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Anti-Inflammatory Activity of Hsp90 Inhibitors in the Human Vasculature

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Molecular chaperones assist the precise polypeptide folding as well as protect from protein accumulation during cellular growth and development. Heat shock protein 90 is a highly conserved cellular chaperone and one of the most abundant proteins in eukaryotic cells and bacteria but it is apparently absent from archaea. It represents 1-2% of total cellular proteins and participates in the stabilization and activation of more than 200 "client" proteins [1].

The Hsp90 crystal structure was first reported 16 years ago. The first breakthrough of the Hsp90 structure was the identification of the N- terminal domain. It consists of a two layer α/β sandwich structure which forms a "pocket" crucial for ATP binding. The biological function of Hsp90 strongly depends on its ability to hydrolize and bind ATP. The middle segment of Hsp90 consists of a large *αβα* domain at the N- terminus of the construct connecting to a small *αβα* domain at the C terminus via a series of α- helices. This domain is the major site for client protein interactions. The C- terminal domain of Hsp90 is crucial for Hsp90 dimerization and is a dimer of a small mixed α/β domain [2].

Cancer cells use the Hsp90 chaperone machinery to protect various mutated and overexpressed oncoproteins from misfolding and degradation. Therefore, Hsp90 is considered a major regulator of oncogene addiction and cancer cell survival and several Hsp90 inhibitors such as 17AAG (tanespimycin) and 17-DMAG (alvespimycin) have been developed in order to serve as anticancer agents and many optimized synthetic, small-molecule Hsp90 inhibitors from are now in clinical trials [3].

Recent studies have revealed a potent anti-inflammatory and anti-oxidative action of Hsp90 inhibitors in vascular tissues [4-8]. Heat shock protein 90 inhibitors were shown to prolong survival, attenuate inflammation and reduce lung injury in murine sepsis [9]. Furthermore they have attenuated LPS induced endothelial hyperpermeability and have protected and restored pulmonary endothelial barrier function [10,11]. In addition to these effects, long term inhibition of Hsp90 destabilized Nox enzymes, an effect which results to decreased production of reactive oxygen species through ubiquitination and degradation of Nox proteins [12,13].

Hsp90 is regulated at several levels, including the ATPase cycle, association with conformation- specific co-chaperones and by post translational modifications. Hsp90 is subjected to several modifications including phosphorylation, acetylation, S nitrosylation, oxidation and ubiquitination which are believed to modulate its function [14]. Phosphorylation at sites in the M- and the C- domains modulates conformational rearrangements during the ATPase cycle of Hsp90 [15].

Androgen deprivation is widely accepted as first line treatment of metastatic prostate cancer [16]. Since the androgen receptor is a client protein of Hsp90, Hsp90 inhibition could be beneficial in hormone-related prostate cancer treatment [17,18]. Interestingly, low concentrations of Hsp90 inhibitors inactivate key anti-apoptotic proteins and sensitize bladder cancer cells to chemoradiotherapy [19].

The Hsp90 client protein, endothelial nitric oxide synthase, is crucial for the erectile response function. In penile tissues eNOS activity and endothelial NO bioavailability is regulated by post-translational molecular mechanisms, such as eNOS phosphorylation, eNOS interaction with regulatory proteins and reactive oxygen species generation [20]. Hsp90 is involved in the physiology of penile erection and the pathophysiology of erectile dysfunction, since this chaperone is involved in eNOS activation and ROS production.The effect of Hsp90 inhibitors in such tissues have not been sufficiently investigated.

Although there is convincing evidence to support the inhibition of prostate cancers by Hsp90 inhibitors, little is known about the effect of these compounds on benign prostate hyperplasia. BPH is a condition related to the abnormal proliferation of prostatic glandular and stromal tissues and is associated with excessive ROS production and inflammatory processes [21]. Hsp90 inhibitors alone or in combination with other anti-inflammatory and anti- oxidative agents [22] might be useful for BPH treatment, since they could synergically reduce the inflammatory and oxidative processes in BPH tissues [12,13,23]. Furthermore, ongoing research on the post translational Hsp90 modifications may lead to the development of a new, more efficient class of Hsp90 inhibitors. This endeavor might reveal potential beneficial effects of these compounds in the wide spectrum of human pathology and especially in the field of urology.

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