SELEZIONE 2022N32

A)

1) Quali considerazioni si possono fare e quali controlli o validazioni sperimentali sono appropriate nel caso in cui il risultato di una PCR per genotyping di un topo transgenico rivela una banda di dimensioni inferiori alle attese.

2) La via di trasduzione di Hippo: aspetti teorici e readouts molecolari e funzionali

B)

1) Quali sono le tue considerazioni, considerando anche criticità e limiti, del sistema CRISPR/Cas9 applicato a colture cellulari.

2) La via di trasduzione canonica di Wnt.

C)

1) Descrivi la Chromatin Immunoprecipitation.

2) cGAS/STING signaling.

D)

1) Strategie per lo studio di un gene tramite inattivazione in cellule di mammifero in coltura

2) Metodologie per lo studio dell'epigenetica

INFORMATICA

A) Descrivere almeno una soluzione informatica per la gestione di colonie murine, anche in relazione alle procedure previste dalla normativa vigente.

B) Soluzioni informatiche per lo stoccaggio sicuro di dati scientifici

C) Soluzioni informatiche per l'analisi statistica di dati scientifici

D) Soluzioni informatiche per garantire la tracciabilità e legittimità del dato scientifico

INGLESE

A) In contrast to normal type | collagen (Col1) heterotrimer (a1/a2/a1) produced by fibroblasts, pancreatic cancer cells specifically produce unique Col1 homotrimer (a1/a1/a1). Coli homotrimer results from epigenetic suppression of the Col1a2 gene and promotes oncogenic signaling, cancer cell proliferation, tumor organoid formation, and growth via a3B1 integrin on cancer cells, associated with tumor microbiome enriched in anaerobic Bacteroidales in hypoxic and immunosuppressive tumors. Deletion of Col1 homotrimers increases overall survival of mice with pancreatic ductal adenocarcinoma (PDAC), associated with reprograming of the tumor microbiome with increased microaerophilic Campylobacterales, which can be reversed with broadspectrum antibiotics. Deletion of Col1 homotrimers enhances T cell infiltration and enables efficacy of

anti-PD-1 immunotherapy. This study identifies the functional impact of Col1 homotrimers on tumor microbiome and tumor immunity, implicating Col1 homotrimer-a3R1 integrin signaling axis as a cancer-specific therapeutic target.

B) Drug resistance in cancer is often linked to changes in tumor cell state or lineage, but the molecular mechanisms driving this plasticity remain unclear. Using murine organoid and genetically engineered mouse models, we investigated the causes of lineage plasticity in prostate cancer and its relationship to antiandrogen resistance. We found that plasticity initiates in an epithelial population defined by mixed luminal-basal phenotype and that it depends on elevated JAK and FGFR activity. Organoid cultures from patients with castration-resistant disease harboring mixed-lineage cells reproduce the dependency observed in mice, by upregulating luminal gene expression upon JAK and FGFR inhibitor treatment. Single-cell analysis confirms the presence of mixed lineage cells with elevated JAK/STAT and FGFR signaling in a subset of patients with metastatic disease, with implications for stratifying patients for clinical trials.

C) Glioblastomas are incurable tumors infiltrating the brain. A subpopulation of glioblastoma cells forms a functional and therapy-resistant tumor cell network interconnected by tumor microtubes (TMs). Other subpopulations appear unconnected, and their biological role remains unclear. Here, we demonstrate that whole-brain colonization is fueled by glioblastoma cells that lack connections with other tumor cells and astrocytes yet receive synaptic input from neurons. This subpopulation corresponds to neuronal and neuralprogenitor- like tumor cell states, as defined by single-cell transcriptomics, both in mouse models and in the human disease. Tumor cell invasion resembled neuronal migration mechanisms and adopted a Lévy-like movement pattern of probing the environment. Neuronal activity induced complex calcium signals in glioblastoma cells followed by the de novo formation of TMs and increased invasion speed. Collectively, superimposing molecular and functional single-cell data revealed that neuronal mechanisms govern glioblastoma cell invasion on multiple levels. This explains how glioblastoma’s dissemination and cellular heterogeneity are closely interlinked.

D) Cellular senescence is an important factor in aging and many age-related diseases, but understanding its role in health is challenging due to the lack of exclusive or universal markers. Using neural networks, we predict senescence from the nuclear morphology of human fibroblasts with up to 95% accuracy, and investigate murine astrocytes, murine neurons, and fibroblasts with premature aging in culture. After generalizing our approach, the predictor recognizes higher rates of senescence in p21-positive and ethynyl-2’-deoxyuridine (EdU)-negative nuclei in tissues and shows an increasing rate of senescent cells with age in H&E-stained murine liver tissue and human dermal biopsies. Evaluating medical records reveals that higher rates of senescent cells correspond to decreased rates of malignant neoplasms and increased rates of osteoporosis, osteoarthritis, hypertension and cerebral infarction. In sum, we show that morphological alterations of the nucleus can serve as a deep learning predictor of senescence that is applicable across tissues and species and is associated with health outcomes in humans.