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(54) Title: BAG3 METHODS AND USES FOR TREATMENT OF INFLAMMATION

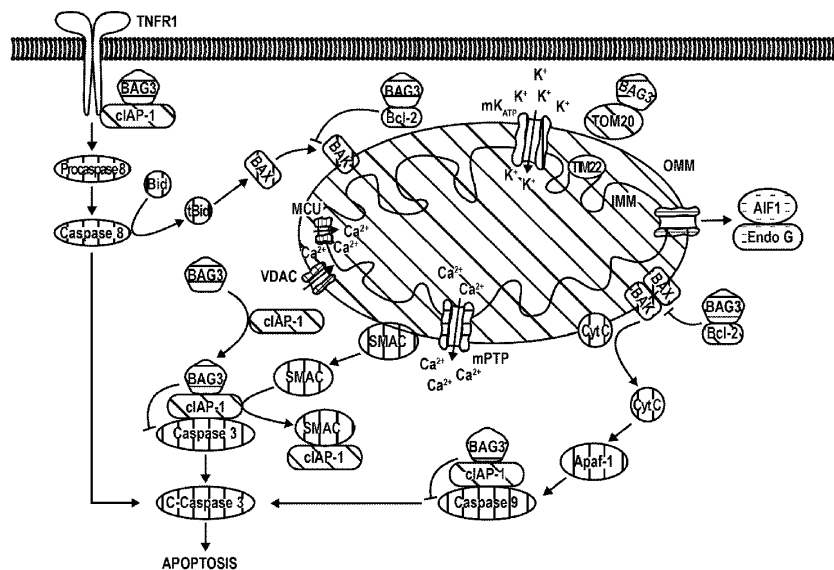


Figure 9

(57) **Abstract:** Bag3 is a multifunctional protein expressed predominantly in the heart, the skeletal muscle, the central nervous system and in many cancers. Although BAG3 was cloned only a decade ago, studies have shown that genetic variants, particularly those that result in haplo-insufficiency, can lead to severe left ventricular dysfunction; however, the full mechanisms responsible have remained obscure. To obviate the influence of heart failure itself on the biology of Bag3, transgenic mice harboring a single allele knock-out were studied between 8 and 10 weeks of age before any obvious signs of heart failure were evident. The results were surprising and informative. First, it was found that despite a normal phenotype, young Bag3^{+/-} had marked changes in the proteome that were characterized by changes in proteins associated with metabolism and apoptosis. Consistent with this

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finding, a decrease in the levels of critical proteins charged with maintaining the mitochondrial membrane potential was observed. It was also found that young mice shifted from a balance between the extrinsic and intrinsic pathways of apoptosis. However, in the presence of stress and the absence of Bag3 there was a shift from a balanced to an extrinsic dominant system (cleaved caspase 8). The diverse array of critical pathways regulated by Bag3 suggests a more important role especially during stress and that this role might include serving as an intracellular glue that holds proteins where they can be most effective rather than having them meet accidentally.