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JOINT MEETING OF BIOSCIENCE SOCIETIES

LXII ANNUAL MEETING OF ARGENTINE SOCIETY OF CLINICAL INVESTIGATION (SAIC)

LIII ANNUAL MEETING OF ARGENTINE SOCIETY OF BIOCHEMISTRY AND MOLECULAR BIOLOGY (SAIB)

LXV ANNUAL MEETING OF ARGENTINE SOCIETY OF IMMUNOLOGY (SAI)

MEETING OF ARGENTINE SOCIETY OF ANDROLOGY (SAA)

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ANNUAL MEETING OF ARGENTINE SOCIETY OF PHYSIOLOGY (SAFIS)

MEETING OF ARGENTINE SOCIETY OF HEMATOLOGY (SAH)

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ange staining. Furthermore, an increment of hypodiploid cells was detected by flow cytometry analysis. In conclusion, we demonstrated that a specific combination of safingol and 2´NF synergistically inhibited mammary tumor cell proliferation. This finding encourage us to study the molecular mechanisms involved in this effect and to consider this drug combination as a potential therapy for mammary cancer treatment.

Keywords: flavonoids, safingol, mammary tumor, antiproliferative effect, synergism

GENETICS AND MOLECULAR BIOLOGY 7

(318) TRANSMEMBRANE-DOMAIN SHAPE IS A NOVEL ENDOCYTOSIS SIGNAL FOR SINGLE-SPANNING MEMBRANE PROTEINS

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Endocytosis is crucial for all cells as it allows them to incorporate material from the extracellular space and control the availability of transmembrane proteins in the plasma membrane. The classical model for endocytosis of membrane proteins involves cytosolic signals that interact with adaptor proteins, driving active concentration of cargo in endocytic vesicles. In yeast, endocytosis followed by recycling to the plasma membrane results in a polarised distribution of membrane proteins by a kinetic mechanism. Here we report that increasing the volume of the residues that constitute the exoplasmic half of the transmembrane domain in the yeast SNARE Sso1, results in its polarised distribution at the plasma membrane. Expression of this chimera in strains affected in either endocytosis or recycling revealed that this polarisation is achieved by endocytic cycling. A bioinformatics search of the *Saccharomyces cerevisiae* proteome identified several proteins with high-volume exoplasmic hemi-TMDs. Our experiments indicate that TMDs of these proteins can confer a polarised distribution to the Sso1 cytoplasmic domain, indicating that the shape of the TMD can act as a novel endocytosis and polarity signal *in yeast.* Additionally, high-volume exoplasmic hemi-TMDs can act as an endocytosis signal in mammalian cells in culture.

(556) ATP RELEASE DEPENDS ON AUTOPHAGIC STIMULATION AND RAB21 IN HELA CELLS

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ATP exocytosis has emerged as an important autocrine/paracrine signal to trigger responses regarding platelet aggregation, inter-astrocytes communication, cell migration, differentiation, etc. The molecular mechanisms underlying this process have not been well defined so far. In addition, autophagy-dependent ATP release was shown to be an important process involved in immunogenic cell death and inflammation. Autophagic exocytosis has been also implicated in IL-1β, IL-18, galectin-3 secretion and presentation of antigens to the major histocompatibility complex. The regulation of this process is poorly understood. Our group has previously shown that there is an important role of the v-SNARE protein VAMP7 in the autophagic ATP exocytosis. Since there is a close connection between VAMP7, the small GTP-ase Rab21 and autophagy we decided to investigate the role of this Rab protein, its guanine-nucleotide exchange factor VARP and another Rab related to VARP (Rab32) in the autophagic exocytosis of ATP. HeLa cells were transiently transfected with GFP-Vector, YFP-Rab32wt, YFP-Rab32T39N (negative dominant mutant), GFP-Rab21wt, GFP-Rab21T33N (negative dominant mutant) and/or RFP-LC3. Then we incubated this cells in full medium, resveratrol 50nM and rapamycin 50nM for 4 hours or starvation medium for 2 hours. We used LC3B or VARP antibodies to detect endogenous proteins. Lysotracker red was put 30 minutes before the incubation finished. For ATP release assays, we used the luciferin-luciferase kit to measure the amounts of ATP in the extracellular medium. We took samples at 0, 30, 60, 90, 120, 180 and 240 minutes after the autophagic stimulus began. We found that autophagy leads to a redistribution of Rab32 or Rab21 molecules to the cell periphery, where they colocalized with LC3 and VARP. ATP release was significantly increased in starvation and in less content in resveratrol condition. Our results suggest a role for Rab21, Rab32 and VARP in the autophagic exocytosis of ATP.

Keywords: Rab21, ATP release, Autophagy, Rab32, VARP

(759) CAMP REGULATES PHAGOSOMAL MATURATION DURING *STAPHYLOCOCCUS AUREUS* INFECTION

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Staphylococcus aureus is a microorganism that causes serious diseases in humans and it is known to induce an autophagic response in the host cell upon infection. We have previously demonstrated that the virulence factor a-hemolysin (Hla) is responsible of this autophagic response and it is used by the microorganism for escaping from its containing phagosome labelled with the autophagic protein LC3. We have further demonstrated that the autophagy induced by this bacterium is independent of the canonical PI3K/Beclin1 pathway and, instead, it is regulated by an AMPc/Epac/Rap2b pathway. In the current work we studied the implication of this pathway in the maturation of the *S. aureus* phagosome. We have found that treatment of infected cells with the second messenger cAMP, besides of regulating the autophagic response induced by *S. aureus,* also regulates its phagosome maturation by altering the recruitment of the small GTPase Rab7. We further found that the cAMP analogue, 8pCPT, which is able to specifically activate Epac1 also alters Rab7 association to the *S. aureus* phagosome. Likewise, overexpression of YFP-Epac1 itself has the same inhibitory effect. However, when we analyzed the effects of Rap2b, a downstream target of Epac1, the recruitment of Rab7 wasn't impaired. Therefore, our results indicates that cAMP regulates the maturation of the *S. aureus*-containing compartment in an Epac dependent but Rap2b independent-manner suggesting that other effectors might be involved.

Keywords: Staphylococcus aureus, phagosome, Rab7, cAMP.

(793) THE *C. elegans* DAUER LARVA UNCOVERS A ROLE FOR CHD7/8 IN AUTOPAGHY REGULATION

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Abstract: In harsh environments, the nematode *C. elegans* develops into a dauer larva, a stress-resistant, metabolically altered and long-lived variant of the L2-stage larva. The nuclear hormone receptor DAF-12 plays important roles in development and aging and is required for dauer formation. We identified DAF-12 target genes by chromatin immunoprecipitation. To address the relevance of these genes, we conducted an RNAi screen for dauer suppressors. Inhibition of *chd-7* (chromodomain helicase DNA-binding protein) leads to developmentally arrested, abnormal dauers that are sensitive to SDS and have impaired fat accumulation. Notably, the allele *chd-7(gk290)* forms abnormal dauers with these same features, validating our screen. Longevity of *daf-2(e1370)* and *glp-1(e2144)* mutants is significantly impaired by *chd-7(gk290)* and *chd-7* overexpression increases lifespan. Loss of *chd-7* function resembled mutations in autophagy genes allowing us to uncover roles for *chd-7* and its mammalian ortholog in this process. Specifically, both *chd-7(gk290)* worms expressing the autophagy sensor GFP::LGG-1 and