



ANGIOGENIC EFFECTS OF THE HIF-1 α WITH TRIPLE-POINT MUTATIONS EVALUATED BY ULTRASOUND MOLECULAR IMAGING

ACC Poster Contributions

Georgia World Congress Center, Hall B5

Sunday, March 14, 2010, 9:30 a.m.-10:30 a.m.

Session Title: Contrast Echocardiography

Abstract Category: Contrast Echocardiography

Presentation Number: 1035-205

Authors: *Jian Ping Bin, Jia-jia Xie, Jue-fei Wu, Li Yang, Ming-yan Li, Guang-quan Hu, Jing-jing Cai, Yun-bin Xiao, Ping-sheng Wu, Nanfang Hospital, Southern Medical University, Guangzhou, People's Republic of China*

Background: Hypoxia-inducible factor-1 α (HIF-1 α) is a key transcription factor that regulates genes involved in oxygen homeostasis. While it is highly unstable at normoxic conditions due to the degradation of HIF-1 α by hydroxylation. Recently, a new HIF-1 α bearing triple-mutations of P402, P564 and N803 (TM) was successfully constructed, and its sound effect on angiogenesis was defined in vitro. However, it has not been addressed in vivo. Ultrasound molecular imaging (UMI) has a potential for detection of angiogenesis. We, therefore, hypothesized that TM has a superior potential on neovascularization and UMI could early assess the angiogenic effects.

Methods: 84 mice under unilateral artery ligation were equally divided into 4 groups. Adenovirus (Ad) -mediated genes of Ad-LacZ, Ad-nature HIF-1 α (Ad-NH), Ad-double mutant HIF-1 α 564/803 (Ad-DM) and Ad-TM were locally injected, respectively. The mRNA and protein expressions of HIF-1 α , angiopoietin-1 and VEGF in ischemic muscle were examined by RT-PCR and Western blot analysis. UMI was performed after intravenous injection of microbubbles with α v-integrin antibody (MB α v) or isotype antibody (MBiso). Video intensity (VI) was measured. The densities of capillary and arterioles were analyzed using antibodies against CD31 and α -actin, and the expression of endothelial α v-integrin was detected with antibody against α v-integrins.

Results: The mRNA expressions of HIF-1 α , angiopoietin-1 and VEGF revealed 1.4 to 2.1-fold increase in the Ad-TM as compared to the Ad-NH and Ad-DM. The protein expressions of HIF-1 α and VEGF in the Ad-TM were also obviously higher than those in other groups. VI of the ischemic muscle with MB α v in all groups was significantly higher, the highest VI in the Ad-TM was up to 4-fold, than that with MBiso after only 7-day of treatment. As expected, the similar evidence in expression of endothelial α v-integrin was noted. The densities of capillary and arterioles in the ischemic muscle of the Ad-TM were greater than those of other groups in 2-4 weeks of treatment.

Conclusions: TM has an optimal HIF-mediated angiogenic effects in mouse model of limb ischemia. UMI with MB α v may be useful in the early assessment of therapeutic angiogenesis.