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ity (14). As water uptake rates are higher in expanding cells, differential access to water along the root circumference may generate sizable differences in water potential. Yet, experimentally demonstrating the existence of such gradients at this scale is very challenging. More research is necessary to uncover how root cells sense water potentials and how signals detected in outer cells are transmitted to inner root tissue. Interestingly, Orosa-Puente *et al.* observed that ARF7 SUMOylation occurs when roots are exposed to air, even though they have been unable to demonstrate if ARF7 is differentially SUMOylated in a root exposed to an air-water interface. Nonetheless, this finding suggests that the absence of water on its own serves as an informative cue for developmental decisions without depending on changes in cellular osmolarity.

Because water is such a critical resource for plant growth and development, it is not surprising that plants have evolved additional adaptive mechanisms. Although hydropatterning can increase root surface contact with water, the steering of growth direction by hydrotropism places this organ in water-available sites. Thus, if lateral roots primed by hydropatterning emerge at sites that become dry, hydrotropic growth allows them to maneuver toward water.

Considering the strong negative impact of precipitation variability on crop yield (15), breeding crops with a predefined root system architecture may be less appropriate than exploiting plasticity and sensing mechanisms to improve root adaptability to spatial and temporal variations of soil moisture. In this context, it will be interesting to determine the contribution of hydropatterning to water and nutrient uptake under challenging water regimes and to investigate how water and nutrient signals are integrated to shape root system architecture. Thus, manipulating the molecular mechanism uncovered by Orosa-Puente *et al.* and tapping into possible natural allelic variation for hydropatterning have potential for breeding crops that are better able to withstand environmental stresses. ■

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CARDIOLOGY

Unusual transcription factor protects against heart failure

Cleaved fragment of a cardiomyocyte structural protein moonlights as a transcription factor

By Arun Padmanabhan^{1,2} and Saptarsi M. Haldar^{1,2,3}

The heart pumps blood to the rest of the body in a coordinated and steadfast manner. This pumping function is achieved through synchronous contraction of billions of cardiomyocytes (heart muscle cells), which is governed by phasic increases in intracellular calcium. As such, cardiomyocytes have evolved intricate cellular structures that tightly couple external electrical impulses to the triggering of calcium ion release from intracellular stores and subsequent activation of force-producing proteins, a process termed excitation-contraction (E-C) coupling. A key component of this molecular ultrastructure is the cardiac dyad, a microdomain that juxtaposes the plasma membrane L-type calcium channel with the calcium-sensitive ryanodine receptor (RyR) channel complex, the molecular gatekeeper for the release of calcium ions from sarcoplasmic reticulum stores in cardiomyocytes. The cardiac dyad is physically stabilized by a membrane-associated scaffold protein called junctophilin-2 (JP2), which facilitates physiologic calcium release during E-C coupling. Excessive stress or injury to cardiomyocytes results in defective E-C coupling, reduced pumping capacity, and the clinical syndrome of heart failure, a leading cause of death worldwide. On page 1375 of this issue, Guo *et al.* (1) report the surprising discovery that during cardiac stress, a proteolytically cleaved fragment of JP2 can translocate to the cardiomyocyte nucleus and function as a transcription factor that can protect against heart failure pathogenesis. Thus, in addition to its “day job” as a structural protein, this suggest that JP2 can “moonlight” in the nucleus as part of a homeostatic feedback response to cardiac stress.

Heart failure, a syndrome in which pumping function cannot meet demand, is the final common clinical manifestation that results from diverse forms of cardiac injury, such as

excessive mechanical stress, myocardial infarction, or exposure to toxins. This condition is typified by progressive structural remodeling of the geometry of the heart, activation of inflammatory and profibrotic pathways, cardiomyocyte hypertrophy, and abnormalities in cellular calcium homeostasis, E-C coupling, metabolism, and gene expression. During heart failure pathogenesis, JP2 is proteolytically cleaved by a family of intracellular calcium-dependent proteases called calpains, an event that compromises JP2 function and impairs E-C coupling (2, 3). Mapping the precise cleavage site within JP2 revealed that this proteolytic event generated a novel N-terminal fragment, which the authors named JP2NT. It was initially thought that JP2NT was an inert by-product of the cleavage event and had no specific cellular function. However, Guo *et al.* found that JP2NT contains a functional nuclear localization sequence and a putative helix-turn-helix motif that confers DNA binding activity. These features suggested that JP2NT could function as a transcription factor that directly regulates cardiomyocyte gene expression.

Analyses of JP2NT-overexpressing cardiomyocytes revealed that JP2NT predominantly functions as a transcriptional repressor. JP2NT-repressed genes were enriched for those known to be activated in heart failure, including those that regulate cardiac hypertrophy, fibrosis, and inflammation. These unbiased analyses also revealed that JP2NT genomic binding sites strongly colocalized with binding sites for the MEF2 (myocyte enhancer factor 2) family of transcription factors, which are known drivers of heart failure pathogenesis (4, 5). The study of Guo *et al.* supports a model in which JP2NT inhibits transcriptional function of MEF2, possibly via competitive binding for MEF2 DNA response elements.

The ability of JP2NT to transcriptionally repress MEF2 activity and inhibit heart failure-associated gene programs suggests that JP2NT might play a protective role in heart failure pathogenesis. Indeed, mice overexpressing JP2NT that were subjected to a widely used model of cardiac pressure overload (6) had improved cardiac function and reduced indices of heart failure, whereas

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JP2NT functions as a cardiac transcription factor

Full-length JP2 is a scaffolding protein in cardiomyocytes that is essential for calcium homeostasis and E-C coupling. During cardiac stress, JP2 is proteolytically cleaved by calpain to release an N-terminal fragment (JP2NT), which translocates to the nucleus and functions as a transcription factor that represses MEF2 activity and protects against heart failure pathogenesis.

mice in which the JP2NT nuclear localization signal is ablated developed more severe heart failure. Together, these data support the idea that during cardiac stress, proteolytic release of JP2NT from the cardiac dyad in cardiomyocytes plays a protective role in heart failure pathogenesis, possibly by repressing MEF2 transcriptional activity (see the figure).

The paradigm that membrane-tethered precursor proteins can be proteolytically cleaved to unleash transcription factors is not new. Therefore, this newly discovered role for JP2NT must be considered alongside known cellular pathways that use this mechanism—for example, Notch signaling, the SREBP (sterol regulatory element-binding protein) pathway, and the ATF6 arm of the unfolded protein response. These examples share three notable features: a proximal physiological cue that triggers proteolysis, release of a cleaved fragment from its membrane-tethered parent protein, and a downstream transcriptional effector function that is homeostatically responsive to the proximal physiological cue. In canonical Notch signaling, plasma membrane Notch receptors are activated by cell-cell contact, prompting Notch receptor proteolysis and release of the Notch intracellular domain (NICD), which translocates into the nucleus and regulates expression of developmental gene programs that are appropriate for the type of cell contact (7, 8). In the SREBP pathway, the upstream cue is cholesterol deprivation, which

is sensed by the SREBP cleavage-activating protein complex in the endoplasmic reticulum, ultimately resulting in proteolytic release of SREBP transcription factors, which translocate to the nucleus to regulate gene programs that adapt to the low-cholesterol state (9, 10). In the third example, unfolded proteins in the endoplasmic reticulum lead to transport of ATF6 to the Golgi membrane, where it is cleaved by Golgi-associated proteases, releasing a transcription factor that regulates gene programs involved in alleviating the stress caused by unfolded proteins (11).

In these three examples, the proteolytic cleavage of the parent protein reflects the primary cellular function of the pathway. By contrast, full-length JP2 is a professional scaffolding protein for the cardiac dyad that moonlights as a transcription factor during cardiac stress. In that case, what is the true physiological role of the JP2 cleavage pathway? Because full-length JP2 is in the cardiac dyad, we postulate that its cleavage might be a physiological transducer of local calcium excess, mechanical stretch, or oxidative stress. Although the characterization of JP2NT-overexpressing mice by Guo *et al.* is an important first step, more detailed phenotyping of their mice harboring an ablated JP2 nuclear localization signal will be required to better understand the physiological function of JP2NT. Similarly, the generation of cells or mice in which the endogenous JP2 cleavage site or DNA binding domain is inactivated will be informative. A more precise understanding of how calpain family members, or other endogenous proteases, are activated and targeted to the dyad will also provide essential clues to the homeostatic role of this cleavage event. Additionally, it will be critical to delineate the full spectrum of endogenous JP2NT transcriptional targets and interaction partners, as JP2NT is likely to have effects beyond regulating MEF2 function. It will also be important to solve the structure of JP2NT to elucidate the biophysical basis for DNA binding. Following up on these exciting findings by Guo *et al.* is certain to uncover new mechanisms of cardiac homeostasis; such knowledge may be harnessed to create much-needed therapies for heart failure. ■

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ASTRONOMY

Escaping atmospheres of extrasolar planets

The study of helium absorption opens a new window on escaping exo-atmospheres

By Matteo Brogi

The atmospheres of planets orbiting other stars (exoplanets) are windows into their chemical composition and physical properties. For a planet that orbits closely to its star, the intense stellar irradiation can induce substantial atmospheric loss, a phenomenon that can be detected if the planet is transiting through an excess absorption of starlight by gas that is escaping the planet's atmosphere. On pages 1384 and 1388 of this issue, Allart *et al.* (1) and Nortmann *et al.* (2), respectively, report two independent measurements of planetary helium with remote, ground-based spectroscopy in the near-infrared. Their findings mark the first time that helium is detected from the ground and is unambiguously associated with the planet's orbital motion. The high spectral resolution of the observations allows direct tracking of helium's velocity and verifies that it trails the planet along its orbit.

The atmosphere of a close-in exoplanet can escape under the strong irradiation from the parent star (3, 4). For a giant planet, the total mass loss over the lifetime of the system is negligible. However, for a small exoplanet, the entire atmospheric envelope can be stripped off, and this phenomenon may produce a gap in the occurrence of the exoplanet as a function of its distance from the parent star (or radius of its orbit) (5, 6).

Most previous studies have focused on the detection of hydrogen escaping from exoplanets (7). Hydrogen is the most abundant chemical element in the Universe and it dominates the composition of giant

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