Politecnico di Torino

DIMEAS SEMINAR

MELANOMA CHEMORESISTANCE: PROMISING THERAPEUTIC INTERVENTIONS AND INNOVATIVE EXPERIMENTAL APPROACHES

SPEAKER

Barbara Marengo

Associate Professor at the University of Genoa

Abstract

Metastatic melanoma is currently among the most aggressive and difficult to treat human cancer, since many patients develop resistance after six months of treatment. Indeed, although BRAF inhibitors such as Vemurafenib (PLX4032) have importantly changed the therapeutic landscape for patients harboring BRAFV600 mutation, therapy failure is frequently observed. This condition of therapy resistance can be the result of the constitutive activation of MAPK-dependent signalling pathway and of the metabolic rewiring of cancer cells. In this context, metastatic melanoma cells explanted from patients with BRAFV600E or BRAFV600D mutations were chronically treated with Vemurafenib in order to create an in vitro model that mimics the clinical evolution of drug resistance. Metabolic analyses showed that resistant melanoma cells maintain an efficient mitochondrial respiration in comparison to therapy-sensitive counterparts, and display a greater content of antioxidant glutathione. The administration of metabolic modulators such as Terpestacin (Complex III inhibitor) and Metformin (Complex I inhibitor and AMPK activator, commonly used as an antidiabetic drug) has highlighted that the resistance of two cell populations depend on distinct components of the mitochondrial respiratory chain.

Taken together, these results emphasize that melanoma is a dynamic and constantly evolving system, which must be investigated with equally dynamic and evolutionarily cutting-edge experimental tools. The next frontier lies precisely in moving beyond static 2D cultures and focusing attention and efforts on the development of 3D tumor models and bioreactor-based platforms capable of reproducing oxygen, nutrient, and drug gradients in real time. Therefore, the multidisciplinary integration that can be achieved with these advanced systems could not only bridge the gap between in vitro models and the clinical environment, but also, and more importantly, guide the design of next-generation combination therapies useful for counteracting metastatic melanoma and overcoming chemoresistance

Biography

Barbara Marengo is a biologist with a PhD in Biology and Pathology of Aging and a specialization in Clinical Pathology. She is currently an Associate professor of General Pathology at the University of Genoa. She is a member of the PhD course in Experimental Medicine and is responsible for the scientific training of young researchers. Her research focuses primarily on studying the mechanisms of chemoresistance in human neuroblastoma and melanoma cells, with particular attention on the role of antioxidants and redox metabolism, in order to identify new therapeutic strategies. She has many scientific collaborations and, more recently, her interest is also focused on the development of nanoparticle-based therapies. In 2012, she received a Young Investigator Award at the Society for Free Radical Research International congress in London, and a Young Investigator Award for the Best Scientific Contribution at the Italian Society of Pathology and Translational Medicine congress in Udine. She is the author of 69 publications in international journals and has presented at many national and international conferences.

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