Visceral obesity has become the most frequent preventable condition accounting for diseases such as hypertension and diabetes, two of the major risk factors for coronary artery disease, stroke, and chronic renal failure.1–3 Despite the awareness aiming to reduce the prevalence of obesity, the number of obese patients continues to rise and now includes even developing countries, and increasingly children are affected.4,5 In fact, if this trend continues, 26 million children in Europe will be overweight or obese by the year 2010, rising by approximately 1.3 million per year.5,6 The annual health costs related to obesity have been estimated close to 100 billion USD in the United States,7,8 illustrating the enormous economic burden the disease obesity carries.

What are the mechanisms contributing to the high cardiovascular risk brought about by obesity? Obesity is a low-grade inflammatory condition9 and typically characterized by increase in visceral adipose tissue. Visceral fat is both a source and target of inflammatory cytokines and growth factors, which directly may affect preadipocyte differentiation via signaling cascades implicated in cell growth such as Ras-Raf-ERK-1/2.10 Adipose tissue also contains inflammatory cells, including cytokine-producing macrophages.9 In addition, adipocytes express a fully functional NADPH oxidase system that maintains local production of reactive oxygen species,11 which in turn either work as signaling molecules or further stimulate production of growth factors implicated in adipogenesis.12,13 Previous work has investigated effects of preadipocyte differentiation on expression of Nox4,14 a component of the vascular NADPH oxidase, and Mahadev et al demonstrated that Nox4—via H2O2—regulates insulin-mediated phosphorylation of the insulin receptor and its substrate, insulin receptor substrate (IRS)-1.15 However, whether Nox4 actively takes part in adipogenesis has remained unknown.

In the present issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Schröder and coworkers now provide us with a new mechanism by which Nox4 controls preadipocyte differentiation.16 These investigators found that Nox4 represents the switch between insulin-induced proliferation of preadipocytes and differentiation through activation of MAPK phosphatase-1 (MKP-1). Insulin lowers not only blood glucose by facilitating its uptake into target tissues, but is also an important regulator of adipogenesis. Schröder et al further show that insulin-mediated differentiation of preadipocytes depends on the formation of H2O2, likely derived from Nox4, either directly or through conversion from superoxide anion.17 Silencing of Nox4 gene expression attenuated insulin-induced H2O2 production. A causal role of H2O2 was further confirmed by overexpressing or supplementing cells with catalase, both of which blocked preadipocyte differentiation. Overexpression of Nox4 reduced ERK-1/2 phosphorylation and serine phosphorylation of IRS-1, which was accompanied by a concomitant increase in tyrosine phosphorylation of IRS-1, thereby promoting metabolic insulin signaling. The authors further demonstrate that regulation of MKP-1, which is known to dephosphorylate ERK-1/2,18 was dependent on Nox4. Overexpression of Nox4 is associated with a parallel increase in MKP-1 expression, resulting in insulin-mediated differentiation of preadipocytes (Figure). Taken together, this study importantly links Nox4-derived H2O2 to the differentiation of preadipocytes into...
adipocytes, even in the absence of insulin. Given the high prevalence of vascular and renal disease in obese patients, the present work raises the question whether Nox4 also levels modulate adipose tissue homeostasis in vivo.

Interestingly, the authors also report difficulties associated with RNA silencing, as they found that although nine probes were claimed to be specific by the manufacturer, several of the siRNA used also blocked other Nox isoforms, and only 1 out of 9 was specific for Nox4.16 According to siRNA manufacturers, siRNA technology is not entirely specific for the genes of interest, and standard siRNA may silence multiple genes unrelated to the gene of interest or have unspecific effects.16,19–21 New developments in RNA silencing may help to reduce this problem. Therefore, the work by Schröder et al is one more piece adding to the puzzle that seemingly specific new technology often comes with unexpected limitations.20,21

Nox4-derived reactive oxygen species have been implicated in coronary heart disease, hypertension, and renal failure, mainly because of the detrimental effects of excessively high levels of reactive oxygen species.22–24 Whether known activators of Nox4, such as the renin–angiotensin system27 which becomes activated during obesity,25 also cause predis舀cytes to differentiate and thereby stimulate obesity development is a tempting hypothesis and would by supported by the work of Schröder et al.16 One therefore might ask the question whether drugs known to inhibit NADPH oxidase such as statins or angiotensin receptor blockers affect predis舀cyte differentiation and proliferation. The latter has been shown by Mori and associates,26 and it appears that the work by Schröder et al has succeeded to provide us with one important missing link that might explain these previous observations.26

Despite all the advances in research we should keep in mind that abdominal obesity, the visually apparent consequence of visceral preadipocyte differentiation, continues to be a major health issue around the world affecting both adults and children.1–6 Should we fail to get radical about obesity in time, today’s children might not live up to our expectations.27

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Disclosures

None.

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