

Appendix: Abstract of research project

RESEARCH AREA 1: Neuro-oncology

1. Glioblastoma multiforme(GBM)

1.1.1 GBM:Epigenetic regulators and small signaling molecules as therapeutic targets for GBM (Illi B. Salvatori L.-IBPM)

Glioblastoma multiforme (GBM), is still the most devastating and incurable brain tumour in the adult. The oncoprotein Myc is highly expressed in a wide variety of tumours, including GBM. In particular, it is required for the maintenance of the stem properties of Glioblastoma Stem Cells (GSCs), responsible for tumour recurrence and resistance to radio- and chemotherapy. The main focus of this research line is the identification of novel Myc post-translational modifications which may act as a switch to control Myc functions. Ongoing experiments show that Myc is both asymmetrically and symmetrically dimethylated by the protein arginine (R) methyltransferases PRMT1 and 5 respectively, being symmetric dimethylation typical of GSCs in their stem conditions, while asymmetrically dimethylated Myc is found in differentiating and less aggressive GSCs. Therefore, we believe that the modulation of differentially modified forms of Myc may control its deregulated activity during glioblastomagenesis and/or GBM progression. Moreover, the functional interaction between Myc, PRMT5 and PRMT1 will be investigated also at genomic level, in terms of chromatin co-occupancy and transcriptomic outcome.

Collaborations:

Mai A. (Dept. of Chemical Pharmaceutics, Sapienza University Rome)

Nanni S. (Institute of Medical Pathology, Università Cattolica, Rome)

1.1.2 GBM: Effect of Nitric Oxide in glioblastoma stem cells (Salvatori L Illi B:-IBPM)

Glioblastoma (GBM) is the most common malignant brain tumor. It features local cancer stem cells (glioblastoma stem cells, GSCs) responsible for enhanced resistance to therapies and tumor recurrence. One potential approach to eradicate GSCs is to force these cells to undergo terminal differentiation. Therefore, the role of differentiation-inducing drugs is receiving increasing attention. Nitric oxide (NO) is an intercellular and intracellular signalling molecule in the brain and is involved in neural development. It plays also key roles in GBM pathophysiology as it is implicated in induction of apoptosis, radio- and chemosensitization. On these bases, we are currently exploring the effect of NO on patient-derived GSCs biological properties. In particular, we aim to understand the molecular mechanisms underlying NO influence on the maintenance of GSCs subpopulation and its pro-differentiation ability.

1.1.3 GBM: Neuroglobin a protein necessary for cell protection in hypoxia condition (Savino C.-IBPM)

Neuroglobin (Ngb) is expressed in brain and is involved in protection of neurons from hypoxia and is likely to be a sensor of hypoxia in cells to trigger neuroprotection, through involvement in anti-apoptotic or anti-oxidant pathways. Nevertheless, its functional role in the cell is not completely understood and it seems to be involved in several interactions with other proteins in different catalytic/signalling pathways. Moreover, Ngb is expressed in glioblastomas and is especially found in tumor regions adjacent to necrosis. Ngb structure is

peculiar: it contains a large internal cavity and displays larger conformational transition upon ligand binding. Detailed analysis of the role of the structural elements determining its dynamics will provide a sounder basis to unravel its still unclear physiological function and mechanism of action. This goal will be achieved using the following techniques: X-ray crystallography, Time resolved X-ray crystallography (TR-XRD) and Time resolved Small and Wide angle X-ray Scattering (TR-SWAXS).

1.1.4 GBM: Sorcin a protein involved in MultiDrug Resistance (Ilari A., Colotti G.-IBPM)

Sorcin belongs to the penta EF-hand (PEF) protein family; as other members of this family, upon calcium binding, Sorcin becomes able to interact with binding partners as Ryanodine Receptors (RyRs). Sorcin is one of the most expressed calcium binding proteins in many brain cancers and is considered a histological marker for malignant glioma. Sorcin plays also an important role in multidrug resistance (MDR) in tumors, since its expression confers resistance to doxorubicin and to other chemotherapeutic drugs. In order to overcome the MDR in brain cancer, one of the possible strategy could be to inhibit the mechanisms of MDR induced by sorcin. For this purpose we aim at identifying peptide able to bind sorcin with high affinity thereby inhibiting the sorcin induced MDR.

Collaborations:

Fazi F. (Sapienza University)

Calì T. (Padua University)

1.1.5 GBM: Mesenchymal stem/stromal cells as a possible anti-angiogenetic approach for glioblastoma treatment (Falchetti ML-IBCN)

Glioblastoma (GBM), the most aggressive astrocytic tumor of the adult, is characterized by a prominent angiogenesis. Mesenchymal stem/stromal cells (MSCs) are a very attractive therapeutic opportunity due to two main peculiarities: the innate tropism for tumor lesions and the ability to uptake and release huge amounts of drugs. Therefore, MSCs can be loaded with chemotherapeutic drugs and used as a Trojan horse for a specific drug delivery to tumors. Moreover, considerable attention to the effects of MSCs secretome on the tumor microenvironment has recently gained considerable attention. We previously demonstrated that MSCs of human origin, derived from bone marrow as well as from adipose tissue, exert an anti-tumorigenic effect on GBM growth in murine xenograft models of orthotopic tumors. MSCs were effective both on the tumor bulk, as we modelled by engrafting the U87MG tumor cell line, and on patient-derived cancer stem cells (CSCs), which represents the tumor cell subpopulation responsible for tumour recurrence and resistance to therapy. Paclitaxel loading didn't significantly enhance the MSCs anti-tumor activity, suggesting that MSCs per se are responsible for the observed impairment of tumorigenicity. Now, we plan to address the effectiveness of MSCs delivery on neoangiogenesis. We will compare the effectiveness of adipose tissue, bone marrow and placental tissue-derived MSCs. Moreover, the tumor tropism and effectiveness on tumorigenicity of MSC-derived microvesicles will be addressed as well.

1.1.6 GBM: Analysis of new molecular and cellular biomarkers and of natural tumor-selective cytotoxic drugs (Dell'Albani P. - IRIB)

Glioblastomas (GBM) are the most aggressive and deadliest brain tumours. Their infiltrative nature and the existence of cancer stem cells, able to relapse new glioma foci, highlight the need for the identification of new and cell-specific biomarkers that could be used as therapeutic targets also. The analysis of Notch receptors among the four grade glioma, both in freshly resected gliomas and in

primary cultures, has highlighted a high expression of Notch-4 in GBM and low levels of Notch-1. Furthermore, the use of two Quercetin-derivatives has revealed cell-specific toxicity against glioma cells, while normal astrocytes and fibroblasts had very limited effects. Since GBMs are very heterogeneous neoplasms, future research should combine recent advances and try to target specific biomarkers, as key molecules, or disrupt their role in signalling pathways activated.

Collaboration:

Department of Neurosciences, University of Catania, Catania, Italy;

Department of G.F. Ingrassia, Section of Anatomic Pathology, University of Catania, Catania, Italy;

Dep of Pharmaceutical Sciences, Section of Biochemistry, University of Catania, Italy.

1.2 Medulloblastoma (MB)

1.2.1 MB: Noncoding RNA in brain tumors (Caffarelli E., Laneve P.-IBPM)

The main focus is on the role of the noncoding RNAs (microRNAs, long noncoding RNAs, circular RNAs) as crucial components of the regulatory networks orchestrating neuronal differentiation programs in mammals. The final aim is to understand how their deregulation may impact on brain tumors. In the last few years, we identified specific neuronal microRNAs (miRNAs) crucial for cell decision between proliferation and differentiation, and new molecular circuitries in which they function as potential onco-suppressors. According to their relevant role, their expression is significantly deregulated in primary brain tumors. Long noncoding RNAs (lncRNAs) are highly tissue-specific drivers of cancer phenotypes: we are studying novel lncRNAs involved in neuronal differentiation and specifically deregulated in medulloblastoma. One of them, functioning as a microRNA sponge, controls the expression of four specific Group 4 medulloblastoma driver genes, representing a novel biomarker and a potential therapeutic target for this enigmatic class of tumors.

Collaborations:

Ferretti E. (Dept of Molecular Medicine Sapienza University, Rome)

1.2.2 Medulloblastoma: new therapy with the chemokine Cxcl3, targeting the migration of neoplastic precursor cells (Tirone F., Ceccarelli C., Micheli L., D'Andrea G. IBBC)

Our laboratory studies the development of the cerebellum, in normal and in the pathological conditions leading to medulloblastoma, the cerebellar tumor. Medulloblastoma is the most aggressive pediatric tumor and about 30% of medulloblastomas arise from cerebellar granule cells (GCPs) undergoing transformation, following activation of the Shh pathway.

We have identified two genes, Tis21/Btg2 and Btg1, which regulate the proliferation and the migration of normal and neoplastic GCPs, and we demonstrated that both genes are medulloblastoma suppressors.

We have observed that the chemokine Cxcl3, target of Tis21, promotes the migration of the GCPs outside the proliferating area of the cerebellum, inducing their differentiation and the arrest of tumorigenesis. We are studying this new therapy in Shh-type medulloblastoma models generated by us.

Collaborations:

Dr. Angela Mastronuzzi, Hospital Bambino Gesù, Rome

1.3 The potential role of the secreted vesicles as biological regulator in the pathogenesis of Neurofibromatosis type I and II (Citrigno L. IRIB)

Neurofibromatosis (NF) type 1 is a condition characterized by changes in skin coloring

(pigmentation) and the growth of tumors along nerves in the skin, brain, and other parts of the body. The signs and symptoms of this condition vary widely among affected people. Non-coding RNA (ncRNA) species have emerged in as molecular fingerprints and regulators of tumor's growth, pathogenesis and progression. Exosomes-mediated vesicular export processes reduce intracellular levels of specific ncRNA in EV donor cells while creating a pool of EV-associated ncRNA in the extracellular space and bio fluids that enables their uptake by other recipient cells; both aspects have functional consequences. Using a Next Generation Sequencing approach, we want to determine the presence and the differences of mRNAs, miRNAs, and lncRNAs within exosomes in patients affected by different forms of NF

Collaboration:

Hussman Institute for Human Genomics, Miami FL; Cedar Sinai Medical Center – Los Angeles, CA