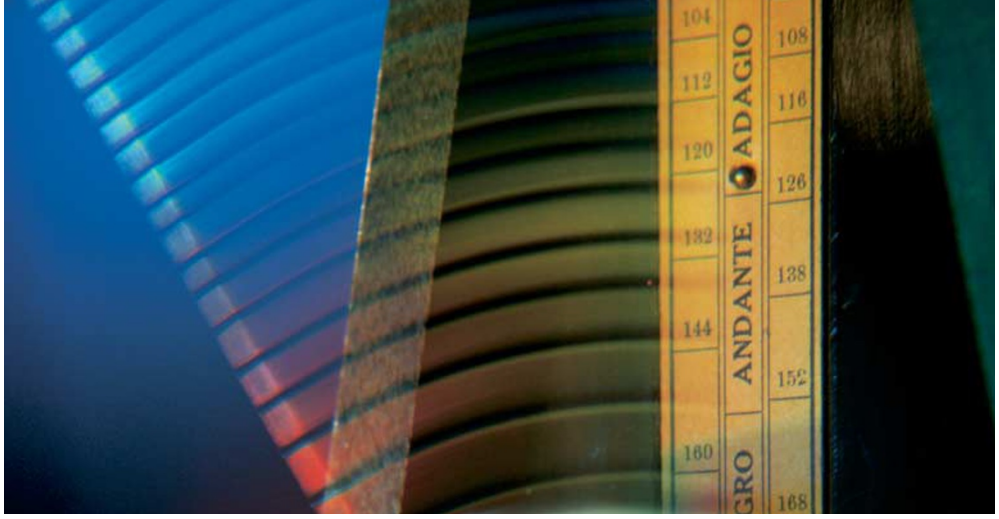

TARGET VALIDATION

Regulating the beat

Heart disease is the leading cause of death in industrialized nations and is characterized by diverse cellular abnormalities associated with decreased ventricular function. In the March issue of *Nature Medicine*, Jeffery Molkentin and colleagues report a new strategy to treat heart disease by inhibiting the enzyme protein kinase C-α (PKC-α). The authors' findings help to explain the mechanisms behind heart muscle contraction, and indicate that PKC-α could be a pharmacological target for treating human heart failure.

At the onset of many forms of heart disease, cardiac hypertrophy (excessive cellular growth) and ventricular remodelling (changes in wall thickness and/or chamber volume) occur as a compensatory response to maintain cardiac output. These changes eventually lead to increases in oxygen consumption, greater vascular resistance, chamber dilation, wall stiffening and fibrosis, which ultimately impair the ability of the ventricles to pump blood and lead to overt failure. The hypertrophic response results from growth of the contractile cells, called cardiomyocytes, and is associated with changes in gene expression, including elevated PKC-α expression. During heart failure, contractility is also compromised by a deficiency in the release and uptake of calcium ions within the myocytes themselves. The PKC family comprises at least twelve serine/threonine kinases that form three sub-groups on the basis of sensitivity to calcium and lipids. The functions of many individual PKC isoforms are still obscure, especially that of PKC-α, which is the dominant isoform expressed in the heart.

Myocyte contraction and relaxation are directly regulated by intracellular calcium cycling. Calcium ions enter through the voltage-dependent sarcolemma membrane, which induces the release of a large amount of calcium from the sarcoplasmic reticulum (SR) storage compartment through the ryanodine receptor. Myocyte relaxation is initiated by sequestration of calcium back into the SR through the activity of the SR/ER calcium pump (SERCA2). Signalling from β-adrenoceptors controls the magnitude and timing of calcium release through effects that impact SERCA2 function, as well as other calcium-handling proteins.

Molkentin and colleagues show that PKC-α directly controls the activity of those key enzymes that regulate heart muscle contraction. Mechanistically, modulation of PKC-α activity affects dephosphorylation of the SERCA2 inhibitory protein phospholamban and affects both SR calcium loading and the magnitude of subsequent calcium release. The authors used three mouse models of heart disease to show that deleting the gene that encodes PKC-α from the diseased heart improves its function. In two of the models, the technique helped the mice survive longer.

Antagonizing PKC-α should enhance the calcium signalling response and therefore increase the force of contraction of the myocardium. However, current classes of inotropic drugs that augment calcium cycling, such as β-adrenoceptor antagonists or phosphodiesterase inhibitors, have shown adverse outcomes in clinical trials. However, PKC-α functions downstream from the action of classic inotropic agents, and might therefore be less problematic and offer new hope for treating heart failure; kinases are attractive therapeutic targets because of their central role in cellular signalling and have now become the second most important group of drug targets, after G-protein-coupled receptors.

Melanie Brazil

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