Egr-1, an inducible switch in the cardiovascular response to injury

The vascular system normally facilitates the passage of blood, nutrients and oxygen throughout the body whilst maintaining a non-thrombogenic surface. Our blood vessels therefore play a key role in homeostasis. In response to vascular injury however there is a prompt sequence of molecular events that involve multiple signaling and transcriptional pathways that can lead to disease. Recent work indicates that Egr-1 is among the most responsive immediate early genes across a range of human cell types and has helped redefine our understanding of these key genes into classifications.

Early growth response-1 (Egr-1) is not generally expressed in normal arteries but is rapidly induced after injury. Egr-1 is also inducibly expressed in the myocardium after ischemic reperfusion injury. There are hundreds of genes that are stimulated by Egr-1, including growth factors, extracellular matrix proteins and transcriptional regulators such as Egr-1 itself. Egr-1 is one of many zinc finger transcription factors that belong to the Cys_2-His_2 subtype. Egr-1 binds to GC-rich elements in the promoters of responsive genes and in concert with other interacting proteins, drives gene expression. Egr-1 itself can undergo a range of post-translational modifications including acetylation, ubiquitination, phosphorylation, and SUMOylation to modulate gene expression.

This review compiles a wide range of findings obtained from different laboratories on the role played by Egr-1 in the pathogenesis of vascular disorders. Approaches that have been used to explore the functions of Egr-1 have included shRNA, siRNA, microRNA, DNAzymes, oligonucleotide decoy strategies as well as mice deficient in Egr-1.

For example, we recently reported that miR-191 negatively regulates Egr-1 in SMCs and controls neointima formation after balloon injury in rat carotid arteries. miR-191 suppresses Egr-1 expression and inhibits ki-67 proliferation marker expression. Secondly, in pig myocardium subjected to ischaemia-reperfusion injury, Egr-1 DNAzymes reduce infarct size and improve cardiac functional recovery. The DNAzyme inhibits Egr-1 and intercellular adhesion molecule-1 expression. It also reduces tumor necrosis factor-alpha, tissue factor, plasminogen activator inhibitor-1 expression and myocardial myeloperoxidase activity. Thirdly, a lentiviral vector carrying Egr-1 shRNA reduces intimal thickening in iliac arteries after balloon injury in rats induced by nicotine. Finally, Egr-1 decoy oligonucleotides inhibit expression of Egr-1 and hyperplasia in vein grafts of hypercholesterolemic and non-hypercholesterolemic rabbits.

This review also cites observations using Egr-1 deficient mice. Whereas Egr-1 expression increases in vein grafts in wild-type mice, neointimal area in vein grafts in Egr-1 knockout mice is reduced by over 50%. Moreover Egr-1 deficiency in chimeric mice deficient in Egr-1 in their hematopoietic compartment show poor aneurysm formation in an angiotensin II-independent $CaCl_2$-induced model of *abdominal aortic* aneurysm.

These findings, taken together indicate that Egr-1 may represent an attractive target for therapeutic intervention in vascular disease.

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