BAG3 protein is involved in melanoma cells survival and in Vemurafenib resistance

Guerriero L 1, Rosati A 1,2, Turco MC 2,3

1 Department of Pharmacy (DIFARMA), University of Salerno, Fisciano (SA), Italy
2 BIOUNIVERSA SRL, University of Salerno, Fisciano (SA), Italy
3 Department of Medicine and Surgery, University of Salerno, Baronissi (SA), Italy

BAG3 protein, a member of BAG family of co-chaperones, has a pro-survival role in several tumour types. BAG3 anti-apoptotic properties relies on its characteristic to bind several intracellular partners, thereby modulating crucial events such as apoptosis, differentiation, cell motility and autophagy. In human melanomas, BAG3 positivity is correlated with the aggressiveness of the tumour cells and can sustain IKK-γ levels, allowing a sustained activation of NF-κB. Furthermore, BAG3 is able to modulate B-RAFV600E levels and activity in thyroid carcinomas. B-RAFV600E mutation is the most frequent detected in malignant melanomas and is targeted by Vemurafenib, a molecule used for the treatment of advanced melanoma. However a subset of patients resulted not sensitive or acquired resistance to this molecule. Here we show that BAG3 down-modulation interferes with B-RAF levels in melanoma cells and sensitizes them to Vemurafenib treatment. Furthermore, in an in vitro model of acquired resistance to Vemurafenib, we demonstrated that the down-modulation of BAG3 protein can resensitize this cells to B-RAFV600E specific inhibition. Further studies are focused in demonstrating our hypothesis that the molecular interactions between BAG3 and mutated BRAF can represent a target for novel multi-drugs treatment design.