

NEW MOLECULAR TARGETS FOR OVERCOMING DRUG RESISTANCE IN TRIPLE NEGATIVE BREAST CANCER

De Luca F.¹, Di Iorio C.², Ratto D.², Priori E.C.^{1,2}, Favaron C.¹, Inguscio C.R.¹, Ferrari B.¹, Savino E.³, Roda E.^{1,4}, Bottone M.G.¹ and Rossi P.²

1. Cell Biology & Neurobiology Lab, Biology & Biotechnology "L. Spallanzani" Dept, UniPV, Italy.
2. Neurophysiology & Integrated Physiology Lab, Biology & Biotechnology "L. Spallanzani" Dept, UniPV, Italy.
3. Mycology Lab, Earth & Environmental Science Dept, DSTA, UniPV, Italy.
4. Clinical & Experimental Toxicology Lab, Pavia Poison Centre, CNIT, Toxicology Unit, ICS Maugeri Spa, IRCCS Pavia, Italy.

fabrizio.deluca01@universitadipavia.it

Triple negative breast cancer (TNBC) is an aggressive cancer with patient survival rarely exceeding five years. TNBC is also the most difficult breast cancer subgroup to treat due to its unresponsiveness to current clinical targeted therapies (e.g., hormonal therapy protocols or chemotherapeutics), high rate of recurrence, and poor prognosis. The lack of a targeted therapy and the TNBC heterogeneity highlighted the urgent need to identify novel therapeutic targets and develop effective medicines capable to overcome drug resistance also hindering the typical TNBC metastatic pattern (i.e., frequent occurrence of distant metastases, mainly localized in lung, central nervous system, and bones) often associated with poor prognosis. One of the most promising sources for potential drug discovery in cancer therapy is compounds of fungal origin, i.e., medicinal mushrooms, which display anti-cancer, onco-immunological, and immunomodulating activities, also improving quality of life during chemotherapy. "Micotherapy U-care" is a novel medicinal mushroom blend supplement consisting of a mixture of mycelium and sporophores extracts of five species (*Agaricus blazei*, *Ophiocordyceps sinensis*, *Ganoderma lucidum*, *Grifola frondosa*, and *Lentinula edodes*), which has been proposed as a promising anti-cancer adjuvant. In particular, our previous studies testing the effect of Micotherapy U-care oral supplementation in a 4T1 triple-negative mouse BC model, demonstrated both an indirect action, i.e. decrease of inflammation and oxidative stress, paralleled by a direct effect on cancer cell leading to reduction of lung metastases and apoptotic pathway activation. In the present investigation, we deepened the knowledge about the alternative molecular mechanisms by which Micotherapy U-care could be able to overcome drug resistance in TNBC. In particular, using complementary techniques, alternative cell death pathways will be explored including mitophagy, and, contextually, mitochondrial fission and fusion dynamics will be investigated, as crucial events involved in TNBC growth and metastatization.