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EDITORIAL COMMENT

Tit for TAK1

Reciprocal Regulation of Inflammasome Signaling in Cardiac Hypertrophy*

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Heart failure remains a leading cause of death and morbidity worldwide, and it frequently follows adverse myocardial remodeling. Although originally coined to describe the cellular and environmental changes in the myocardium following myocardial infarction, the term has been expanded to include the response to the myocardium to both acute and sustained pathological conditions, including pressure overload. In response to pressure overload, adaptive hypertrophic growth and catecholamine release enable a compensatory increase in contractility to preserve cardiac output known as compensated cardiac hypertrophy.[1] However, the continued persistence and development of hypertrophy ultimately leads to heart failure and decompensated heart function or decompensated cardiac hypertrophy. How this progression occurs remains poorly understood, with multiple pathways, including metabolic dysfunction, oxidative stress, extracellular matrix remodeling, and apoptosis, being implicated.

In the study by Li et al[2] in this issue of *JACC: Basic to Translational Science*, the authors investigated the role of an alternative driver of hypertrophy decompensation: nod-like receptor family pyrin domain containing 3 (NLRP3). NLRP3 has become a hot topic in cardiac research as a contributor to a variety of cardiovascular diseases including atherosclerosis, myocardial infarction, and in this case, cardiac hypertrophy. Canonically, NLRP3 is a pattern recognition receptor that acts as a part of the innate immune system, detecting damage-associated-molecular patterns.[3] Damage-associated-molecular pattern recognition enables cells to recognize patterns generated by endogenous stress, triggering inflammatory pathways to mount an immune response and repair damaged tissue. Normally, NLRP3 requires a 2-signal process to activate. First, a signal from foreign pathogens or endogenous cytokines primes the NLRP3 inflammasome, then a second signal from an external DAMP activates the NLRP3 inflammasome. Upon activation, an inflammatory cascade occurs with procaspase 1 cleavage to generate caspase 1. Caspase 1 cleaves and enables subsequent secretion of inflammatory cytokines IL-1β and IL-18, as well as cleaving Gasdermin D (GSDMD). GSDMD then induces pyroptosis-inflammatory programmed cell death.

Li et al[2] sought to further investigate the role of NLRP3 in cardiac hypertrophy through the use of an in vivo transverse aortic constriction (TAC) pressure overload model and in vitro cell cultures. Similar to previous studies, 4 weeks after TAC, NLRP3$^{-/-}$ mice displayed significantly better cardiac functions, showed less tissue remodeling and fibrosis, and had attenuated Caspase-1, IL-1β, and IL-18 cleavage compared with their WT counterparts. NLRP3$^{-/-}$ also experienced lessened cardiac hypertrophy and changes to cardiomyocyte size. In vitro neonatal mouse ventricular myocytes were treated with angiotensin II to promote cardiomyocyte hypertrophy. Administration of a selective inhibitor of NLRP3 provided similar protective effects of decreased cellular hypertrophy, NLRP3 cascade activation, pyroptosis, and cell membrane destruction. To investigate whether downstream mediators of NLRP3 are required for the NLRP3 knockout's cardioprotective effects, cardiomyocyte specific overexpression of Caspase-1 or GSDMD was induced in

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NLRP3$^{-/-}$ mice. Increased expression of either of these mediators almost completely ablated previously found cardioprotective effects and strongly supports that the progression of the NLRP3 cascade all the way to pyroptosis is required for cardiac hypertrophy observed in this model.

Following this, the authors then examined the role of transforming growth factor β-activated kinase 1 (TAK1) in their TAC NLRP3$^{-/-}$ model. Previous literature has demonstrated that TAK1 plays an important regulatory role in the NLRP3 cascade in myeloid cells, and other studies have found contradictory findings in how TAK1 influences cardiac hypertrophy. The authors found that TAK1 activation levels were highly elevated following TAC, with surprisingly higher elevations in the NLRP3$^{-/-}$ mice. Bioinformatic analysis and coimmunoprecipitation revealed binding interactions between TAK1 and NLRP3 in cardiomyocytes and this could be diminished during hypertrophic conditions in vitro. The concept presented is that NLRP3 sequesters TAK1 to prevent its activation. To evaluate what role TAK1 plays in NLRP3 signaling, cardiac-specific knockouts of TAK1 were created using small hairpin RNA (shTAK1) injected directly into the myocardium. Following TAC, TAK1 deficiency alone promoted pyroptosis, inflammatory cascades, and cardiac hypertrophy in WT mice. Importantly, the absence of TAK1 reversed the cardioprotective effects observed in NLRP3$^{-/-}$ mice and phenocopied the overexpression of Caspase-1 and GSDMD. These findings support a reciprocal relationship for TAK1 and NLRP3 in regulating downstream pyroptotic signaling and cardiac hypertrophy.

When reading the study by Li et al,[2] it is critical to understand the context in which it exists. This paper builds upon previous findings by creating a contained and thorough examination of the NLRP3/caspase-1/GSDMD pathway and its relation to TAK1 in cardiomyocytes in a nonischemic context. In a myeloid cell context, TAK1 is well known to directly regulate NLRP3 activation.[4] TAK1 deficiency has been shown to remove the priming signal requirement for NLRP3 activation, increasing NLRP3-driven inflammation. Other research has also demonstrated positive cardiovascular effects in NLRP3 inhibition or knockout following pressure overload or ischemic injury. As of date, however, no other paper has put these independent findings together and shown that in the absence of an ischemic injury, NLRP3 drives decompensated hypertrophy and is opposed by TAK1.

Moving forward in this field, it will be critical to examine this phenomenon in the context of the myocardium as a whole. In an ischemic injury, acute tissue damage results in a massive inflammatory event. This triggers a wide range of responses in both cardiomyocytes and infiltrating immune cells, in addition to causing a tidal wave of DAMPS to activate various receptors including NLRP3. In cardiac hypertrophy, this massive inflammatory event does not exist; instead, a sustained hypertrophic stress on myocardium results in NLRP3 activation through unknown means. It is important to note that the NLRP3$^{-/-}$ model used in this study is a global knockout and that cardiomyocytes are not the only cells in the myocardium. Other resident cells in the myocardium, such as fibroblasts and macrophages, are very sensitive to physical stimuli, including the stretch experienced during hypertrophy. Mechanical stretch has been shown to activate NLRP3,[5] and it is likely that alongside cardiomyocyte activation, fibroblast and local immune cell populations are also activated and may further promote pyroptotic signaling in the local area. Understanding individual cell contributions in this context would better inform the timing and mechanisms driving this pathological hypertrophic signaling.

Further exploration of the TAK1-NLRP3 relationship is also needed. In contrast to the work presented by Li et al,[2] TAK1 has been conversely shown to promote hypertrophic cardiomyopathy in neonatal mice. When comparing these 2 studies, it is important to consider that neonatal inflammatory profiles and responses are vastly different than that of a mature adult. This is often the case in wound healing and immune responses, and likely is the case when examining sterile inflammation during cardiac hypertrophy. As such, the TAK1-NLRP3 relationship is likely more nuanced and changes under different conditions including age. Further defining how these 2 molecules interact and may affect one another's expression in different settings may be key to understanding whether changes in TAK1 expression seen in heart failure are a cause of decompensation, or merely a symptom.

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