
**Proyecto PID2022-136968OB-I00 financiado por MCIN/AEI/10.13039/501100011033/ y por FEDER Una manera de hacer Europa**

**Identificación del proyecto:**

Estrés oxidativo y de retículo endoplásmico durante la transición epitelio-mesenquima: nuevas vulnerabilidades de las células metastásicas (FERMET)

**Descripción del proyecto:**

Epithelial tumors, such as those generated in colon or breast, often generate metastatic foci that eventually compromise the patients life. Current chemotherapies mostly reduce tumor burden, but their efficacy is too limited since many tumor cells acquire resistance to the treatment. Cancer cells activate epithelial-to-mesenchymal transition (EMT) to dissociate from the primary tumor and invade the neighbor tissues; moreover, EMT also impinges in other tumoral traits since it provides stem cell characteristics, a higher resistance to chemotherapeutic drugs and even modifies the tumor cell metabolism. For instance, EMT promotes alterations in lipid metabolism decreasing the cholesterol levels and increasing membrane fluidity.

Recent results suggest that these modifications can uncover new vulnerabilities of tumor cells since mesenchymal cells show a higher sensitivity to ferroptosis inducers. Ferroptosis is an oxidative non-apoptotic form of cell death induced by endogenous lipid peroxides generated from polyunsaturated fatty acids. In this proposal we plan to analyze a hypothesis based on these results: active invasive tumor cells need elevated levels of unsaturated fatty acids to be fully functional and as consequence they undergo higher levels of lipid peroxidation. This makes these cells sensitive to drugs exacerbating the toxic effects of these lipids, such as ferroptosis inducers. Therefore, cells that have undergone an EMT are more sensitive to oxidative stress (OX) and need a functional system to counterbalance it. We plan to study how an EMT confers cell sensitivity to ferroptosis and how this is associated to other EMT-associated properties. We will also assess the impact of the changes observed in lipid metabolism such as fatty acid poly-unsaturation or cholesterol decrease on EMT and ferroptosis sensitivity.

We also plan to interconnect this OX stress with endoplasmic reticulum (ER) stress, since these two types of stress are associated. Accordingly, Sigma 1 receptor (S1R), a key modulator of ER stress also controls OX stress. Moreover, S1R activity is blocked by antipsychotics, drugs that prevent tumor cell invasion in in vitro assays. We plan to investigate how these two types of stress are interrelated in EMT and if ER stress is also generated and is necessary for an extensive activation of mesenchymal genes and other EMTrelated properties. We will also assess the effect of antipsychotics on EMT using primary tumor cells and animal models and elucidate their mechanism of action.

We believe that this research will shed light on the mechanisms controlling EMT and tumor metastasis, particularly those related to an integrated stress response, and allow us to

determine why cells that have undergone EMT are more sensitive to OX stress-increasing

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compounds and maybe also to ER stress effectors and will allow antipsychotic drugs to be repurposed for antineoplastic use, either alone or in combination with other existing therapies.

**362.500,00€**

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