

Intracellular Survival Signaling Pathways and the Role of Raloxifene in Experimental Reversible Aortic Valve Calcification

Mony Shuvy¹, Suzan Abedat¹, Ronen Beeri¹, Michael Valitsky¹, Sameh Daher¹,
Miriam Kott-Gutkowski², Anca Gal-Moscovici³, Chaim Lotan¹

¹ Cardiovascular Research Center, Heart Institute, ² Silberman Institute of Life Sciences,

³ Nephrology and Hypertension Services, Hadassah-Hebrew University Medical Center,
Jerusalem, Israel

Background- Aortic valve calcification (AVC) is an inflammatory active process. Using our animal model of uremia-induced reversible AVC, we assessed the role of apoptosis in AVC. We also explored the effects of raloxifene- an estrogen receptor modulator on AVC.

Methods and Results - Gene array analysis was performed in aortic valves obtained from 3 groups (n=7 each): calcified valves- from rats fed with the uremic diet, valves after calcification resolution following diet cessation and controls.

Additional aortic valves were obtained from four groups of rats (n=10 each): control, calcified valves, valves after calcification resolution, and valves from rats fed with the same diet who also received raloxifen. Analysis included multislice computed tomography (MSCT), histology, antigen and gene expression.

Gene array results suggested that most apoptosis- related genes were changed in a pro-apoptotic direction in calcified valves. Apoptosis was confirmed in calcified valves. Protein analyses showed a significant decrease in Growth arrest 6 (Gas6), ERK and Akt survival pathways.

Resolution of AVC was accompanied by decreased apoptotic features and up-regulation of these pathways. As observed by MSCT and histology, raloxifene significantly decreased AVC. Its effect was associated with apoptosis inhibition and up-regulation of Gas6, ERK and Akt pathways.

Conclusions- We showed that AVC is involved in apoptosis, and in down regulation of several intracellular survival pathways which are restored after AVC resolution. The beneficial effect of raloxifene in AVC was related to activation of anti apoptotic pathways. This novel observation is important in developing efficient remedies for AVC.