Leptin-induced cardiac hypertrophy: RhoAing a lipid raft down a protective p38 MAPK signalling stream?

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In the current issue of *Cardiovascular Research*, two independent reports provide significant headway in answering these questions. First, Zeidan et al.* describe their elegant studies directed towards understanding the mechanism of leptin-induced cardiac hypertrophy *in vitro*. Thus, they build on previous reports* to show that leptin binding to cardiac Ob-R up-regulates cardiomyocyte caveolae number and content, as determined by cav-3 protein expression. An important feature of this observation was that Ob-R co-localized within intact cardiomyocyte caveolae, and this was critical for the activation of the small monomeric GTPase RhoA. Finally, these actions combined to induce the translocation of phosphorylated p38 MAPK, but not ERK1/2, from the cytoplasm to the nucleus and, hence, cardiac hypertrophy as assessed by increases in cell surface area and protein synthesis. In all of this detailed and completely novel mechanism, the translocation of p38 MAPK depended on intact cardiomyocyte caveolae, the signalling activity of RhoA and its downstream Rho kinase target known as ROCK and intracellular actin dynamics. In this regard, the role of the RhoA/ROCK signalling system is emerging as an important player in cardiac biology. For example, it was recently shown that overexpression and increased *in vivo* activity of RhoA/ROCK proteins in diabetic rat hearts were associated with decreased contractile function, while acute blockade of the pathway ROCK in these animals resulted in improvements in cardiac contractile function both *in vitro* and *in vivo*. Furthermore, several clinical studies have shown that blockade of the ROCK pathway in patients with hypertension, chronic heart failure, and stroke may have beneficial effects. Taken together, these results indicate that the RhoA/ROCK system has an important role in cardiac function and may be a promising therapeutic target. The current and previous results* of Zeidan et al. now extend this paradigm of RhoA/ROCK activity to include leptin-induced cardiac hypertrophy.

While the *in vitro* results of Zeidan et al.* suggest that blockade of the RhoA/ROCK system might be expected to ablate the hypertrophy induced by leptin and that this may be beneficial, in the second elegant set of studies on leptin in this issue, McGaffin et al.* report their *in vivo* findings on leptin therapy in mice with heart failure secondary to permanent left coronary artery ligation.
Thus, chronic ischaemia-induced cardiac injury resulted in the up-regulation of endogenous leptin and Ob-R in cardiac tissue in wild-type C57BL/6J mice which was cardioprotective, whereas in leptin-deficient ob/ob mice, survival, contractile function, and cardiac structure parameters were all significantly worse compared with the wild-type controls. Furthermore, addition of leptin to the ob/ob animals significantly improved these parameters, in association with increased cardiomyocyte STAT3 activation and hsp-70 and TIMP-1 mRNA expression. Thus, the overall effect of leptin upon cardiac status in these animals was found to be beneficial and protective. Unfortunately, McGaffin et al. did not study RhoA/ROCK or p38 MAPK activities, nor did they measure circulating leptin concentrations in their in vivo experiments; conversely, Zeidan et al. did not report STAT3, hsp70 or TIMP-1 activities in their in vitro work.

Compilation of both these timely reports in this issue of Cardiovascular Research suggests the following: in vitro, leptin binding to cardiomyocyte Ob-R up-regulates caveolae content and cav-3 protein to induce RhoA/ROCK activation, increase actin dynamics and the nuclear translocation of p38 MAPK. The nuclear translocation of p38 results in changes in transcriptional regulation to affect a pro-hypertrophic response in the myocyte. In vivo, leptin has a cardioprotective action in response to chronic cardiac ischaemia and subsequent heart failure, which at least partially depends on the up-regulation of cardiac STAT3, hsp-70, and TIMP-1. Obviously, technical differences might underlie these different results, such as the fact that the work of Zeidan et al. was performed in neonatal rat myocytes which display phenotypic differences compared with adult cells.

However, from this summary, several key questions emerge: (i) Does the dependence upon intact, cholestrol-laden caveolae for the in vitro hypertrophic effect of leptin observed by Zeidan et al. provide some insight into underlying mechanisms responsible for the obesity paradox’ of heart failure patients with high BMI?; (ii) What are the important connections between STAT3 and the RhoA/ROCK pathways in cardiac myocytes and how might leptin modulate them?; (iii) Does endogenous cardiomyocyte cav-3/caveolae/RhoA activation have the same effect upon hypertrophy as that observed under leptin stimulation?; (iv) If leptin directly causes cardiac hypertrophy in vivo in the setting of myocardial infarction and heart failure, is it a compensatory protective response, and would RhoA/ROCK inhibition be deleterious to this action? With regards to the last question, a single recent study has provided a partial answer in that post-MI mice receiving 4-week infusions of leptin had improved systolic function and eccentric dilatation compared with control/sham animals; this lone study obviously requires confirmation and validation.

Overall, the reports from Zeidan and McGaffin et al. converge to raise an intriguing and important hypothesis: does leptin induce a compensatory and protective cardiac hypertrophy in response to chronic ischaemic myocardial injury, that is, dependent upon intact caveolae and activation of RhoA/ROCK, p38, STAT3, hsp70, and TIMP-1? A study containing such in vitro and in vivo documentation would be of great interest and would advance the important directions provided by the studies of Zeidan and McGaffin et al.

Conflict of interest: none declared.

References