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Preview

Extracellular HSP90 warms up integrins for an irisin workout

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The hormone-like protein irisin is involved in browning of adipose tissue and regulation of metabolism. Recently, Mu et al. identified the extracellular chaperone heat shock protein-90 (Hsp90) as the activating factor for "opening" αVβ5 integrin receptor, allowing for high-affinity irisin binding and effective signal transduction.

Is exercise good for you? The answer is obviously yes. Regular physical exercise has wide-ranging positive impacts on overall health and well-being, influencing various physiological systems and contributing to longevity and disease prevention. However, what are the immediate effects and consequences of exercise in the muscles? Previous work has shown that peroxisome proliferator-activated receptor-g coactivator 1 alpha (PGC-1α) plays a crucial role in regulating cellular energy metabolism and adaptive responses to physical exercise.[1] It is primarily expressed in tissues with high energy demands such as skeletal muscle, heart, liver, and brown adipose tissue. PGC-1α is also responsible for the synthesis of plasma membrane-bound fibronectin type III domain-containing protein 5 (FNDC5).[2] The carboxy-terminal tail of FNDC5 is in the cytoplasm, whereas muscle contraction triggers proteolytic cleavage of an amino-terminal section of FNDC5 known as irisin. Irisin functions as a myokine, and studies in mice have shown that increasing irisin levels through genetic manipulation or exercise can lead to various health benefits including increased energy expenditure, improved insulin sensitivity, enhanced glucose uptake, and protection against diet-induced obesity.[3] Additionally, irisin has been implicated in the regulation of bone health, cognitive function, and cardiovascular health. In bone, fat, and hippocampus, irisin tends to function primarily via αV integrin receptors, particularly αVβ5.[4] However, it is unclear how a small protein like irisin interacts with and transduces signaling through an integrin receptor.

Mu et al.[5] have now shown that irisin-mediated integrin activation uses a two-step process involving an extracellular molecular chaperone heat shock protein-90α (eHsp90α) (Figure 1). eHsp90α is secreted from skeletal muscle and its secretion is elevated with exercise, although the total levels of cellular Hsp90α in muscle remain unchanged. These findings together with the absence of other secreted chaperones suggested that eHsp90α secretion is an exercise-induced mechanism and not simply released through cellular damage. The published work also indicated that eHsp90α directly binds to the ectodomain of αVβ5 and maintains it in an open conformation (Figure 1). Here eHsp90α appears to function independent of ATP availability. This is an important consideration, as the extracellular ATP concentration is relatively low.[6] The effect of Hsp90α on irisin-mediated activation was tested in mice, and Hsp90α neutralizing antibody treatment caused a significant reduction in irisin-induced integrin signaling. The αVβ5 receptor, once activated by eHsp90α, has a very high affinity (Kd ~30 nM) for the highly glycosylated monomer of irisin (Figure 1). Through biophysical and biochemical experiments, refined by multiple steps of molecular dynamics simulations, Mu et al. were able to generate and refine a docking model with 2.98 Å root-mean-square deviation (RMSD) of the irisin/αVβ5 complex. This structure has important implications for integrin-small ligand dynamics and how irisin mediates its physiological effects.[5]

Hsp90 molecular chaperones are important regulators of signal transduction pathways through their impact on the stabilization and activation of dependent proteins, termed "clients."[7,8] The model described by Mu et al. is reminiscent of previous studies on Hsp90 regulation of client protein ligand affinity. Steroid hormone receptors (SHRs) are a subset of Hsp90 client proteins, and interaction with Hsp90 chaperone complexes promotes ligand affinity for SHRs.[9] Additionally, a previous report demonstrated that eHsp90, in complex with its dedicated extracellular co-chaperone TIMP2, enhanced binding to extracellular client MMP2 and regulated its proteinase activity.[10] Mu et al. have demonstrated an analogous mechanism in which eHsp90α's interaction with αVβ5 integrin promotes interaction with its ligand, irisin. These works collectively introduce a concept for Hsp90 in shaping substrates binding to their ligands.[5]

In summary, Mu et al. showed how a small polypeptide hormone, which exists in the extracellular space at much lower concentration compared to other matrix proteins (the canonical integrin ligands), uses integrin as the receptor to mediate downstream cellular events (Figure 1). This work describes a new two-step mechanism in which a hormone ligand acts through an integrin with the help of a differentially regulated third component.

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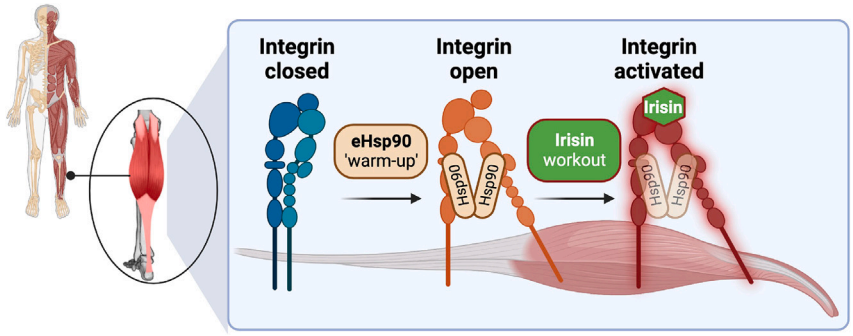

Figure 1. Extracellular chaperone Hsp90 "warms up" integrin for irisin workout
Physical exercise leads to an increase in irisin levels as well as release of the molecular chaperone Hsp90. Irisin alone has low affinity for the closed state of αVβ5 integrin receptor. Extracellular Hsp90 (eHsp90) "opens" αVβ5, allowing for irisin binding with high-affinity and effective signal transduction through its integrin receptor.

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DECLARATION OF INTERESTS

The authors declare no competing financial interests.

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