

Macrophages Dictate the Progression and Manifestation of Hypertensive Heart Disease in Rat

David Kain¹, Chana Yagil², Natalie Landa-Rouben¹, Yoram Yagil², Jonathan Leor¹

¹*Cardiovascular Research Institute, Tel-Aviv University, Sheba Medical Center, Israel*

²*Laboratory for Molecular Medicine and Israeli Rat Genome Center, Faculty of Health Sciences, Ben-Gurion University, Barzilai Medical Center Campus, Israel*

Background:

Inflammation has been implicated in the initiation, progression and manifestation of hypertension. However, the role of macrophages in hypertension-induced cardiac remodeling has yet to be determined.

Methods and Results:

Hypertension was induced in male Sabra salt-sensitive (SBH/y) rats with high salt diet (8%NaCl) over 6 weeks. Hypertensive SBH/y developed left ventricular (LV) hypertrophy, hyper-contractility and a higher LV ejection fraction (EF). Notably, the number of cardiac macrophages was significantly greater in hypertensive SBH/y than in controls. Macrophage depletion was induced after induction of hypertension by intravenous administration of clodronate liposomes at 3-day intervals over 4 weeks (n=9) and was validated by FACS analysis and ED1 (CD68) staining of heart sections. Control hypertensive rats (n=9) were treated with PBS liposomes. Surprisingly, macrophage depletion was associated with attenuation of hypertension in the clodronate-treated group (from 177±2 to 179±2 mmHg) compared to controls (from 179±2 to 184±5 mmHg, p=0.01). LV systolic diameter and volume were smaller; anterior wall thickening, fractional shortening and EF were higher in the macrophage-depletion group, by serial echocardiography studies (p<0.05). The expression of miR-31, which has been implicated in the pathogenesis of cardiac hypertrophy, was decreased (4.6-fold) in the macrophage-depleted hearts compared to controls. Furthermore, 1 month after BP elevation.

Conclusion:

Our findings suggest a significant role of macrophages in the initiation and progression of salt-sensitive hypertensive heart disease in rat. These effects might be partially mediated by miR-31. Macrophages, therefore, could be a potential therapeutic target to treat hypertension and prevent LV remodeling and dysfunction.