Lipodystrophy-Linked LMNA p.R482W Mutation Induces Clinical Early Atherosclerosis and In Vitro Endothelial Dysfunction

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Résumé en anglais	Objective—Some mutations in LMNA, encoding A-type lamins, are responsible for Dunnigan-type-familial partial lipodystrophy (FPLD2), with altered fat distribution and metabolism. The high prevalence of early and severe cardiovascular outcomes in these patients suggests that, in addition to metabolic risk factors, FPLD2-associated LMNA mutations could have a direct role on the vascular wall cells. Approach and Results—We analyzed the cardiovascular phenotype of 19 FPLD2 patients aged >30 years with LMNA p.R482 heterozygous substitutions, and the effects of p.R482W-prelamin-A overexpression in human coronary artery endothelial cells. In 68% of FPLD2 patients, early atherosclerosis was attested by clinical cardiovascular events, occurring before the age of 45 in most cases. In transduced endothelial cells, exogenous wild-type-prelamin-A was correctly processed and localized, whereas p.R482W-prelamin-A accumulated abnormally at the nuclear envelope. Patients' fibroblasts also showed a predominant nuclear envelope distribution with a decreased rate of prelamin-A maturation. Only p.R482W-prelamin-A induced endothelial dysfunction, with decreased production of NO, increased endothelial adhesion of peripheral blood mononuclear cells, and cellular senescence. p.R482W-prelamin-A also induced oxidative stress, DNA damages, and inflammation. These alterations were prevented by treatment of endothelial cells with pravastatin, which inhibits prelamin-A farnesylation, or with antioxidants. In addition, pravastatin allowed the correct relocalization of p.R482W-prelamin-A within the endothelial cell nucleus. These data suggest that farnesylated p.R482W-prelamin-A accumulation at the nuclear envelope is a toxic event, leading to cellular oxidative stress and endothelial dysfunction. Conclusions—LMNA p.R482 mutations, responsible for FPLD2, exert a direct proatherogenic effect in endothelial cells, which could contribute to patients' early atherosclerosis.
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