Five Easy Pieces
The Obesity Paradigm

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Efforts to eradicate cardiovascular disease (CVD) are progressing no faster than The Race for the Cure is in breast cancer. In the case of CVD, although therapies for the ravages of atherosclerosis continue to improve, the prevalence of disease is more than keeping pace. Recently, the World Health Organization has predicted that today’s 17 million deaths worldwide attributable to heart disease and stroke will increase to more than 20 million by the year 2020, thus becoming the leading cause of death and disability in the world. Most commonly blamed factors for the increase in CVD are increases in insulin resistance and type II diabetes as a result of dietary changes and more sedentary lifestyles.

Indeed, the pieces of the puzzle seem to be comprehensible. (1) Accompanying the changes in diet and lifestyle, the prevalence of obesity has exploded. (2) Innumerable studies have established that obesity predisposes to insulin resistance, a harbinger of type II diabetes. (3) Nearly all serum and histochemical markers of inflammation are increased in insulin resistance and diabetes. (4) Obesity also tips the balance between fibrinolysis and thrombosis toward the latter. (5) Obesity is, thus, a major risk factor for CVD and stroke. The data supporting this paradigm are intellectually compelling, and appear as unassailable as the Cadbury Castle (the reputed site of King Arthur’s Camelot) and supported by the scientific community at the highest levels.

So why question this paradigm? Because reports continue to appear that bring the theory into question, most recently the results from the Women’s Health Initiative (WHI) Randomized Controlled Dietary Modification Trial. The WHI enrolled nearly 50,000 postmenopausal women, ages 50 to 79. The subjects were randomized into either an intervention group, in which behavior modification was used to reduce fat and increase the intake of fruit, vegetables and grains, or a control group. Over an average of 8.1 years of follow-up, there was no reduction in CVD (neither in breast nor colon cancer). These findings do not render the hypothesis that obesity contributes to CVD vacuous. Rather, they argue that our knowledge of molecular pathways and factors that influence them remains inadequate, as was proposed in relation to the lack of an effect of diet on breast cancer.

It is in this context that the report of Fujita et al in this issue of Circulation Research is of significant interest. The data presented here link winged helix family transcription factor Foxc2 to the inflammatory cytokine, TGF-β1, and to expression of plasminogen activator inhibitor type-1 (PAI-1), a key regulator of intravascular thrombosis. Foxc2 has been previously implicated in insulin resistance. Targeted overexpression of Foxc2 in mouse adipose tissue produces a phenotype that resists diet-induced insulin resistance and obesity. Human genetic studies also suggested a relationship between Foxc2 and insulin resistance and type II diabetes, albeit less robust than the relationship demonstrated in mice and often of a conflicting nature. For instance, Foxc2 expression is increased in insulin resistant subjects, independent of obesity, a finding at odds with the mouse studies. Carlsson et al reported a relationship between a FOXC2 polymorphism (FOXC2 C-512T) and obesity and dyslipidemia.

Clearly this is a complicated field. Haploinsufficiency differs importantly from transgenic overexpression. Human studies are mixed and difficult to interpret. The polymorphisms studies are of great potential interest, yet we know little on the relative activity of polymorphisms in transactivation of important genes. The findings of Fujita et al suggest additional levels of complexity for the field, but do, at the end of the day, tie obesity and insulin resistance to coagulation at the molecular level—an important finding. Their data convincingly demonstrate that Foxc2 is a transcriptional activator for both insulin and TGF-β1–induced PAI-1 expression in vitro, and that Foxc2+/− mice have lowered expression of PAI-1 in response to TGF-β1 treatment. These findings provide additional links in the burgeoning evidence that inflammation lies somewhere between obesity and atherosclerosis. Another recent study has found that specific markers of inflammation, including TGF-β1, are elevated in obese subjects with insulin resistance. These subjects also had higher levels of markers associated with coagulation disorders.

What is of more potential interest in this report is the findings that FOXO1 attenuated Foxc2-mediated PAI-1 induction in endothelial and preadipocytic cells and this attenuation was significantly abolished by insulin. These findings are consistent with the notion that FOXO1 competes with Foxc2 via the insulin response element (IRE) on the PAI-1 promoter and that FOXO1 antagonizes the synergistic interaction of Foxc2 with small proteins in the induction of PAI-1 in endothelial cells. Matsuzaki et al reported that insulin-induced phosphorylation of FoxO1 results in exclusion from the nucleus and subsequent ubiquitin-mediated proteasomal degradation.

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Foxc2 levels are enhanced via either activation of species in mediating the activation of, and effects of, Foxc2. A strategy would be ineffective. Are highly associated with systemic oxidative stress, and oxidative stress induces PAI-1 expression and activation of Foxo1 gain-of-function mutation causes diabetes by suppressing genes for insulin sensitivity suggests that this is a question worth asking. The answer is far from obvious. Indeed, the report that a Foxo1 gain-of-function mutation causes diabetes by suppressing genes for insulin sensitivity suggests that this strategy would be ineffective.

Putting this all together, this would suggest that FOXO1 might be an interesting therapeutic target and modulating FOXO1 might be one approach to modulating insulin sensitivity. It is known that the expression of FOXO1 is enhanced in caloric restriction and by exercise. Given the role of these interventions in obesity, perhaps modulation of FOXO1 pharmacologically would restore homeostatic balance in obesity. Would small molecule inhibitors of FOXO1 nuclear export inhibit insulin-mediated PAI-1 expression in preadipocytes and endothelial cells? Careful consideration of Fujita et al’s data suggests this is a question worth asking. The answer is far from obvious. Indeed, the report that a Foxo1 gain-of-function mutation causes diabetes by suppressing genes for insulin sensitivity suggests that this strategy would be ineffective.

Finally, it is possible that there is a role for reactive oxygen species in mediating the activation of, and effects of, Foxc2. Foxc2 levels are enhanced via either activation of β-adrenergic–cAMP–protein kinase pathway or through insulin receptor-phosphatidylinositol 3-kinase (PI3-K)–protein kinase B (PKB/Akt) pathway (Figure). Obesity and diabetes are highly associated with systemic oxidative stress, and oxidative stress induces PAI-1 expression and activation of transcription factor NF-κB. In this context, it is worth investigating whether NF-κB activation is one of the mechanisms that ties Foxc2 expression to PAI-1 induction as shown by Li et al.

The 5 components we listed at the start of this commentary that link obesity to CVD and stroke are supported by numerous investigations. On this topic, the more we learn, the more we learn we need to learn more. It is not so different from Jack Nicholson’s character in the 1970 classic, Five Easy Pieces. For him, there was never a definitive ending. Rather his existence was defined by occasionally reaching what appeared to be a plateau, only to realize that there was another mountain just beyond it.

Does the recent WHI study demonstrating no benefit to women on a low fat diet mean that the obesity theory is wrong? Doubtlessly not. There are too many factors, environmental or others, that we do not understand. Even the more straightforward question of the best approach for treatment of obesity remains obscure. More than ever, there are no uniform recommendations on lifestyle changes to combat obesity. Even if there were, it is questionable how widely these recommendations would be adopted and implemented. Many pharmacological targets for the treatment of obesity have been identified, although to date none have proven very effective for sustaining weight loss.

There are no easy answers in this field, as is apparent from the contradicting nature of many reports and the complexity of Foxc2 and FOXO1 interactions, as described above. However, the connection between obesity, inflammation, and atherosclerosis potentially provided by Fujita et al suggests that in addition to conventional measures, it may be important to measure molecular pathways impacted by various obesity treatments.

Questions in this field abound and no current hypothesis is unassailable. Cadbury Fortress, the legendary home of King Arthur’s court, had its chinks, not the least of which is that there is no scholarly agreement on whether King Arthur really existed nor, if he did, if Cadbury Fortress was his home.

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