When the heart struggles to meet the body’s demand for blood supply, it adapts and grows—a condition known as cardiac hypertrophy. Such growth can occur as a healthy response to altered physiological states, such as pregnancy and regular aerobic exercise, or in response to pathological conditions, such as high blood pressure or heart muscle injury. If pathological conditions persist, hypertrophy can lead to functional degradation of the heart and, ultimately, to its failure.

Researchers strive to identify the molecular pathways that lead to physiological and pathological hypertrophy and to understand what causes hypertrophy to transition into life-threatening heart failure. This year has seen the emergence of a number of new molecular mediators and microRNAs as key regulators of pathways that lead to hypertrophy. These finding provide cardiologists with a choice selection of targets for future therapies. Here is our pick of the year’s articles.

**MicroRNA Mediators**

First discovered in the mid 1990s, microRNAs (miRs) are single-stranded RNA molecules of 18 to 25 nucleotides in length that regulate gene expression. In animals, miRs generally bind to complementary sequences in the 3’UTR of a target messenger RNA. This either prevents the transcript from being translated or causes its degradation.

In recent years, a number of miRs have been found to be involved in heart development and disease. The opening shot that launched heart-related miR research was fired by Eric Olson and colleagues in 2007. These investigators showed that cardiac-specific miR-208 (the gene for which resides within an intron of the α-myosin heavy chain gene) is required for myocyte hypertrophy and fibrosis. Maha Abdellatif (University of Medicine and Dentistry of New Jersey, Newark, NJ) describes how miR-208 and other miRs have provided a much-needed boost to the heart failure and hypertrophy field. “We had almost stagnated at some point with the signaling molecules and pathways that we had already known,” she says. “MicroRNAs came and opened a huge door.”

Spring 2009 saw the arrival of a fresh new miR on the heart failure scene: miR-1. In an article published in *Molecular and Cellular Biology* this April, William Pu (Children’s Hospital, Boston, MA) and his colleagues reported that miR-1, an abundant microRNA in the heart, was downregulated in a mouse model of heart failure. The finding prompted the team to investigate miR-1’s mechanism. They discovered that miR-1 targeted the transcripts of the calcium binding protein calmodulin and the transcription factor Mef2, both known mediators of cardiac hypertrophy.

Calcium is released in abundance in the cells of overworked hearts, and bound to calmodulin, it prompts the activation of downstream targets, such as Mef2 and other transcription factors. These transcription factors, in turn, activate genes involved in hypertrophy. That miR-1 directly negatively regulates two key components of the hypertrophy pathway makes it an attractive molecule for further investigation. Finding a means to boost miR-1’s expression might certainly be of therapeutic interest.

The question is, what are the upstream signals that cause miR-1 levels to drop when demands on the heart increase, and how might these signals be stopped? “What we are trying to do now is see where these microRNAs are fitting in the context of the existing pathways,” says Abdellatif.

Although the pathway is not completely worked out for miR-1, in the case of miR-23, another hypertrophy-associated miR, Pei-Feng Li (Chinese Academy of Sciences, Beijing, China) and colleagues have discovered precisely where it fits. The group reported in the *Proceedings of the National Academy of Sciences* in July that miR-23 (known to be prohypertrophic) was activated by the transcription factor NFAT, a major target of calcium/calmodulin signaling. MiR-23 itself targeted and prevented the translation of the mRNA for muscle-specific ring finger protein 1 (MuRF1), a known antihypertrophic factor. Thus, unlike with miR-1, inhibiting miR-23 would be the goal for future therapies.

“MiR-23/NFAT article is nice in the sense that it’s integrating the old with the new,” says Abdellatif.

Boosting miR-1 or inhibiting miR-23 may or may not be enough to halt hypertrophy. It all depends on how the molecular pathways fit together. In a *Journal of Clinical Investigation* article published this September, Callis et al. showed that simply increasing the expression of just 1 miR—miR-208a—was sufficient to cause hypertrophy and abnormal cardiac conduction. Thus, working out whether these miRs share upstream signaling pathways will be imperative for the development of successful therapies.

There is still much work to be done, but these reports and others are gradually placing the miR pieces into the cardiac pathway.
hypertrophy puzzle. As Abdellatif says, “We don’t know exactly how they fit in yet, but we know that they’re doing something critical!” That miRs are vital for the proper functioning of the heart is further underscored by a recent report in Circulation Research by Rao et al., which shows that genetically deleting an essential component of the machinery that generates miRs (dcr8) leads to ventricular malfunction, resulting ultimately in dilated cardiomyopathy and premature death.

Other Mediators
MiRs may have the limelight, but there have been a number of other molecular mediators of cardiac hypertrophy discovered this year that look set to shake up the stagnant signaling pathways.

Delvac Oceandy (University of Manchester, UK) and colleagues reported in Circulation this October that RASSF1A, an inhibitor of the small GTPase Ras, was downregulated in both mouse and human hypertrophic hearts. Ras has long been known to be activated by prohypertrophic stimuli and to induce hypertrophy when overexpressed. The team showed that a mouse knockout of RASSF1A enhanced cardiac hypertrophy, whereas RASSF1A overexpression was protective.7

Another small GTPase, Cdc42, in contrast to Ras, was shown recently to prevent cardiac hypertrophy in mice. Jeffery Molkentin (Cincinnati Children’s Hospital Medical Center, Cincinnati, OH) and colleagues showed in The Journal of Clinical Investigation that Cdc42 was specifically upregulated in the heart after pressure overload and that mice lacking cardiac Cdc42 exhibited greater hypertrophy and transitioned to heart failure more rapidly. Cdc42 exerted its protective effect by activating the kinase, JNK, which antagonizes calcium/calmodulin signaling.8

Mahesh Gupta (University of Chicago, IL) and colleagues reported in The Journal of Clinical Investigation recently a novel antihypertrophic factor and a novel pathway.9 The factor was the histone deacetylase SIRT3, which had previously only been shown to be upregulated in cardiac hypertrophy, and the pathway involved reactive oxygen species. Gupta and colleagues showed that SIRT3 activated antioxidant genes, which led to a decrease in reactive oxygen species, which, in turn, suppressed the prohypertrophic factor, Ras.

Interestingly, the group found that during mild hypertrophy, including physiological hypertrophy, both short and long isoforms of SIRT3 were abundant. In severe hypertrophy, however, the long isoform of SIRT3 dominated. Although the significance of this observation is not yet clear, it may represent an important difference between physiological and pathological hypertrophy.

The transition from mild to pathological hypertrophy and, more specifically, to heart failure was the subject of an article by Joan Heller Brown (University of California, San Diego, CA) and her team published in The Journal of Clinical Investigation this May.10 The team discovered that CaMKII, a target of calcium/calmodulin that is activated in hypertrophic hearts, is not actually necessary for hypertrophy, much to their surprise. Instead CaMKII seemed to be important for the transition from hypertrophy to cardiac failure. Mice subjected to hypertrophic stimuli grew large hearts, regardless of whether they had or did not have CaMKII. However, the mice that lacked CMKII were protected against heart failure and death. “The real important issue is what makes the hypertrophy become bad,” says Heller Brown, “because that’s what people die from.”

An article from Eric Olson (UT Southwestern Medical School, Dallas, TX) and colleagues published in the Proceedings of the National Academy of Sciences in February suggested, in contrast, that CaMKII could promote hypertrophy.11 It is not clear why this group got a different result, but for one thing, says Heller Brown, Olson’s group did not specifically compare hypertrophy and heart failure. Another possible explanation for the difference is the severity of the induced hypertension. Other hypertrophic pathways might bypass CaMKII if the stimuli were strong enough, thus you would still see hypertrophy in the absence of CaMKII. Whatever the reason for the discrepancy, both articles conclude that blocking CaMKII would be a beneficial therapeutic strategy.

What to Do About All These Targets?
It is all very well having so many new molecules and mechanisms to investigate, but what is the best way for researchers to set about targeting them in therapy? Jean Sebastian Hulot (Université de Paris, France) suggests that an article published recently in Circulation by Suckau et al. might hold the answer.12

Suckau et al. used a viral vector called AAV9 to deliver an antisense RNA to heart cells to silence a prohypertrophic factor called phospholambin. “I think that is very new and interesting,” says Hulot. AAV9 naturally targets cardiac cells and has been used before for overexpressing genes of interest in the heart, but never before for RNAi. “This was the first article to report this strategy,” says Hulot, “but now we can use the strategy to investigate other targets.”

Hulot suggests that the strategy might not only be useful in therapy, it might also provide a cleaner method for generating cardiac conditional knockouts. One of the problems of creating conventional conditional knockouts, he says, is that the drugs used to induce the knockout can create unrelated phenotypes of their own. The AAV9 RNAi approach circumvents this major limitation.

Could the AAV9 approach be modified to target the current stars of the heart failure field—the miRs? “Absolutely,” says Hulot. Knocking out miRs, he explains, involves the use of small, specifically designed nucleotide molecules called antagoniRs. “I don’t know anyone that is able to put this antagoniR into the AAV9 vector,” he says, but adds excitedly, “that should be something coming in the next months or year.” Stay tuned.

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