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Cell-permeable peptide shows promise for controlling cardiovascular disease

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Atherosclerosis – sometimes called "hardening of the arteries" – is a leading cause of death and morbidity in Western countries. A cell-permeable peptide containing the NF-kB nuclear localization sequence (NLS) shows promise as a potential agent in controlling the development of atherosclerotic disease. This study is published in the May 2013 issue of *The American Journal of Pathology*.

Atherosclerosis is a chronic inflammatory disease of the arterial and vascular wall. The objective of many therapeutic compounds is to modulate atherogenesis – the process that leads to the formation of fatty tissue-containing plaques that stick to the cell wall. Numerous cellular and molecular inflammatory components are involved in the disease process, and uncontrolled activation of pro-inflammatory transcription factors, such as nuclear factor-kB (NF-kB), plays a significant role. Several NF-kB inhibitors are in phase II-III clinical trials against various inflammatory diseases, but most cardiovascular research is still in the preliminary laboratory experimental phase.

Investigators in Spain, the United States, the United Kingdom, and Germany studied the anti-inflammatory and atheroprotective effects of a cell-permeable peptide containing the NF-kB NLS. *In vitro* tests clearly established that NLS peptide blocks the nuclear import of activated NF-kB and inhibits NF-kB activation in vascular cells. These findings were corroborated *in vivo* in ApoE knockout mice, an experimental model relevant to human atherosclerosis. In these experiments, the mice were fed a high-fat diet and treated with either NLS peptide or vehicle

(control group).

The results showed that systemic administration of NLS peptide reduced the nuclear NF-kB activity in vascular smooth muscle cells (VSMCs) and macrophages of aortic plaques of mice. More importantly, NLS peptide inhibited lesion development in mice either at the onset of atherosclerosis (early treatment) or after the development of advanced plaques (delayed treatment), without affecting serum cholesterol levels. The results also demonstrated that NLS peptide alters plaque composition and inflammation in atherosclerotic lesions.

"The NF-kB system is a crucial factor regulating the expression of genes in different steps of the atherosclerotic process, from early phases characterized by lipid modification, chemotaxis, adhesion of leukocytes, monocyte differentiation, foam cell formation, and inflammatory cytokine expression to more advanced lesions involving cell death, migration and proliferation of VSMCs, and fibrous cap formation," explained lead investigator Carmen Gomez-Guerrero, PhD, of the Renal and Vascular Inflammation Laboratory, IIS-Fundación Jiménez Díaz, Autonoma University, Madrid, Spain.

"Our study demonstrates that targeting NF-kB nuclear translocation hampers inflammation and atherosclerosis development and identifies cell-permeable NLS peptide as a potential anti-atherosclerotic agent," she said. "These properties make cell-permeable NLS peptide a promising prevention/intervention strategy to inhibit inflammation in cardiovascular diseases."

More information: "Peptide inhibitor of NF-κB translocation ameliorates experimental atherosclerosis," by Beñat Mallavia, Carlota Recio, Ainhoa Oguiza, Guadalupe Ortiz-Muñoz, Iolanda Lazaro, Virginia Lopez-Parra, Oscar Lopez-Franco, Susann Schindler, Reinhard Depping, Jesus Egido, and Carmen Gomez-Guerrero (DOI:

dx.doi.org/10.1016/j.ajpath.2013.01.022). It appears in The American Journal of Pathology, Volume 182, Issue 5 (May 2013)