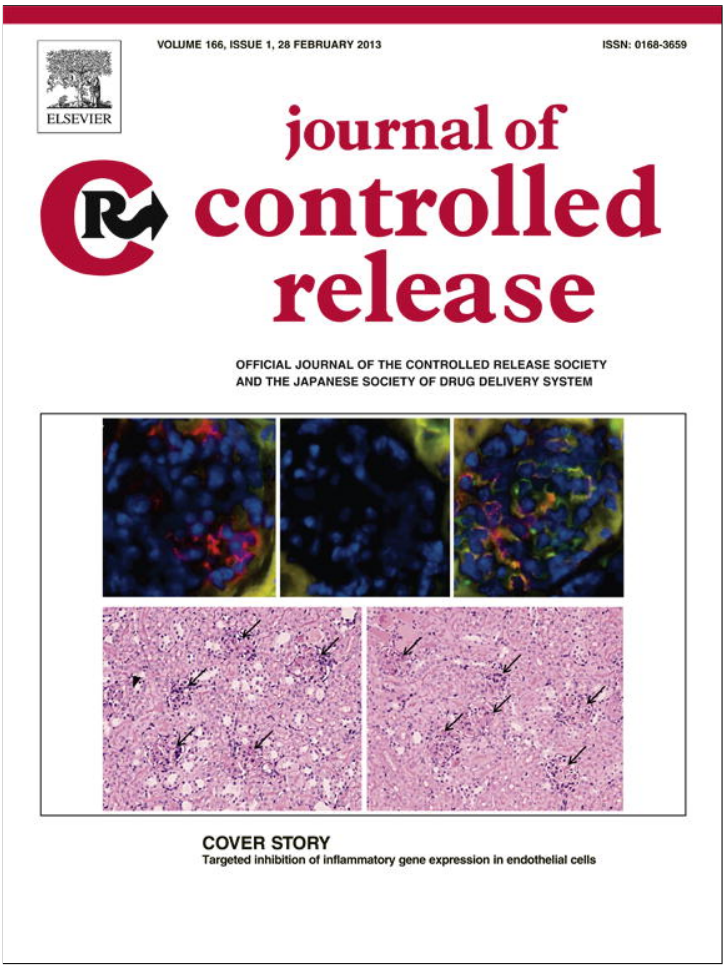

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Cover story

Targeted inhibition of inflammatory gene expression in endothelial cells

In the last decade endothelial cells have gained increasing attention as an attractive target for therapeutic intervention due to their role in the pathophysiology of many diseases, and easy accessibility for intravenously administered therapeutic compounds. In cancer, endothelial cells actively form new tumor blood vessels (angiogenesis). In (chronic) inflammatory diseases such as rheumatoid arthritis, inflammation of the bowel, atherosclerosis and inflammatory kidney disease, the endothelial cells engage in leukocyte infiltration and angiogenesis. Since many of these diseases are difficult to treat, new therapeutics with superior pharmacological efficacy and lower side effects are necessary for the successful treatment of chronic inflammatory diseases and cancer.

Upon inflammation or tissue damage, endothelial cells are activated through pro-inflammatory cytokines, such as interleukin (IL)-1 or tumor necrosis factor (TNF)-α. This local activation of endothelial cells triggers the expression of adhesion molecules, cytokines, chemokines and coagulation factors, allowing leukocytes to bind to the endothelium and to infiltrate in the diseased, underlying tissue. Though normally tightly controlled, this process is derailed in chronic inflammatory diseases resulting in uncontrolled endothelial cell activation and leukocyte recruitment, tissue damage and loss of function. Pro-inflammatory activation of endothelial cells is mainly controlled by the action of intracellular nuclear factor (NF)-κB and p38 mitogen-activated protein kinase (MAPK) signaling. Thus, it is hypothesized that inhibition of these signaling pathways would reduce leukocyte recruitment to the inflamed area, inhibit the vicious circle of cell activation, and improve disease status [1].

The local activation of the endothelium allows for selective drug delivery to these cells via, among others, the adhesion molecules E-selectin and vascular cell adhesion molecule (VCAM)-1. These targets are extensively internalized by receptor mediated endocytosis after binding of drug delivery systems. Thus, the drug delivery systems harnessed with monoclonal antibodies against E-selectin of diseased endothelial cells result in local, endothelium restricted, pharmacological effects and a decreased disease progression. Alternatively, endothelial cell activation can be interfered with by inhibiting NF-κB or p38 MAPK signaling at the gene level. Targeted in vivo delivery of siRNA to endothelial cells, however, is hampered by the lack of an efficacious siRNA delivery system [2].

In this issue, Kuldo et al. delivered a therapeutic gene into endothelial cells using an antibody retargeted adenovirus [3]. To selectively redirect the poly(ethylene glycol) (PEG)-modified virus to deliver the transgene into activated endothelial cells, monoclonal antibody against E-selectin or VCAM-1 was covalently attached to the distal end of the PEG chains. The authors employed a dominant negative mutant of IκB (dnIκB) as a therapeutic transgene. Upon expression, dnIκB competes with endogenous IκB for the binding to NF-κB. Since dnIκB is not phosphorylated upon endothelial cell activation, translocation of NF-κB to the nucleus is blocked. As a result, redirected dnIκB-encoding adenoviruses are expected to inhibit the expression of a number of pro-inflammatory genes including adhesion molecules, cytokines and chemokines. In the glomerulonephritis mouse model, redirected homing of the retargeted virus to glomerular endothelial cells was established by double staining of the virus and the endothelial cells by fluorescence microscopy analysis of kidney sections. Moreover, in vivo treatment of mice suffering from glomerulonephritis with E-selectin targeted modified adenoviruses resulted in local down regulation of the pro-inflammatory adhesion molecules E-selectin and VCAM-1.

Tropism-modified adenoviruses were shown to deliver dnIκB, a therapeutically interesting gene, into diseased endothelial cells. The authors will continue their investigations to elucidate the relationship among the amount of transgene delivered in the endothelial cells, the intracellular processing, subsequent transcription and translation of the transgene, and dnIκB functionality. New information from such studies will be critical to the translation of the microvascular endothelium-targeted gene therapy for treatment of inflammatory diseases.

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