Expression of human FIX-ITV using gene transfer allowed hemostasis to be achieved in hemophilia A mice as assessed by a laser-induced injury thrombus formation assay. Furthermore, hemophilia A mice with inhibitory antibodies still achieved hemostasis after tail-clip assay. The half-life of this protein at 37°C in plasma was roughly equal to that of wild-type FIX. If the half-life of FIX-ITV in vivo in humans indeed resembles that of wild-type FIX of ~ 18 to 24 hours, FIX-ITV could result in a prolonged hemostatic activity in patients, which could translate into less-frequent dosing and perhaps a cheaper overall cost of treatment in patients. In addition, because AA8–mediated gene therapy with a wild-type FIX gene has recently been shown to be effective for patients with hemophilia B, it is feasible that gene therapy with a sequence that encodes FIX-ITV could result in a long-term therapeutic effect in hemophilia A patients with inhibitors.

The major concern with a FIXa protein that does not require FVIIIa for activity is that this could induce thrombosis. Although there was no evidence of spontaneous clot formation in mice that expressed FIX-ITV in this study, the duration of expression was relatively short, and the risk of thrombosis will need to be evaluated carefully in the future. Despite this concern, there is a real need for new bypass reagents that have a more-prolonged duration of action than FVIIa or FEIBA, and the benefits of this protein may well outweigh its risk.

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cially isolated by Hisaw and colleagues in 1926, relaxin was named for its capacity to soften the pubic symphysis.2 Produced primarily by the corpus luteum in both pregnant and nonpregnant women, relaxin peaks during the luteal phase of the menstrual cycle, declines in the absence of pregnancy, and rises again early in gestation under the stimulus of human chorionic gonadotropin. During pregnancy, additional relaxin is produced by the chorion and the decidua. Gestational functions of relaxin include softening the cervix, relaxing the uterine musculature, and enhancing endometrial angiogenesis.2 As a modulator of the cardiovascular changes of pregnancy, relaxin is both a potent systemic and renal vasodilator. Increased vascular gelatinase activity and activation of the endothelin B receptor–nitric oxide pathway help mediate the vasodilatory effects of relaxin.3,5

Pregnancy is characterized by dense vascu-logenesis and angiogenesis in the placenta.4 Segal and colleagues have shown that relaxin may contribute to vascularization by mobilizing, activating, and enhancing homing of CD34+ bone marrow–derived endothelial cells (BMDECs) to sites of neoangiogenesis, thus demonstrating a novel function for relaxin during pregnancy and in vascular homeostasis (see figure). Relaxin also increases

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Relaxin’ with endothelial progenitor cells

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Segal and colleagues in this issue of Blood report their findings about an additional new function for the hormone relaxin: turning on bone marrow–derived endothelial progenitor cells to sites of neoangiogenesis.1

Relaxin mobilizes bone marrow–derived endothelial progenitor cells to sites of vascularization.

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intraacellular nitric oxide in human endothelial progenitor cells, which has previously been shown to be critical for BMDEC function. Moreover, Segal et al demonstrate that the NO inhibitor L-NAME and inhibitors blocking the downstream PI3K/AKT pathway can prevent relaxin from stimulating BMDEC chemotaxis. Segal et al have also shown that effects of relaxin on BMDEC function are mediated through the major relaxin receptor RXFP1.

The findings by Segal et al have important implications for vascular homeostasis during health and in disease. Typically, factors that mobilize endothelial progenitor cells, such as G-CSF, are associated with an entire orchestra of like-minded pro-inflammatory players; however, relaxin is unique in its ability to mobilize and activate BMDCES as a putative anti-inflammatory molecule. While this provides a significant advantage for relaxin as an intriguing therapeutic agent in vascular injury states, we do not fully understand the nature of this phenomenon. Although Segal et al have demonstrated that relaxin-induced neovessels are lined by BMDCES, the role of relaxin as the primary conductor of vasculogenesis or as an accompanist remains to be determined. It would be important to evaluate whether relaxin may in addition promote the production of paracrine cues important for angiogenesis and endothelial repair. Nitric oxide has been shown to be important in mediating relaxin’s biologic effects; however, there are other, equally important molecular pathways that were not investigated, such as vascular endothelial growth factor signaling that is downstream of relaxin. Finally, the dosing of recombinant relaxin used by Segal et al was supra-physiologic. Future studies evaluating either relaxin or its receptor-deficient mice during states of physiologic angiogenesis and in diseases (such as in tumor angiogenesis) are needed to fully assess the role of relaxin in vascular health.

Because of relaxin’s potent effects on the cardiovascular system, it has been studied as a therapy for congestive heart failure. A recent randomized phase 2 clinical trial reporting favorable results demonstrated a decrease in cardiovascular mortality and improvement in dyspnea relief. Not only because relaxin is a systemic and renal vasodilator, but also because it is a naturally occurring peptide in pregnancy, a phase 1 safety study of relaxin in women with severe preeclampsia is ongoing, with the goal of increasing placental blood flow and improving maternal hypertension and renal dysfunction. Although circulating levels of relaxin are not altered in pre-eclampsia, relaxin therapy may be particularly beneficial in ameliorating the increased risk of preeclampsia and fetal growth restriction noted in women with egg donor pregnancies (who get pregnant using in vitro fertilization and have no corpus luteum). Circulating numbers of endothelial progenitor cells in pre-eclamptic pregnancies are decreased, which now provides another reason why relaxin therapy may prove useful in pre-eclampsia. Relaxin may also be useful in treating cardiovascular disease in postmenopausal women who have lost normal ovarian function.

In summary, relaxin now joins a distinguished ensemble of molecules that have the capacity to regulate endothelial progenitor cell number and function, with a prospect of being identified as a principal player in gestational vasculogenesis, angiogenesis, and vascular remodeling. Insights from this study by Segal et al as well as prior work suggest that recombinant relaxin may be useful in treating diverse vascular diseases.

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