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A natural biodrug targeting melanoma cells with varying p53 status

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Melanoma is the malignant tumour of the melanocytes, responsible for majority of deaths caused due to skin cancer worldwide. The most challenging aspect of melanoma is the development of multiple drug resistance (MDR) rendering the tumour resistant to chemotherapy. Dacarbazine, a FDA approved drug for melanoma has not been successful in chemotherapy as melanomas develop resistance mechanisms leading to rejection of chemotherapy. A number of factors have been studied for attributing MDR to melanoma cells. P-glycoprotein (P-gp) is one of the most commonly studied drug resistant markers that are overexpressed in melanoma. The p53 status is one of the most critical aspects that play a role in inhibiting apoptosis in cancer cells. Failure of existing chemotherapeutic regimens in the management of melanoma has led to the search for finding alternatives including novel synthetic or naturally available potentially safe anti-cancer agents that help in targeting drug resistant melanoma. We have reported earlier that orally fed bovine lactoferrin (bLf) acts as a potent adjuvant alongside chemotherapeutic agents to cause apoptosis in B16-F10tumours. In this study, extending our previous work, we investigated the anti-cancer efficacy of bLf inmelanoma cell lines with varying p53 status. Two forms of bLf, iron free (Apo-bLf) and >98% iron saturated (Fe-bLf or holo-bLf) have been used to test their effects on SK-MEL-2 (p53 wild type) and SK-MEL-28 (p53 negative) melanoma cells. Both Apo-bLf and Fe-bLf were efficiently internalised into SK-MEL-2 and SK-MEL-28 through receptor mediated cellular uptake of bLf. Increase in the expression of receptors associated with bLf uptake was noted in SK-MEL-2 and SK-MEL-28 when treated with Apo-bLf and Fe-bLf. A significant decrease in the migratory, invasive and colony forming (clonogenic) capacity of the cells was observed when treated with Apo-bLf and Fe-bLf. Interestingly, Fe-bLf and Apo-bLf had a significant effect in reducing the tumour spheroid forming ability of both SK-MEL-2 ($p \leq 0.001$) and SK-MEL-28 ($p \leq 0.001$) respectively proving the ability of bLf in targeting 3D model of tumours. bLf also showed an upregulation in the p53 protein expression and derangement of actin structure of the melanoma cells leading to apoptosis. Importantly, decrease in the expression of anti-apoptotic protein, survivin was observed with both Apo-bLf and Fe-bLf treatments. P-gp and CD-133 expression was downregulated with bLf treatments proving its role in targeting drug resistant melanoma cells and also proving its potential as a carrier for chemotherapeutic drugs. In SK-MEL-2 Fe-bLf proved to have more effect in causing apoptosis, reducing the tumour spheroid formation and P-gp expression whereas Apo-bLf proved more effective in SK-MEL-28. This variation could be due to the Fe metabolism in cells that have varying p53 status. This study recognises the potential role of bLf as a natural therapeutic that can combat various MDR strategies involving stem cells and drug resistant markers in melanoma. Being a natural molecule, bLf will provide a safer and pain-free solution to targeting MDR melanomas.

Biography

Neha Singh has completed her Master's in Applied Microbiology from Vellore Institute of Technology University (VITU) with the highest grade awarded for a thesis dissertation. She is now pursuing her PhD at the School of Medicine, Deakin University and has been awarded the International Postgraduate Research Scholarship. She has 3 peer-reviewed publications and has presented her work at the Sydney Nanomedicine Conference in 2012 and at the Institute of Frontier Materials conference in 2012 and 2013.

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