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EDITORIAL COMMENT

The Hippo in the Clinic

An Ancient Signaling Pathway That Regulates Growth and Development Confronts a Modern Pandemic of Obesity, Diabetes, and Heart Failure*

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The relentless expansion of the worldwide waist (1,2) has led to accelerating rates of glycemic, liver, and heart failure, some cancers, and degenerative joint disease in persons around the globe (3). "Heart failure," a clinical syndrome that until the arrival of the obesity pandemic was typically categorized by cardiac enlargement with sodium and water overload, has become, in the modern era of ubiquitous obesity, a concatenation of multiple chronic conditions (4) that clinically present as a dysfunction of diastolic filling (5). The physiology of heart failure with preserved ejection fraction is strongly related to central obesity and diabetes (6); the clinical syndrome of heart failure with preserved ejection fraction (colloquially HEFPEF) can be defined by a point system (7). These operational definitions just hint at the clinical reality: that the phenotype of diastolic heart failure lies at the intersection of obesity (reflecting poor nutrition and associated high dietary sodium content), with type 2 diabetes, hypertension, social stress, and aging (8). The modern heart failure patients' internal milieu is unprecedented in evolutionary history.

It is curious that none of the recent reviews of diastolic dysfunction heart failure and its obesity phenotypes discuss an ancient signaling pathway that regulates growth and development central to every aspect of cardiovascular physiology, from apoptosis to Z-discs: the Hippo signaling pathway (Hippo) (9). The Hpo gene, which was discovered in the fruit fly, is homologous with the mammalian kinases Mst1 and Mst2 (10). Hippo regulates downstream levels of Yes Associated Protein (YAP), which interacts with transcriptional regulator TEAD1. Hippo is a highly conserved premetazoan kinase cascade; it possibly developed in response to selective pressure to facilitate communication between unicellular organisms (11). The nearly simultaneous discovery by 5 laboratories of the gene Hpo (its evocative name Hippo inspired by the overgrowth of the Drosophila eye imaginal disc with cellular disarray resembling the head of a hippopotamus) is reviewed (12,13). Hippo has been shown to regulate cell-to-cell contact, cell death and repair after myocardial infarction, dedifferentiation of cardiomyocytes to fibrocytes, and differentiation of stem cells to cardiomyocytes. It plays a regulatory role in the interaction of glucose and the heart (14).

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In this issue of *JACC: Basic to Translational Science*, Ikeda et al. (15) present a proof of concept experiment of Hippo and its downstream effector YAP in a male mouse model of "metabolic syndrome" as defined by the intersection of obesity, type 2 diabetes, hypertension, and inflammation in their high fat diet (HFD), pressure overload (PO) via transverse aortic constriction (TAC) model. They have shown, in a series of publications (16,17), how YAP and associated transcriptional effector TEAD are modified. They investigated the interaction of these interventions with levels of YAP and associated pathways in their model, and after blockade of the pathways with verteporfin, which is a small-molecule specific inhibitor

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of the YAP pathway (18). They also obtained interesting proof of concept data from myocardial biopsy specimens from human subjects with and without type 2 diabetes; they found that the concentration of YAP in the biopsy specimens was proportional to the patient's hemoglobin A_{1C} level.Based on these findings, they speculate that inhibitors of YAP or transcriptional effector TEAD1 may be effective in treating heart failure, as frequently seen in patients with type 2 diabetes and hypertension.

Of note in the Ikeda et al. (15) study is the possible interaction of glycemic dysregulation with PO in their HFD mouse model, where YAP overexpression, instead of protecting cardiomyocytes, may induce dedifferentiation and apoptosis. A model of metabolic syndrome in swine fed a high-fat diet and with PO with TAC has been published; an editorial expresses caution and support for animal models of metabolic syndrome (19).

Because of its role in regulating tissue growth, and its effect on tumorigenesis, there is interest in finding pharmacologic blockers and enhancers of Hippo; hundreds of compounds are currently being tested to block the central kinase of Hippo (20). Triastuti et al. (21) have used a blocker of the central Hippo kinase, to demonstrate that increase of the YAP-complex protects the mouse heart against PO. There are concerns regarding chronic treatment with small molecule kinase inhibitors because of the association of Hippo with tumorigenesis (20).

About a third of patients with aortic stenosis have type 2 diabetes (22). How the natural history of aortic stenosis could be modified by the interactions of type 2 diabetes with the central pressure and often volume overload of aortic stenosis, by manipulation of Hippo, is unstudied and speculative.

In summary, Hippo interacts with all levels of cardiovascular physiology. The mouse model used by Ikeda et al. (15) and others has provided important insights regarding Hippo and the heart, which may lead not only to treatment for diabetic pressure overload cardiomyopathy, but also for myocardial regeneration and prevention of heart failure after myocardial infarction (23). Hippo: it really is big.

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