Systemic delivery of miRNA-loaded nanoparticles blunts resistance to targeted therapy in BRAF-mutant melanoma

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The therapeutic landscape of BRAF-mutated metastatic melanoma has dramatically changed over the last years thanks to the advent of target therapy (MAPKi) and immunotherapies. However, the efficacy of these therapies is still plagued by the onset of drug resistance. microRNAs (miRNAs) have emerged as orchestrators of non-genetic mechanisms adopted by melanoma cells to challenge therapies. In this context, our research group has recently identified a panel of oncosuppressive miRNAs able to counteract the development of drug resistance. Firstly, we explored the therapeutic potential of two oncosuppressive miRNAs, namely miR-204-5p and miR-199b-5p. In order to assess the therapeutic potential of these two microRNAs in vivo we decided to formulate them into Lipid Nanoparticles (LNPs) and to deliver them systemically by i.v. injection. This approach has been developed to overcome the rapid degradation in the bloodstream and the poor intracellular uptake ofmicroRNAs. We demonstrated that LNPs co-encapsulating miR-199b-5p and miR-204-5p inhibit tumor growth both in vitro and in vivo in combination with target therapy and significantly delay the onset of drug resistance. Mechanistically, we showed that they act by directly reducing melanoma cell growth and also by hampering the recruitment and reprogramming of pro-tumoral macrophages.More recently, we observed that another oncosuppresive miRNA previously identified in our laboratory, namely miR-579-3p, which acts by modulating a different set of target genes such as BRAF itself and the oncogenic MDM2, is able to impair the development of resistance to MAPKi invivo when delivered by LNPs. These promising results encouraged us to start developing new LNP formulations able to simultaneously deliver all the three above mentioned oncosuppressive miRNAs, in order to hit multiple oncogenic signaling and to achieve a greater level of inhibition of melanoma cell growth. Overall, these findings have strong translational implications to propose new combinations making use of RNA therapeutics for melanoma, in particular for patients who have developed resistance to current therapies.