ment of cofactors and regulatory molecules, such as FKBP12.6 (also known as calstabin-2). Binding of FKBP12.6 to each RyR2 monomer in the normal heart is thought to prevent channel leakiness by maintaining a specific conformation of the RyR2 complex. But in heart failure, PKA-mediated phosphorylation promotes loss of FKBP12.6 and enhances leakiness through an altered RyR2 conformation (**Fig. 1b**). In this manner, loss of FKBP12.6 from the complex leads to calcium leak during relaxation, leading to depletion of sarcoplasmic reticulum calcium content—less contractility—and greater propensity for arrhythmias. Previously, increased phosphorylation of the RyR2 monomers was attributed to reduced phosphatase association with the RyR2 complex[4].

The hypothesis proposed by Marks and colleagues has been challenged by others, and has raised unresolved issues. For example, others have not identified an increase in phosphorylation of RyR2 in animal models of heart failure, a dissociation of FKBP12.6 after RyR2 phosphorylation or an increase in calcium leak after phosphorylation of RyR2 (refs. 6–9). Moreover, heart failure is generally associated with a decline in responsiveness of β-adrenergic receptors and desensitization by PKA-mediated phoshorylation, as well as a general increase in phosphatase activity in the heart. Thus, the reported increase in phosphorylation of RyR2 by PKA during heart failure was counterintuitive.

The new study, however, addresses one significant aspect of the controversy[3]. Marks and colleagues showed that the local concentration of cAMP in the region between the L-type calcium channel and RyR2 complex is controlled by phosphodiesterase 4D (PDE4D), which is anchored to the RyR2 complex. In heart failure, reduced levels of PDE4D permitted a local rise in cAMP and increased PKA activity, leading to hyperphosphorylation of RyR2 (**Fig. 1b**).

In mice, disruption of the gene encoding PDE4D increased levels of localized cAMP, increased phosphorylation of RyR2 and decreased interaction of FKBP12.6 with RyR2 (ref. 3). These mice also had increased arrhythmias and sensitivity to heart failure. More provocatively, genetic inhibition of RyR2 phosphorylation prevented loss of FKBP12.6, reduced heart failure and decreased arrhythmias in mice lacking the gene encoding PDE4D after myocardial infarction.

Thus, the recent report by Marks and colleagues suggests that local control of cAMP levels is a primary determinant of RyR2 calcium leak, progression of heart failure and arrhythmia. Reduced activity of PDE4D and increased phosphorylation of RyR2 during heart failure probably predisposes an individual to disease.

These results have two medical ramifications: PDE4D-inhibitory drugs might predispose an individual to arrhythmia and increase the risk for developing heart failure; and heart failure may be alleviated by selective activation of PDE4D using pharmacologic agonists. Alternatively, other therapeutic approaches are plausible, like a gene therapy strategy to increase local PDE4D activity or pharmacologic strategies that antagonize local PKA activity or enhance FKBP12.6 interaction with the RyR2 complex.

Although some issues remain unresolved, Marks and colleagues have further strengthened the hypothesis that RyR2 leakiness contributes to progression of heart failure and arrhythmia, suggesting the importance of correcting this molecular defect through therapeutic strategies.

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Wasting away

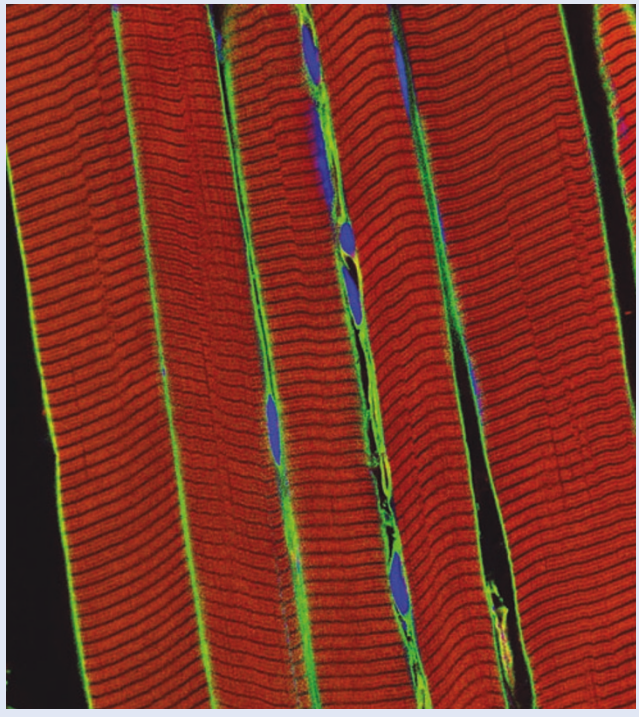
Skeletal muscle wasting, or cachexia, contributes to death in one-third of all cancer patients, but what triggers the muscle wasting is still a mystery. Swarnali Acharyya and colleagues (*Cancer Cell* **8**, 421–432) now show that one of the players in muscular dystrophy, the dystrophin glycoprotein complex (DGC), has a crucial role in cancer cachexia.

This complex forms a bridge between the cytoskeleton and the extracellular matrix to protect muscle cells from injury when they contract. The researchers found that tumor-bearing mice that show muscle wasting also had wrinkled and possibly leaky muscle cell membranes. This phenotype is similar to what has been seen in muscular dystrophy. Normal muscle cells, as shown here, have smooth membranes (laminin, extracellular matrix component, in green; actin in red, DNA in blue).

What's more, key components of the DGC were abnormally modified or their levels reduced in muscle fibers of tumor-bearing mice—affecting the function of the complex. Increasing dystrophin expression in the mouse skeletal muscle could prevent wasting in the tumor model.

The findings may be relevant to humans, as a similar pattern of DGC dysregulation was observed in people with gastrointestinal cancer. Whether the dysregulation occurs as a cause or effect of this wasting is unclear, but it points to a new direction for therapy.

Alison Farrell



Courtesy of Thomas Deerinck and Mark Ellisman.