POSTER SESSIONS

Poster Session 1

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PS1-1 / CDK4/6 inhibitors and antiprogestins: therapeutic combination in breast cancer experimental models with high levels of progesterone receptor isoform A
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Luminal breast cancers are susceptible to an endocrine therapy. Palbociclib (PALBO), a CDK 4/6 inhibitor, is currently used in combination with endocrine therapy to treat advanced hormone receptor-positive breast cancer (BC). However, with time patients acquire resistance. Therefore, alternative therapies are required to reduce BC mortality. We have recently reported that BC patients with tumors expressing higher levels of isoform A of the progesterone receptor (PRA) than isoform B (PRB) may benefit from an antiprogestin treatment. The aim of this study was to evaluate the effect of PALBO in combination with the antiprogestin mifepristone (MFP) in the T47D BC model. We have already shown that MFP (10 nM) inhibits cells proliferation of T47D and T47D-YA cells (expressing only PRA) but not of T47D-YB cells (expressing only PRB). PALBO (100 nM) inhibited cell proliferation in the three cell lines. The combination of MFP and PALBO induced an additive inhibitory effect only in T47D and T47D-YA cells ($p < 0.001$). To confirm these results *in vivo*, we inoculated T47D cells into NSG female mice. When the tumors were palpable, mice were treated with PALBO (20 mg/kg sc x 5 days a week) and/or MFP (0.5 mg/pellets; suboptimal dose), or vehicle. Only the drug combination was effective inducing a significant inhibition of tumor growth ($p < 0.01$) confirming the therapeutic potential of this combo. Ongoing studies will unravel the mechanism related with both pathways crosstalk.

PS1-2 / Parameters associated with metastatic dissemination are differentially modulated by specific isotypes of the retinoic acid receptor (RARs) in triple negative mammary cancer models
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Migration and adhesion are highly related to metastatic dissemination and retinoid system is implicated in their modulation. Objective: To evaluate the effect of activating each retinoic acid receptor (RAR) isotypes in migration, soluble MMPs activity, adhesion and metastatic potential in LM38LP and 4T1 triple negative murine cell lines. Both express all RAR isotypes except for RARβ in 4T1. Cells were treated with RARα agonist AM580 (200nM), RARβ agonist AC55649 (2μM), RARγ agonist BMS961 (50nM) or vehicle (DMSO). Migratory potential was evaluated by wound healing assay. AM580 and AC55649 reduced LM38LP migratory capacity ($p < 0.05$) while AM580 increased migration in 4T1 ($p < 0.05$). MMPs were analyzed by zymography. AM580, AC55649 and BMS961 decreased soluble MMP2 activity in LM38LP. On the contrary, AM580 increased MMP2 and MMP9 activity in 4T1. Besides, AM580 and AC55649 diminished LM38LP adhesive capacity while AC 55649 increased this in 4T1. In an experimental lung metastasis assay, cells treated with agonists where inoculated in BALB/c mice. The AC55649 pretreatment increased metastatic potential of LM38LP ($p < 0.05$) while BMSS961 increased metastasis in 4T1 cell line ($p < 0.05$). We hypothesize that the differences in RARβ expression between the cell lines could be responsible of opposite responses in biological effects studied. The increment in metastasis by RARβ/γ activation could be due to selection of a minority population with greater plasticity to colonize the metastatic site.

PS1-3 / Effect of 2'-nitroflavone on the expression of receptors associated with EGFR activity in breast cancer cells
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Flavonoids were proposed as chemopreventive and chemotherapeutic agents *per se* or in combination with traditional antitumoral drugs. Epidermal growth factor receptor (EGFR) is associated with tumorigenesis of several tissues and it can be involved in the molecular mechanism of action of several flavonoids. With the aim of investigating if a combinatory therapy involving 2'-nitroflavone (2'NF), a synthetic flavonoid with antitumor properties, and EGFR inhibitors would be a possible effective treatment for breast cancer, we studied if this flavone modulates the expression of EGFR or other receptors that interact or modulate EGFR activity. MDA-MB-231 and MCF-7 breast cancer cells were treated with 2´NF at different concentrations for 48 h. Afterwards, the protein content of EGFR, ErbB2, ER alpha, Met and IGF-IR were assessed by immunoblotting. Besides, PARP cleavage and phosphorylation of p38 were determined in the same experimental conditions. Results showed that 2´NF produced a reduction on the content of ErbB2 and IGF-IR in MDA-MB-231 cells, while in MCF-7 cells a decrease on the expression of EGFR, ErbB2 and ER alpha was observed. Both cell lines presented an increment in p38 phosphorylation and PARP cleavage upon 2'NF treatment. In conclusion, 2'NF demonstrated to have effects on the expression of receptors associated with EGFR activity which could justify a possible combinatory therapy involving 2'NF and EGFR inhibitors.

PS1-4 / Analysis of Akt molecular, subcellular and tumoral code as an explanatory and predictive tool for the effectiveness of therapies against breast cancer
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Cancer is a highly heterogeneous disease with significant cell-to-cell variability. Therefore, understanding the sources of this heterogeneity might help to design new therapies. Akt is a therapeutic target for cancer treatment and it is known to be regulated through numerous posttranslational modifications (PTMs) as well as to be recruited to different subcellular compartments. However, little is known about how a cell determines which substrates and functions Akt should regulate. Our hypothesis is that the Akt molecular code, *i.e.* the profile of PTMs of Akt, can determine its subcellular localization and vice versa, thus establishing the subset of Akt substrates and functions that Akt displays after each stimulus/cellular context. The aim of this study is to determine modification and subcellular localization patterns of Akt and its substrates in different mammary cell lines, both normal and tumor, and to analyze if a correlation between these variables and the resistance/sensitivity of these cell lines to antitumor drugs can be established. Using a strategy that combines automated imaging and quantitative measurement of Akt localization, we discovered novel Akt modifications and localizations. Preliminary results show that phosphorylation and localization patterns of Akt and its substrates differ between normal and tumor mammary cell lines. A bioinformatic study was performed to analyze association of Akt substrates grouped by cell compartment and different types of neoplasms.

PS1-5 / A potential strategy to prevent drug resistance: Chromosome instability can be prevented with no changes in the induction of cell death after Chk1 depletion
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The DNA damage response (DDR) is a complex network that assists the completion and fidelity of DNA replication upon DNA insults. Because cancer cells are subject to high levels of replication stress they heavily rely on the DDR. Conventional anticancer therapy exploits this vulnerability by inhibiting DDR effectors. Checkpoint Kinase 1 (Chk1) is a crucial mediator of the DDR whose inhibition is undergoing clinical evaluation, especially in prostate, ovarian and triple-negative breast cancers. It is currently accepted that DDR inhibitors trigger cell death as a consequence of increased replication stress and the ensuing chromosome instability (CIN). The link between replication stress and cell death has been validated in Chk1-deficient cell models; however, no unambiguous relationship has been established between replication stress, CIN, and cell death. Given that CIN fuels drug resistance, elucidating the molecular triggers of CIN and their relevance to cell survival is central to cancer research. We will present data, published in Calzetta et al., Sci. Adv., 2020, that unravel the identity of the molecular effectors of CIN activated by Chk1 deficiency. Unexpectedly, the pathway leading to CIN is independent of the one causing replication stress-dependent cell death. We propose that cancer treatment with Chk1 inhibitors might be improved by repressing the CIN pathway identified by us to avoid or reduce the generation of mutations that promote drug resistance.

PS1-6 / Exploring the role of hyaluronan and CD44 in resistance to ErbB-2-targeted therapies in breast cancer
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Hyaluronan (HA), through interaction with its receptor CD44, induces tumor progression. ErbB-2, a member of ErbB family of membrane receptor tyrosine kinases, migrates to the nucleus (NErbB2) where it acts as a transcription factor/coactivator to modulate proliferation and resistance to anti-ErbB-2 agents in breast cancer (BC). Accumulation of HA is associated with poor prognosis and promotes resistance to anti-ErbB-2 agent trastuzumab (TZ) in BC. Although crosstalk between HA/CD44 and ErbB-2 pathways has been reported, how their molecular interactions mediate TZ resistance remains unknown. Our *in silico* studies showed that TZ-resistant cells presented higher CD44 levels than TZ-sensitive ones. Stimulation with the ErbBs ligand heregulin (HRG) induces NErbB-2 translocation, acquired-TZ resistance and proliferation in SKBR3 cells. HRG also increased CD44 expression in SKBR3. In a *de novo* TZ-resistant BC model, JIMT1, the constitutive levels of nuclear CD44 (NCD44) and NErbB-2 were further enhanced by HA stimuli. Treatment with the chemical inhibitor of HA synthesis 4-methylumbelliferone (4MU) decreased not only HA levels but also NErbB-2 in JIMT1 cells. Furthermore, 4MU inhibited proliferation and migration of JIMT1 cells similarly to the inhibition observed when ErbB-2 was excluded from the nucleus via transfection with hErbB-2ΔNLS mutant. 4MU also inhibited HRG-induced proliferation in SKBR3. Our findings highlight the blockade of HA synthesis as a novel therapeutic strategy in TZ-resistant BC.

PS1-7 / GEF-H1 drives tumor formation, motility, invasion and metastasis in breast cancer
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RhoGTPases family are involved in several biological process including gene transcription, cell polarity,