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BOOK OF ABSTRACTS

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0328-R-P

Study of the antitumor potential of stauprimide in breast cancer

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Stauprimide, a semi-synthetic derivative of staurosporine, was characterized in 2009 as a potent differentiation-enhancing compound in embryonic stem cells [1]. Although it was first thought that this compound could maintain the properties of staurosporine as a non-selective inhibitor of protein kinases (especially potent in inhibiting tyrosine kinases), it was found that its potential as an inhibitor of these proteins was not particularly remarkable, ruling out this as its main mechanism of action for the differentiation-enhancing effect. However, a clear effect of stauprimide on embryonic stem cells was identified as an inhibitor of CMYC expression, a key factor in the maintenance of stem cell pluripotency [1]. Given the involvement of CMYC in cancer development, and the effect of stauprimide inhibiting its expression, this compound was proposed as a possible antitumor drug in the treatment of renal cancer [2].

In this work we have studied the in vitro antitumor effect of stauprimide in the context of breast cancer, exploring also the possible mechanisms of action by which stauprimide exerts its effects. The detected activity of this compound on the human adenocarcinoma model used in our studies suggests its potential usefulness in antitumor pharmacological strategies.

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[1] Zhu et al. (2009). Cell Stem cell, 4:416. DOI:10.1016/j.stem.2009.04.001. [2] Bouvard et al. (2017). PNAS, 114(13), 3497- 3502. DOI:10.1073/pnas.1702663114.

0330-R-P

Intravenous immunoglobulin treatment modulate monocytes in patients with haematological malignancy

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INTRODUCTION: Secondary immunodeficiency (SID) is a common complication of haematological malignancies (HM) and their chemotherapeutic protocols. The immunological deregulation could be expressed as a specific antibody deficiency manifested by recurrent infections mainly affecting respiratory system and sepsis. Intravenous gammaglobulins (IVIg) is widely established as a prophylactic treatment in SID. Nevertheless, IVIg hold other important features as immunomodulation and homeostatic effects which are not well defined in SID patients.

AIM: This is a proof of concept study to determinate the myeloid-derived suppressor cells (MDSCs) profile in peripheral blood in SID patients receiving IVIg for the first time.

METHODS: We evaluated the myeloid profile in 6 SID patients with HM (four with non-Hodgkin lymphoma and two with chronic lymphocytic leukemia) associated to recurrent infections, before and after the first infusion of IVIg. Freshly collected blood samples were analysed by multiparametric flow-cytometry. The populations were characterized based on the surface expression of MDSCs and monocyte subsets.

RESULTS: In our cohort, we observed a significant expansion of MDSCs population (HLA-DR^{low}CD14^{+}) after IVIg infusion in comparison with baseline levels (37.42% to 59.70% p=0.0192). Regarding monocytes profile, a significant decrease in non-classical (4.18 % to 0.45% p=0.0210) and intermediate subset (11.00% to 5.73% p=0.0452), with a significant increase in classical monocytes (82.15% to 90.2% p=0.0064) was observed after the infusion.

CONCLUSIONS: Our preliminary results suggest that increased blood MDSCs could derivate from the egression of monocytes and macrophages precursors from the bone marrow due to IVIg treatment. The ability of gammaglobulin to modulate the macrophages polarization deserves further characterization in HM setting.

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0332-P

Optimization of Three-dimensional Prostate Cancer Models as useful Platforms for Drug Screening

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The heterogenous nature of prostate cancer (PCa) represents a significant stumbling block to the development of effective therapeutic approaches [1]. The study of potential PCa treatments primarily employs monolayer cultures of in vitro-adapted cell lines; however, this traditional two-dimensional (2D) scenario remains far from clinical reality.

Therefore, we aimed to develop three-dimensional (3D) PCa models, which display in vivo-like characteristics that include enhanced cell-cell interactions and oxygen gradients [2, 3], as an advanced means to screen potential therapeutic strategies.

We optimized conditions for homospheroid formation using the hanging drop method with the androgen-sensitive VCaP and androgen-insensitive PC3 prostate cancer cell lines. We then compared the effect of inhibitors of poly (ADP-ribose) polymerase and androgen biosynthesis and conventional therapeutic agents via cell viability assays in 2D and 3D culture. We also optimized the formation of heterospheroids comprising VCaP-GFP and hTERT-PF179T cancer-associated fibroblasts to understand the role of the tumor microenvironment in PCa treatment responses.

Optimized formation conditions generated larger PC3 homospheroids and more compact VCaP homospheroids. Interestingly, the same concentrations of our candidate therapeutics displayed lower activity in the 3D PCa models when compared to the 2D models, suggesting increased resistance. We are currently undertaking further studies to explore the root causes of this effect. Optimized formation conditions for heterospheroid formation employed a 1:1 ratio of cells and similar conditions to homospheroid formation.

We optimized homospheroid formation using the VCaP and PC3 prostate cancer cell lines by the hanging drop method and corroborated the utility of these models in drug testing by demonstrating significantly different outcomes compared to 2D models. We also optimized heterospheroid formation by the hanging drop method, combining VCaP-GFP cells and cancer-associated fibroblasts. This model will allow us to explore the fundamental role of the tumor microenvironment in treatment response and resistance to promote the development of efficient therapeutic approaches for prostate cancer.

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0368-R/M-P

The impact of diet-protein content in telomerase regulation

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Higher telomere length (TL) is associated with longevity, while telomeres shortening are related with some non-communicable diseases (NCDs) such as cancer or cardiovascular disease, and with higher risk of mortality. Telomerase RNA component (TERC) and peroxiredoxin-1 (PRDX1) are involved in the regulation of Telomerase, an enzyme capable to extent TL. Diet could play a role in telomere shortening by regulation of cellular oxidative stress and by modulate the expression of certain genes involved in Telomerase Activity (TA) as presented before. This paper study how low-protein diet (LPD) and leucine deprivation (LEU(-)) in tandem with fibroblast growth factor 21 (FGF21) can affect the relative gene expression of Terc and Prdx1 in mice. Murines with and without FGF21 were fed with LPD and LEU(-), with corresponding Control Diet (CD) group for each one. Relative liver mRNA levels of Terc and Prdx1 were determined by RT-qPCR. Results suggested that diet-protein content and FGF21 could impact on Terc and Prdx1 expression by modulating oxidative stress of the cell. LPD synergized with FGF21 to increase Prdx1 mRNA levels (p=0.00096), but inconsistency and the contradictions of the findings did not allow to suggest accurate conclusions and for that reason further investigations with better designs are needed.

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Microvascular endothelial cell autophagy regulates neutrophil trafficking

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A key feature of an inflammatory reaction is tissue infiltration of neutrophils, a response that requires breaching of endothelial cells (ECs) that line the vascular lumen (*1*) (*2*). In recent years numerous metabolic, catabolic and redox sensitive pathways have been implicated in the regulation of leukocyte trafficking. In particular, autophagy, an evolutionary conserved process that enables the delivery of