16 MAY

11.30 A.M. ROOM B108 POVO 2

GIANNINO DEL SAL

DEPARTMENT OF LIFE SCIENCES, UNIVERSITY OF TRIESTE INTERNATIONAL CENTRE FOR GENETIC ENGINEERING AND BIOTECHNOLOGY-TRIESTE IFOM ETS-THE AIRC INSTITUTE OF MOLECULAR ONCOLOGY-MILAN

Turning "Cold" Tumors "Hot": Novel Targets to Restore Immune

Response in Breast Cancer

Tumors operate as complex and dynamic ecosystems composed of cancer cells, stromal components, immune populations, and a continuously remodeled extracellular matrix (ECM). Both metabolic and biomechanical cues from the altered ECM play pivotal roles in shaping tumor heterogeneity and the immune landscape of the tumor microenvironment (TME), with direct implications for therapeutic responsiveness. In breast cancer, increased ECM stiffness is associated with nutritional and mechanical stress, metabolic rewiring, reduced immune infiltration, and the emergence of "immune-cold" phenotypes - hallmarks of resistance to both chemotherapy and immunotherapy. Given this context, it is critical to **identify actionable molecular** determinants that regulate the immune-cold TME in fibrotic tumors, with the goal of improving immunotherapy efficacy and overcoming treatment resistance. We have identified targets whose inhibition reactivates the cGAS/STING/IFN-I axis, leading to enhanced immune infiltration in both primary breast tumors and metastatic sites. These findings hold promise for restoring antitumor immunity and resensitizing fibrotic, immune-excluded tumors to chemotherapy and immunotherapy - offering a strategy

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to overcome resistance in treatment-refractory cancers.



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