Egr-1, a Major Link Between Infection and Atherosclerosis?

To the Editor:

The study of Bea et al. recently published in Circulation Research, investigated the role of Chlamydia pneumoniae infection in mouse macrophages on the induction of tissue factor (TF) via activation of Egr-1. Chlamydial infection of RAW mouse macrophages clearly resulted in enhanced Egr-1 protein expression and a subsequent time-dependent increase in TF mRNA expression and procoagulatory activity. We can confirm the postinfectious Egr-1 induction described by Bea et al. In addition, we can expand their findings and demonstrate a broader regulatory influence of Egr-1 on proatherosclerotic factors in C pneumoniae–infected mononuclear cells that is not limited to prothrombotic molecules and not restricted to mouse macrophages.

We performed similar experiments as Bea et al. but used blood monocytes from healthy blood donors and found that infection with the cardiovascular chlamydial strain CV-6 (isolated from a 68-year-old man with coronary restenosis) significantly induced Egr-1 mRNA expression (15.8-fold ± 4.7, n = 5; P < 0.01; RT-PCR, LightCycler, Roche Molecular Biochemicals) after 1 hour. This is in line with the results of Bea et al, who observed maximum Egr-1 protein levels in the nuclei of infected RAW cells at 1 to 2 hours after infection. In contrast to Bea et al. who focused on TF expression in mouse macrophages, we were interested whether Egr-1 is involved in the regulation of C pneumoniae–induced expression of the vascular endothelial growth factor (VEGF), which has been recently incriminated to promote atherosclerotic lesion formation and thus might also link infection and atherosclerosis. Enhanced VEGF immunoreactivity within the vessel wall was associated with increased recruitment of mononuclear cells and with the development of intimal thickening in a rat cardiac allograft model.

Infection of human blood monocytes with C pneumoniae significantly enhanced VEGF mRNA expression (9.4-fold ± 5.0, n = 5; P < 0.05; RT-PCR, LightCycler) compared with noninfected cells. In accordance with Bea et al., C pneumoniae–induced activation of Egr-1 and subsequent upregulation of VEGF in human blood monocytes was not abolished by heat treatment of the chlamydiae. Compared with Guha et al., who showed that lipopolysaccharide (LPS) from Escherichia coli is a potent stimulus of Egr-1 in human monocytic cells, our results indicate that Egr-1 induction in human blood monocytes requires viable chlamydiae and is not mediated by the heat-stable chlamydial LPS alone. Furthermore, we could show that Egr-1 induction in human monocytic cells is not specific for C pneumoniae, as coinfection of blood monocytes with Salmonella enterica enteritidis and Staphylococcus aureus also resulted in a rapid and distinct enhancement of Egr-1 mRNA expression. However, these pathogens are not chronically present in the circulation. Although C pneumoniae is the pathogen best described in relation to atherosclerosis so far, our findings encourage the hypothesis that the “pathogen burden,” used as a paraphrase for infections with multiple pathogens (eg, C pneumoniae, Helicobacter pylori, herpes simplex virus), may predispose to the development of atherosclerosis in humans.

Our investigation supports the results from Bea et al. that the MEK-ERK1/2 MAP kinase pathway plays a superior role in the regulation of Egr-1 in C pneumoniae–infected mononuclear cells, as coinfection with the ERK1/2 inhibitor U0126 (Calbiochem) completely blocked postinfectious Egr-1 mRNA expression. Interestingly, the C pneumoniae–induced expression of VEGF mRNA in human monocytes was partially inhibited through blocking of the p38 kinase pathway with SB203580 (Calbiochem) but not to the same extent as blocking of the ERK1/2 kinase pathway. Whereas enhanced expression of VEGF in response to the stimulation with LPS via the p38 kinase pathway has been described previously, our results newly depict the enhanced VEGF expression via ERK1/2 kinase and Egr-1 activation to be dependent on the presence of viable pathogen.

Taken together, the recent article by Bea et al. convincingly describes the central role of Egr-1 activation in the induction of tissue factor expression in mouse macrophages via the MEK-ERK1/2 pathway linking infection and procoagulatory activity. Platelet-derived growth factor (PDGF) could be another candidate, as it was previously shown that Egr-1 binds to the proximal PDGF-A and PDGF-B promoter regions. Our findings on C pneumoniae–infected human blood monocytes expand this view and indicate that enhanced Egr-1 expression may be a common step in the regulation of proatherosclerotic factors involved in the pathogenesis of atherosclerosis not limited to promoting procoagulatory activity. Detection of C pneumoniae in blood monocytes within the circulation of humans favors this pathogen as a causative agent for enhanced Egr-1 activation in blood monocytes among others.

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