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Modeling BRAF inhibitor resistance in melanoma reveals a strategy to forestall drug resistance

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Mutational activation of BRAF is the most prevalent genetic alteration in human melanoma, with >50% of tumors expressing the $BRAFV^{600E}$ oncoprotein. Moreover, the marked tumor regression and improved survival of late stage BRAF-mutated melanoma patients in response to treatment with vemurafenib demonstrates the essential role of oncogenic BRAF in melanoma maintenance. However, since most patients relapse with lethal drug resistant disease, understanding and preventing mechanism(s) of resistance is critical to providing improved therapy. To that end we investigated the causes and consequences of vemurafenib resistance using two independent primary human patient-derived melanoma xenograft models in which drug resistance is selected by continuous vemurafenib administration. In one of these models, resistant tumors show continued dependency on $BRAFV^{600E}$→MEK→ERK signaling due to elevated $BRAFV^{600E}$ expression. Most importantly, we demonstrate that vemurafenib-resistant melanomas become drug dependent for their continued proliferation, such that cessation of drug administration leads to regression of established drug-resistant tumors. We further demonstrate that a discontinuous dosing strategy, which exploits the fitness disadvantage displayed by drug resistant cells in the absence of the drug, forestalls the onset of lethal drug-resistant disease. These data highlight the concept that drug resistant cells may also display drug dependency, such that altered dosing may prevent the emergence of lethal drug resistance. Such observations may contribute to sustaining the durability of the response of melanomas to BRAF inhibitor therapy with the ultimate goal of curative therapy for the subset of BRAF mutated melanoma patients.

Molecular mechanisms triggered by oncogenic Ras isoforms in cancer cell lines: The underestimated role of oxidative stress

Maurizio Bellavia
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This lecture will address the molecular basis of the different effects of Ha-Ras and Ki-Ras expression in cancer cell lines. In particular the speech will underline the importance of intracellular localization of the two Ras isoforms in leading to different biological cellular outcomes. Furthermore it will be highlighted that the peculiar ability of Ha-Ras to stimulate intracellular oxidative stress could be crucial for cancer cell evolution towards a metastatic phenotype through ROS (reactive oxygen species)-mediated loss of cell adhesion.

Preliminary experimental data about effects of oncogenic Ha-Ras and Ki-Ras expression in colorectal carcinoma cell lines will be reported; interestingly these data could suggest an opposite regulation of oxidative stress by the two Ras isoforms. Intriguingly Ha-Ras expression is associated to a growth arrest and morphological/molecular changes compatible with EMT (epithelial-mesenchymal transition).

Biography

Maurizio Bellavia got his Degree in Biological Sciences in 2004 and his Ph.D. in Experimental Oncology in 2010. In the first two years after Degree he studied the molecular mechanisms of oncogene amplification in colorectal tumors, suggesting a role of genetic recombination in triggering gene amplification. During his Ph.D., he studied the effect of oncogenic Ha-Ras and Ki-Ras expression in HT-29 colon cancer cells, suggesting that these two Ras isoforms exert an opposite role in regulating oxidative stress and that Ha-Ras specific stimulation of ROS could be one of the main determinants of acquisition of a metastatic phenotype through ROS-mediated loss of cell adhesion.