Group **A** Poster n. **55**

Section n. 7. General genetics and genomics

Dysregulation of NF–Y splicing drives metabolic rewiring and aggressiveness in colon cancer

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NF-Y is an evolutionarily conserved transcription factor that binds specifically to the CCAAT elements of eukaryotic genes, most of which frequently deregulated in cancer. NF-YA, the regulatory subunit of the NF-Y complex, has two isoforms generated by alternative splicing, NF-YAl and NF-YAs, which differ in the transactivation domain.
Transcriptomic data from The Cancer Genome Atlas (TCGA) database highlighted a significant increase in the expression of NF-YAs at the expense of NF-YAl in colorectal cancer (CRC), compared to healthy tissues. Despite this, high NF-YAl levels predict lower patients' survival and distinguish the mesenchymal molecular subtype CMS4, which is characterized by the worst prognosis.
Through the analysis of 3D cellular models, we demonstrated that altered expression of genes related to extracellular matrix and epithelial-mesenchymal transition sustains enhanced migratory and invasive behavior of NF-YAl-transduced cells. Moreover, the integration of metabolomics, bioenergetics and transcriptional analyses demonstrated a direct role for NF-YAl in metabolic flexibility of cancer cells that adjust their metabolism in response to environmental changes to potentiate migration. The zebrafish xenograft model confirmed the metastatic potential triggered by NF-YAl in CRC cells.
Altogether, our data highlight the transcriptional role of NF-YAl in CRC aggressiveness and suggest splice-switching strategies to hinder NF-YAl-induced metastatic dissemination.