

Bag3 P209L myopathies and efficacy of blocking signaling pathways with the therapeutic peptide, MMI-0100

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Background and Hypothesis: The Bcl2-associated anthanogene (BAG) 3 protein is a member of the BAG family of cochaperones, which play a critical role in cellular processes, including protein degradation and turnover. Over 30 Bag3 mutations have been identified, including a Proline209Leucine (P209L) missense mutation which causes a severe childhood cardiomyopathy. The mechanism by which Bag3 mutations causes cardiomyopathy is currently unknown, but the p38/MAPK signaling cascade has been shown to be altered in our animal model that coexpresses the human Bag3 P209L gene. We hypothesized the cell-permeant peptide, MMI-0100, which is known to inhibit MAPK-activated protein kinase 2 (MK2) activity in the p38/MAPK signaling cascade, would alleviate or reduce cardiac dysfunction.

Experimental Design: Echocardiographic analysis of cardiac function of cardiac-specific Bag3 P209L transgenic (and wildtype littermate control) mice (20 – 22 months of age) was assessed by high-resolution ultrasound echocardiography (VisualSonics Vevo 2100, MS550D probe, cardiology package) to document the established disease-related cardiac dysfunction at baseline. Mice were then treated with 100 μ g/kg/day MMI-0100 nebulized daily for 30 days. Follow-up echocardiography was performed at 10, 20, and 30 days of MMI-0100 treatment. Echocardiographic analysis was performed to determine the systolic function (EF %, FS%), chamber dimensions, and wall thickness in systole and diastole using Vevo 2100 Workstation software package.

Results: Blinded analysis of echocardiographic data identified that Bag3 P209L Tg+ mice had a baseline cardiac dysfunction compared to wildtype controls at 20 months of age (WT= 76% EF, 44% FS; Tg+= 66% EF, 36% FS). MMI-0100 treatment significantly attenuated this dysfunction by 20 days of MMI-0100 treatment (WT= 79% EF, 47% FS; Tg+= 80% EF, 48% FS), consistent with demonstrating for the first time MK2's role in mediating p38 signaling in the pathogenesis of Bag3 P209L cardiomyopathy.

Conclusion and Potential Impact: The MMI-0100 peptide has proven efficacious in several animal models of fibrosis driven by p38 signaling, as MK2 is a p38 downstream mediator. Future studies seek to translate the use of the MMI-0100 peptide in pediatric patients with Bag3 P209L cardiomyopathy through compassionate use FDA pathways.