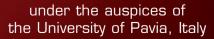
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## THE ROLE OF LACTATE ON METABOLIC REPROGRAMMING IN GLIOBLASTOMA MULTIFORME

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Glioblastoma multiforme (GBM) is the most malignant type of primary brain tumor in humans and it is often associated with a poor prognosis. The Warburg effect is a dominant phenotype of most cancers, which in responsible of excessive conversion of glucose to lactate, and most tumor cells use glycolysis rather than oxidative phosphorylation (OXPHOS) as the main energy metabolic pathway to produce ATP. Although glycolysis is far less efficient than OXPHOS for ATP generation, tumor cells display abnormally high glycolytic rates in order to preserve high ATP levels. Within the glioblastoma tumor microenvironment (TME), tumor cells, stromal cells, and infiltrating immune cells continuously interact and exchange signals through various secreted factors including cytokines, chemokines, growth factors, and metabolites. Glioma cells in the TME transform immune cells to suppress anti-tumor immune cells and evade immune surveillance. In a number of malignancies such as glioma, myeloidderived suppressor cells (MDSCs) have been shown to infiltrate malignant tissues having critical role in the network.

The aim of the present study was to evaluated the role of Lactate on metabolic reprogramming in an *in vitro* model of glioblastoma multiforme. Our results suggested that Lactate (5 mM) induces a significant increase in cell proliferation, migration and invasion and was able to regulate positively mitochondrial biogenesis and increased 0XPHOS genes, showing that it is involved in metabolic switch of GMB cell line.

In addition, we observed that Lactate induce a significant expansion of Treg and M-MDSCs in Healthy control PBMCs, confirming that it is involved in immune-escape mechanisms. In conclusion, the Lactate pathway may be a therapeutic target in Glioblastoma.

## FOURTH SESSION: SEXUAL BEHAVIOR AND DIMORPHISM

## SEXUALLY DIMORPHIC EFFECT OF GENISTEIN ON HYPOTHALAMIC NEURONAL DIFFERENTIATION IN VITRO

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Developmental actions of estradiol in the hypothalamus are well characterized. This hormone generates sex differences in the development of hypothalamic neuronal circuits controlling neuroendocrine events, feeding, growth, reproduction and behavior. In vitro, estradiol promotes sexually dimorphic effects on hypothalamic neuritogenesis. Previous studies have shown that developmental actions of the phytoestrogen genistein result in permanent sexually dimorphic effects in some behaviors and neural circuits *in vivo*. In the present study, we have explored if genistein, like estradiol, affects neuritogenesis in primary hypothalamic neurons and investigated the estrogen receptors implicated in this action. Hypothalamic neuronal cultures, obtained from male or female embryonic day 14 (E14) CD1 mice, were treated with genistein (0.1 µM, 0.5 µM or 1 µM) or vehicle. Under basal conditions, female neurons had longer primary neurites, higher number of secondary neurites and higher neuritic arborization compared to male neurons. The treatment with genistein increased neuritic arborization and the number of primary neurites and decreased the number of secondary neurites in female neurons, but not in male neurons. In contrast, genistein resulted in a significant increase in primary neuritic length in male neurons, but not in female neurons. The use of selective estrogen receptor antagonists suggests that estrogen receptor  $\alpha$ , estrogen receptor  $\beta$  and G-protein-coupled estrogen receptors are involved in the neuritogenic action of genistein. In summary, these findings indicate that genistein exerts sexually dimorphicactions on the development of hypothalamic neurons, altering the normal pattern of sex differences in neuritogenesis.

## TRIBUTYLTIN ALTERS THE DEVELOPMENT OF BRAIN CIRCUITS CONTROLLING FOOD INTAKE

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Spreading of metabolic syndrome is a raising concern. Recent findings highlight the possible involvement of environmental metabolic disruptors or obesogens (*i.e.*, compounds which may interfere with neuroendocrine system impairing the control of energetic balance) in this multifactorial disease. Organotins, as