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Anti-inflammatory Actions of hsp90 Inhibitors

John D. Catravas

Vascular Biology Center and Department of Pharmacology, Medical College of Georgia, Augusta, GA, USA

SUMMARY

Although inflammation has been implicated in the pathogenesis of most cardiovascular disease, appropriate anti-inflammatory drugs are sparse. COX inhibitors are single-target agents that lack wide-spread efficacy, whereas glucocorticosteroids exert widespread anti-inflammatory actions, but also severe side effects. Heat shock protein 90 (hsp90) inhibitors may fill this void. Hsp90 exists in complexes with numerous pro-inflammatory ("client") proteins; these complexes promote client protein survival and, in the case of many enzymes, also optimize their activity. Accordingly, hsp90 inhibitors produce anti-inflammatory effects by preventing the association of hsp90 with its pro-inflammatory client proteins resulting in their deactivation and/or degradation.

We have recently reported that the hsp90 inhibitor, 17-AAG (tanespimycin), prevents, as well as repairs endothelial cell hyper-permeability, *in vitro* and *in vivo* (*Am J Respir Crit Care Med 176:667-75, 2007; Am J Resp Cell Mol Biol 39: 551-59, 2008; Amer J Physiol Lung Cell Mol Physiol. 294(4):L755-63, 2008*). More recent work suggests that 17-AAG also inhibits the release of a wide spectrum of pro-inflammatory cytokines from human peripheral blood monocytes, attenuates the right ventricular hypertrophy, vascular remodeling and inflammation associated with pulmonary arterial hypertension, and reduces the inflammation and airway hyper-reactivity in a mouse model of allergic asthma. The specific targets of 17-AAG in these studies are under investigation; initial findings point towards $pp60^{src}$, hsp27, IκK and GSK-3β as key mediators.

17-AAG has recently finished phase II clinical trials as an anti-neoplastic agent, exhibiting a favorable profile of generally mild side effects. It remains to be determined whether a similar profile will characterize the anti-inflammatory use of 17-AAG and other hsp90 inhibitors.