

**PHARMACOLOGICAL INDUCTION OF LEUKOTRIENE B4 12-HYDROXYDEHYDROGENASE (LTB4DH) IN HUMAN NEUTROPHILS AND ITS POTENTIAL IN THE TREATMENT OF MYOCARDIAL INJURY**

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**Objectives:** The aim of this study was designed to test the hypothesis that LTB4 inactivation could serve as specific control of LTB4-mediated infiltration of human neutrophils into ischemic myocardium.

**Background:** Leukotriene B4 (LTB4) is not only a lipid chemoattractant mediating the recruitment of neutrophils into ischemic tissues, but also activates neutrophils to release lysosomal enzymes and to generate reactive oxygen species (ROS). Inhibition of LTB4 is a potential therapeutic strategy for interrupting the vicious cycle involving progressive recruitment and sustained activation of neutrophils within infarcted myocardium. LTB4 12-hydroxydehydrogenase (LTB4DH) converts LTB4 to less active metabolite 12-keto-LTB4. Thus, activation of LTB4DH would provide specific control of LTB4 activities in neutrophils. **METHODS:** We induced LTB4DH expression by two different active compounds, gallic acid (GA) from Radix Peonae Rubra and the compound RA-C from Radix Astragali, respectively.

**Results:** We found that GA and RA-C in combination induced LTB4DH expression in a dose and time dependent manner. LTB4DH induction resulted in reduced LTB4 level, inhibited chemotaxis and enhanced apoptosis in human neutrophils. Importantly, co-administration of GA and RA-C significantly reduced infarct size in a rat model of myocardial infarction. These results strongly suggest that LTB4DH induction is a strategy to resolve neutrophil-mediated inflammation by enhancing the degradation rather than by inhibiting the production of LTB4. Selective elimination of LTB4 will allow simultaneous inhibition of the recruitment and effective induction of apoptosis of neutrophils, leading to the resolution of neutrophil-induced inflammation in infarcted myocardium.