often occurs as ascites in advanced stages contributing to a bad prognosis. During the progression of the disease, adipocytes (ADPs) are reprogrammed into cancer-associated ADPs (CAAs), however, it is still poorly understood how they are integrated into the OC signaling network.

To tackle this question, we analyze the reprogramming of ADPs into CAAs upon ascites incubation in two in vitro models of adipogenesis (3T3-L1 and 3T3-F442A) as well as in primary ADPs isolated from gonadal fat (C57/BL6 mice).

The expression of most of the ADP markers tested (i.e., Fasn, Lpl) was decreased upon reprogramming (as measured by RT-qPCR). A downregulation of pro-inflammatory cytokines (i.e., Il-6) was also observed. In contrast, the adipogenic marker Fabp4 was up-regulated in CAAs, as previously described for other tumors. Of note, the triglyceride content of ADPs was also altered.

We further investigate the impact of reprogramming on the secretome of ADPs by analyzing the extracellular vesicles (EVs) in terms of quantity and phenotype by nano-flow cytometry (nFCM). Our results showed an increased release of EVs from CAAs compared to control ADPs with an altered tetraspanin coating (i.e., Cd63 and Cd81), indicating a potential alteration of the EV biogenesis and cargo loading in CAAs.

Moreover, preliminary functional assays using ID8 cells (epithelial OC cell line) revealed higher migration rates of cancer cells upon stimulation with the CAA-derived secretome. Additionally, co-culture experiments of ID8 cells and CAAs validated these observations. We aim to further investigate potential EV-mediated effects on proliferation, invasion, and chemoresistance in OC cells. In addition, follow-up experiments are planned to further characterize the phenotype, biogenesis, and cargo of CAA-derived EVs as well as how they are integrated into the OC signaling network.

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Role of HGF/c-Met in liver regeneration during chronic cholestatic damage

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HGF/c-Met signaling plays a critical role for liver regeneration during chronic damage through its mitogenic, survival, and morphogenic effects on hepatocytes and hepatic progenitor cells/oval cells (OC). Nevertheless, the molecular mechanisms underneath HGF/c-Met pro-regenerative effects are not fully elucidated. To analyze the impact of c-Met overexpression on liver regeneration upon cholestatic injury and on hepatocyte and oval cell function we have used a transgenic mouse model (Tg-Met) with a moderate overexpression of c-Met receptor in the liver (albumin-positive cells) submitted to chronic feeding with a diet supplemented with the cholestatic agent 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC). Results show that overexpression of c-Met leads to a diminished liver damage, evidenced by lower levels of serum biomarkers of liver damage such as bilirubin and alkaline phosphatase. Interestingly, decreased damage is associated with a decreased OC expansion and an enhanced hepatocyte proliferation. In parallel, Tg-Met livers display enhanced an upregulation of the Nrf2 nuclear factor, an altered expression profile of enzymes involved in glutathione metabolism, and increased levels of reduced glutathione and less reactive oxygen species during DDC treatment, along with an improved profile of pro-fibrotic markers. These findings evidence that a moderate overexpression of c-Met in hepatocytes is sufficient to promote a strong antioxidant response in the liver that efficiently protects against chronic cholestasis thus allowing an optimal liver regeneration.

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Patología molecular y cristalografía de rayos X arrojan nueva luz sobre estructura-función de la carbamil fosfato sintetasa 1 humana (CPS1)

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La CPS1 es la entrada-interruptor del ciclo de la urea, operada por su activador esencial N-acetil-L-glutamato (NAG). Este ciclo es clave para la detoxificación del amonio derivado del catabolismo de las proteínas.

Nuestras dos estructuras cristalinas de CPS1 humana sin ligandos o unidas a 2ADP, K+, Mg2+ y NAG, demostraron (De Cima et al. Sci Reports2015) su composición por 6 dominios globulares, dos de ellos catalíticos y homólogos, otro de activación por NAG y un cuarto de integración, quedando por determinar la función de sus dos dominios N-terminales (~400 aas.), reminiscentes de la subunidad menor de las CPSs anabólicas bacterianas. Hemos abordado la determinación de dicha función mediante mutagénesis dirigida, usando los datos genéticos de pacientes con déficit de CPS1 como atajo para elegir qué mutaciones introducir. En 30 mutantes humanos de estos dominios, producidos en y purificados de un sistema de baculovirus/células de insecto, hemos realizado ensayos de estabilidad, de actividad enzimática, y determinado las constantes cinéticas para los sustratos y el NAG. Los resultados indican un importante papel estabilizador de los dominios N-terminales, explicando su conservación en CPS1 a pesar de que han perdido la función ancestral glutaminasa de la subunidad menor de las CPSs bacterianas. Las estructuras ya determinadas, representativas de ambos extremos del proceso de activación de la CPS1, junto con una nueva estructura presentada aquí para una forma intermedia de activación pre-unión de NAG, fundamentan estructuralmente dicho papel estabilizador, a la vez que arrojan luz sobre el inicio del proceso de activación.

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A 29-gene signature associated with NOX2 discriminates acute myeloid leukemia prognosis and survival

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Acute myeloid leukemia is the most commonly diagnosed leukemia among adults and is characterized by being highly heterogeneous. Recent genetic profile analyses of AML patients have shown mutations in up to 250 genes and more than 14 different frequent cytogenetic alterations. Last investigations are having little translation to the clinic and further knowledge is needed to improve current risk classification and therapeutical strategies. Metabolic rewiring and enhanced levels of reactive oxygen species (ROS) are emerging as important hallmarks of AML and thus putative therapeutic targets. By comparing gene expression between bone marrow cells from AML patients and healthy donors, we found decreased expression levels of genes forming NOX2 complex (CYBB, NCF1, NCF2 and NCF4) in AML. Moreover, NOX2 complex genes display a variable expression pattern in AML, which led us to create CYBB-level groups. An analysis of the differential expression of 941 metabolic genes in CYBB, NCF1, NCF2 and NCF4 expression groups reported mostly shared genes. 28 genes involved in immune response and metabolic processes show a linked expression with NOX2. The gene-expression signature composed by the 28 genes plus CYBB (29G) efficiently separates healthy and AML samples according to their prognostic group via Linear Discriminant Analysis. Canonical Biplot analysis was performed to determine the contribution of each 29G to the prognosis discrimination so as IFI30, CD36, HK3, CYP1B1, PXDN, ALOX5, BLOC1S1, FBP1, SCO2, SQOR and DAGT2 excelled relevant. An index (EI) was computed considering the expression and the contribution of each gene to the discriminant analysis. Such expression index has been used to distinguish AML patients in general, and intermediate patients in particular, in terms of OS or EFS. A low 29G expression index (EI) was linked to a higher survival. All these features make 29G a useful tool for AML prognosis, which could complement the current ELN scheme, for better management and therapeutics decisions.

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Analysys of pathogenicity of PTPN13 mutations in patients with bone marrow failure and acute lymphoblastic leukemia

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