



Knockdown of the putative *Lifeguard* homologue *CG3814* in neurons of *Drosophila melanogaster*

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ABSTRACT. Lifeguard is an integral transmembrane protein that modulates FasL-mediated apoptosis by interfering with the activation of caspase 8. It is evolutionarily conserved, with homologues present in plants, nematodes, zebra fish, frog, chicken, mouse, monkey, and human. The *Lifeguard* homologue in *Drosophila*, *CG3814*, contains the Bax inhibitor-1 family motif of unknown function. Downregulation of *Lifeguard* disrupts cellular homeostasis and disease by sensitizing neurons to FasL-mediated apoptosis. We used bioinformatic analyses to identify *CG3814*, a putative homologue of Lifeguard, and knocked down *CG3814/LFG* expression under the control of the *Dopa decarboxylase* (*Ddc-Gal4*) transgene in *Drosophila melanogaster* neurons to investigate whether it possesses neuroprotective activity. Knockdown of *CG3814/LFG* in *Ddc-Gal4*-expressing neurons resulted in a shortened lifespan and impaired locomotor ability, phenotypes that are strongly associated with the degeneration and loss of dopaminergic

neurons. Lifeguard interacts with anti-apoptotic Bcl-2 proteins and possibly pro-apoptotic proteins to exert its neuroprotective function. The co-expression of *Buffy*, the sole anti-apoptotic Bcl-2 gene family member in *Drosophila*, and *CG3814/LFG* by stable inducible RNA interference, suppresses the shortened lifespan and the premature age-dependent loss in climbing ability. Suppression of *CG3814/LFG* in the *Drosophila* eye reduces the number of ommatidia and increases disruption of the ommatidial array. Overexpression of *Buffy*, along with the knockdown of *CG3814/LFG*, counteracts the eye phenotypes. Knockdown of *CG3814/LFG* in *Ddc-Gal4*-expressing neurons in *Drosophila* diminishes its neuroprotective ability and results in a shortened lifespan and loss of climbing ability, phenotypes that are improved upon overexpression of the pro-survival *Buffy*.

Key words: Lifeguard; Bcl-2; Buffy; Neurons; *Drosophila*; CG3814