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ISOLATION OF CANCER STEM CELLS FROM CANCER OF UNKNOWN PRIMARY ORIGIN (CUP) AND GENERATION OF A NOVEL *IN VIVO* MODEL OF EARLY, SPONTANEOUS AND MULTIPLE METASTASES BY SUBCUTANEOUS TRANSPLANTATION

Federica Verginelli, D'Ambrosio Antonio, Carollo Rosachiara, Benvenuti Silvia, Senetta Rebecca, Pisacane Alberto, Geuna Elena, Gentile Alessandra, Marsoni Silvia, Balsamo Antonella, Montemurro Filippo, Sapino Anna , Comoglio Paolo M., and **Boccaccio Carla**
Candiolo Cancer Institute, Italy

Cancer of unknown primary origin or CUPs, represent 3-5% of all cancers with a very poor prognosis (overall survival: 9 months). Patients display unpredictable and precocious metastatic dissemination in the absence of a clinically detectable primary lesion. Histologically, CUPs display mostly epithelial morphology but, invariably, they lack expression of lineage markers that allow unambiguous identification of the tissue of origin. Today many efforts are aimed to develop new molecular diagnostic tools to predict the primary tissue and guide to a more rational therapeutic choice. However, the aberrant molecular mechanisms underlying CUP pathogenesis are largely obscure. Here, we show for the first time the isolation and the extensive *in vitro* and *in vivo* characterization of cancer stem cells isolated from CUPs, as cultures named "agnospheres". Specifically, agnospheres are able to grow in suspension and in the absence of growth factors, they express well-known stem cell markers and are endowed with self-renewal ability and long term propagation *in vitro*. They repopulate a tumor when transplanted subcutis in immunocompromised mice at very low number (i.e. as few as 10 cells, stem cells frequency: 5-15%). Most importantly, after subcutaneous transplantation, agnospheres recapitulate the whole metastatic cascade, generating metastases in multiple organs (lung, lymph nodes, thymus...) within a month (estimated metastatic stem cell frequency: 1-2%). For the first time to our knowledge, cancer stem cells have been isolated from CUPs, and phenotypically and functionally characterized. We generated a new cancer stem cell model endowed with extremely high tumor-initiating ability and impressive precocious metastogenic potential in different organs. Agnospheres may represent an unprecedented tool for investigating the molecular mechanisms responsible for the metastatic process in general, and to assess the anti-metastatic effect of approved or new therapeutic compounds.

BIOGRAPHY

Federica Verginelli has accomplished her PhD in Cellular and Molecular Biology at the Tor Vergata University in Rome (Italy), and a 4-years post-doc at the Montreal Neurological Institute (Canada). She is now research associate at the Candiolo Cancer Institute (Italy). She is author of 10 publications that have been cited 297 times, and her publication H-Index is 8.

federica.verginelli@ircc.it