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Microenvironment-dependent intratumoral heterogeneity in the self-renewal and tumorigenic differentiation of ovarian cancer

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Intratumoral heterogeneity challenges existing paradigms for anti-cancer therapy. We have previously demonstrated that the human embryonic stem cells (hESC)-derived cellular microenvironment in immunocompromised mice, enables functional distinction of heterogeneous tumor cells, including cells which do not grow into a tumor in conventional direct tumor xenograft platform. We use six clonally expanded cancer cell subpopulations derived from human ovarian clear cell carcinoma of a single tumor, to demonstrate striking intratumoral phenotypic heterogeneity that is dynamically dependent on the tumor growth microenvironment. These cancer cell subpopulations, characterized as cancer stem cell subpopulations, faithfully recapitulate the full spectrum of histological phenotype heterogeneity known for human ovarian clear cell carcinoma. Each of six subpopulations displays a different level of morphologic and tumorigenic differentiation wherein growth in the hESC-derived microenvironment favors growth of CD44+/aldehyde dehydrogenase positive pockets of self-renewing cells that sustain tumor growth through a process of tumorigenic differentiation into CD44-/aldehyde dehydrogenase negative derivatives. Strikingly, these derivative cells display microenvironment-dependent plasticity with the capacity to restore self-renewal markers and CD44 expression. Furthermore, we delineate the distinct gene expression and epigenetic profiles of two such subpopulations, representing extremes of phenotypic heterogeneity in terms of niche-dependent self-renewal and tumorigenic differentiation. By combining Gene Set Enrichment, Gene Ontology and Pathway-focussed array analyses with methylation status, we propose a suite of robust differences in tumor self-renewal and differentiation pathways that underlay the striking intratumoral phenotypic heterogeneity which characterized this and other solid tumor malignancies.

Biography

Maty Tzukerman has completed her Ph.D at the age of 33 years from the Technion - Israel Institute of Technology and postdoctoral studies from La Jolla Cancer Research Foundation, La Jolla, California. She then joined the research team of Ligand Pharmaceuticals Inc. as a senior research scientist and conducted research on the estrogen receptor transcription regulation in osteoporosis and malignant development, from which she holds several patents. She joined the Rappaport Faculty of Medicine, Technion and the Rambam Medical Center at Haifa, Israel, and her research focused on tumorigenesis properties in a human cellular microenvironment derived from human embryonic stem cells, tumor - stroma interactions and heterogeneity of cancer cell types within tumors. Together with Prof. Karl Skorecki she developed a novel pre-clinical experimental model for studying tomorigenesis processes and for preclinical testing of anticancer therapies in a human cellular microenvironment. Her studies underscore the potential experimental utility of the model to support and enable the growth of important subsets of self-renewing ovarian cancer stem cells which evade growth in conventional systems. She has published more than 38 papers in reputed journals

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