SOCIETÀ ITALIANA DI FARMACOLOGIA

MODELLO PER INVIO RELAZIONE DI METÀ E FINE PERIODO

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TIPOLOGIA DI BORSA RICEVUTA: Borsa per brevi periodi all'estero

TIPOLOGIA DI RELAZIONE (es.: metà periodo o finale): Metà periodo

TITOLO DELLA RELAZIONE: "Glicolisi e via dei pentoso fosfati come possibili target utili per ripristinare la sensibilità al cisplatino nelle cellule di cancro al seno – Glycolysis and pentose phosphate pathway as possible targets to restore sensitivity to cisplatin in breast cancer cells

RELAZIONE:

Breast cancer is the second most common cancer in the world and women who have this disease show a high rate of relapse [1]. Triple-negative breast cancer (TNBC) is a subtype of breast cancer that is clinically defined by the absence of expression of estrogen and progesterone receptors (EP/PR) and HER2 protein. It is characterized by its unique molecular profile, aggressive behavior, distinct patterns of metastasis, and lack of targeted therapies; hence, surgery and chemotherapy, individually or in combination, appear to be the only available modalities [2]. The use of cisplatin and carboplatin in treatment of TNBCs is currently investigated in clinical trials and initial results indicate a beneficial effect for cisplatin in neoadjuvant chemotherapy. In spite of this, one major challenge in cisplatin therapy is drug resistance which can be intrinsic or occur after several cycles of therapy [3,4].
Although several studies regarding cisplatin resistance have been performed, the molecular mechanisms are not completely understood. Emerging evidence supports the idea that the reprogramming of the metabolic pathways of cancer cells could sustain drug resistance [5].

Therefore, the goal of my project is to explore the alterations of the metabolic pathways in triple negative breast cancer cells which present an intrinsic resistance to cisplatin, with the aim to identify possible targets to overcome the chemoresistance.

For this work different TNBC cell lines were tested for cisplatin resistance and, from previous studies conducted in collaboration with professor Toker,3 lines were chosen. HCC 1143 and HCC1937 are resistant to cisplatin treatment while MDA-MB 468 are sensitive to cisplatin.

Compared to normal cells, tumor cells increase their bioenergetic needs; thus, glucose and glutamine play a pivotal role in the progression of cancer, influencing energy metabolism. Thus, we decided to analyze the dependency from glucose and glutamine for their survival.

Results:

1) Glucose metabolism:

-Cells viability in glucose deprivation: We tested the effect of glucose deprivation on cells proliferation and viability and results obtained indicate that resistant cells are more dependent on glucose to their survival respect the sensitive cells.

-mRNA levels of glycolysis enzymes: the mRNA expression of some key enzymes involved in the glycolytic flux was determined by qRT-PCR. GLUT1, GLUT4, PFKM, PKLR, PGK1, PC, and LDHA levels were analyzed in basal conditions. Results show that there are no significant differences in the expression of the glycolytic enzymes between sensitive and resistant cells. Only LDHA is downregulated in HCC1937 and HCC1143 respect the sensitive MDA-MB-468.

2) Glutamine metabolism:

-Cells viability in glutamine deprivation: We tested the effect of glutamine deprivation on cells proliferation and viability and results obtained indicate that HCC1143 cells are more dependent on glutamine to their survival respect the other two cell lines.

-Cells viability after cisplatin treatment and glutamine deprivation: Preliminary results of viability studies obtained by the association of cisplatin treatment and glutamine deprivation, show that in resistant cells (HCC1937 and HCC1143), the association is more effective in reducing cells viability respect the treatment with cisplatin alone. In fact, glutamine deprivation seems to sensitize resistant cells to the chemotherapeutic drug.

-mRNA levels of glutaminolysis enzymes: the mRNA expression of some key enzymes involved in the glutaminolytic flux was determined by qRT-PCR. ASCT2, LAT1, GLS1/2, GDH1/2, GOT1/2, GTP2 and GS levels were analyzed. Results show that in basal conditions, resistant cells present a higher level of LAT1 and GLS1 respect the sensitive cells, and a lower level of ASCT2, GOT1 and GLS2.

c-MYC and the hypoxia-inducible factor (HIF) are two critical factors for tumorigenesis and, acting in concert, these transcription factors reprogram metabolism, protein synthesis, and cell cycle progression to support bioenergetics and cell survival. These two factors are implicated in the regulation of glucose and glutamine metabolism thus we decided to investigate their expression in our cells in order to understand if the resistant phenomena could be linked to a modulation of the metabolism by these factors. Preliminary results show that resistant cells present a higher basal level of c-Myc mRNA and protein.

In the light of the results obtained, the next months will be dedicated to deeply investigate these two metabolic pathways. In particular, metabolomics analysis will be carried out in glucose or glutamine deprivation to possibly detect which pathway is most involved in the resistance phenomena. Based on the results that will be obtained, the subsequent experiments will be planned.

Bibliography:

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