Introduction to HIF Pathway

The evolutionarily conserved hypoxia-inducible factor (HIF) pathway is present ubiquitously in mammalian cells and plays a critical role in the regulation of energy metabolism, especially glucose utilization.\(^1,2\) HIF is a transcription factor consisting of an O\(_2\)-sensitive HIF-\(\alpha\) (HIF-1\(\alpha\) or HIF-2\(\alpha\)) and the O\(_2\)-insensitive HIF-1\(\beta\) subunit.\(^2\) Under most physiologically normoxic conditions (\(>3\%\) O\(_2\)), HIF-\(\alpha\) is hydroxylated by prolyl hydroxylases (PHD) at 2 proline residues located in the oxygen-dependent degradation domain (ODD), which leads to interaction with the von Hippel Lindau protein pVHL and subsequent degradation by proteasomes.\(^3,4\) When tissue oxygenation decreases to, for example, <2\% O\(_2\), HIF-\(\alpha\) hydroxylation diminishes and becomes stabilized. While the PHDs themselves can act as oxygen sensors, the mitochondria has also been proposed as a critical organelle responsible for cellular oxygen sensing, presumably through complex III.\(^5\) Mitochondrial oxygen sensing may be more critical for acute, rapid physiological changes that are needed to respond to hypoxic conditions. In contrast to hypoxia, under aerobic conditions additional mechanisms have been proposed for increased HIF-\(\alpha\). In particular, growth factor receptor tyrosine kinase and protooncogene-mediated pathways can also augment HIF-\(\alpha\) expression through translational regulation.\(^6\) Thus, depending on the tissue microenvironment, different mechanisms can be used to increase HIF-\(\alpha\) levels and transcriptional activity.

Obesity and the Tissue Microenvironment

Obese individuals often suffer a myriad of health issues, including type 2 diabetes, cardiomyopathy, and nephropathy. However, the molecular mechanisms linking obesity with cardiomyopathy are probably multifactorial and depend as much on the genetics of the individual as on environmental factors such as circulating cytokines and chemokines. Cardiomyopathy, in particular, has been proposed to result from faulty endothelial function, reactive oxygen species, and inflammation.\(^7–11\) However, what the causative stimulus is for inflammation and oxidative stress in obese individuals has yet to be clearly determined. In fact, one new hypothesis that explains this link is that microenvironmental changes in the adipose tissue of obese individuals could lead to an inflammatory response, an increase in circulating cytokines, and ultimately to cardiomyopathy and heart failure (Figure). The critical point of this hypothesis is that changes in the adipose tissue lead to cardiomyopathy through secreted factors. Previous studies\(^12–14\) have demonstrated that the adipose tissue in both obese humans and mice can become hypoxic. This is a rather surprising finding that has been largely ignored as adipose tissue is often thought to be well vascularized. Could changes in tissue oxygenation result in increased levels of the HIF-\(\alpha\) family in adipose tissue and lead to inflammation and cardiomyopathy?

In this issue of \textit{JAHA}, Lin et al report a highly novel and important observation regarding HIF function in adipocytes.\(^15\) They generated a series of transgenic mouse models through the conditional deletion of Vhl alone or in combination with Hif1a or Hif2a using the adipocyte-specific ap2 promoter-driven cre. Mice with adipocyte-specific Vhl deletion exhibited cardiomegaly with marked ventricular hypertrophy and cardiac dysfunction within a week after birth, suggesting chronic activation of the HIF pathway in adipocytes has deleterious effects remotely in the neonatal heart. Interestingly, the phenotypes of Vhl deletion could be fully rescued by conditionally deleting both Vhl and Hif2a in adipocytes. In contrast, conditional deletion of Hif1a in adipocytes did not only fail to rescue the Vhl-null phenotypes, and if anything exacerbated the cardiac hypertrophy and dysfunction, which resulted in a shorter lifespan of these mice. The genetic
elevated and significantly correlated with cardiomegaly. Consistent with the proposed link between HIF-2α activation in adipocytes, inflammation, and cardiomyopathy, Lin et al found that deleting Hif2α in VHL-deficient adipocytes was sufficient to completely normalize both inflammation locally in adipose tissue as well as reducing circulating levels of inflammatory cytokines and chemokines. These results are strong evidence that leads us to conclude that adipose inflammation is a major cause of pathological heart hypertrophy and heart failure with HIF-2 activation in adipocytes as a critical underlying mechanism.

HIF-2, Obesity and Cardiomyopathy

This work by Lin et al has a potentially significant impact on understanding the etiology of obesity-associated cardiomyopathy. For decades, it has been known that obesity is closely associated with cardiomyopathy and hypertrophy. In recent years, chronic inflammation emerged as a potential leading cause of obesity-associated heart diseases, but the mechanisms remain to be elucidated.

While the studies performed here have used mouse genetics to demonstrate the importance of HIF-2α in adipocytes leading to cardiomyopathy, both human and mouse adipose tissue develops hypoxia, which could be the pathophysiological signal for HIF-2α induction. Furthermore, hypoxia has also been implicated as a regulator of adipokines and inflammatory cytokines in adipose tissue, supporting the link between inflammation, and cardiomyopathy. The genetic evidence presented by Lin et al has clearly demonstrated that sustained activation of HIF-2 in adipocytes is both necessary and sufficient to induce chronic inflammation in adipose tissues, and elevated levels of secreted inflammatory cytokines. Vhl deletion in adipocytes led to significantly increased expression of Hmox1, Lep, Vegfd/Fgf1, and Serpine1/Pai1 in adipose tissue. Interestingly, elevated expression of these genes is often found in adipose tissue of obese subjects. Among secreted cytokines associated with adipocyte HIF activation, MCP-1 (CCL2) and IL-12 levels were elevated in young and/or adult obese patients. It is also well documented that IL-1β can induce hypertrophic response in cardiomyocytes. It is highly likely that obesity-associated cardiomyopathy results from concerted actions of multiple secreted cytokines and chemokines either directly by adipose tissue or indirectly by other tissues due to secondary effects of HIF-induced adipose inflammation. Nonetheless, the work by Lin et al proposes a new paradigm that establishes HIF-2α as a major driver of the obesity-induced adipose inflammation and the eventual development of obesity-associated cardiomyopathy (Figure). Most importantly, since genetic deletion rescued this phenotype, pharmacological
inhibitors of HIF-2α, which are starting to be developed, could have therapeutic benefit to obese patients, if they could be targeted to adipose tissue specifically.

Disclosures
None.

References

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