TACKLING INTRATUMOR HETEROGENEITY: SEARCHING FOR NEW CURE.

Abstract

Growth of tumors happens to follow the rules of a complex ecosystem, with tumor cells interacting dynamically with tumor microenvironment to respond to intrinsic and extrinsic perturbation. This implies that tumors are highly heterogeneous in composition. Such intra-tumor heterogeneity (ITH) takes place in space (due to topographic constraint and zonation phenomena) and in time, with stage-dependent representation of the cell subpopulation. Factors contributing to such heterogeneity are genetic and epigenetic, with cells within tumor highly differing for the mutational and transcriptional profile, under stress-induced pressure (i.e. chemotherapy, immunotherapy, TKI, biologicals, …). Intriguingly, intra-tumor heterogeneity is also strictly associated to the metabolic profile of cancer cells. Metabolic heterogeneity is recognized not as simple by-product of ITH but an active propeller of therapy resistance and metastatic behavior and a suitable target for metabolic reprogramming by metformin (1). We are exploring the link between metabolic heterogeneity and cancer stem cells targeting.

We have studied ITH in two different model systems of branching vs linear tumor evolution: chiefly, colo-rectal cancer (CRC) and papillary renal cell carcinoma (pRCC).

We have isolated and transcriptionally characterized distinct EphA2 and EphB2 expressing CRC cell subpopulations, by means of a mouse model of CRC carcinogenesis (the AOM/DSS murine model). We have found that the signatures belonging to these cell subpopulations characterized distinct steps of CRC carcinogenesis, and exhibited specific temporal kinetics of expression. Additionally, such cell subpopulations exhibited different spatial distribution. We have thus discovered a miRNA-dependent orchestration of EphB2-specific stem-like properties in earlier phases of colorectal tumorigenesis and the EphA2-specific control of tumor progression, in the latest CRC phases. Moreover, we have demonstrated that EphA2 could be linked to a mechanism of resistance to cetuximab alternative to KRAS mutations. We also found that those signatures were prognostic in large cohorts of CRC patients [2-4]. This work has involved proficuous collaborations with the IRCCS "Regina Elena", National Cancer Institute, Rome and the Cancer Institute, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain.

Further, by integrating whole-genome deep-sequencing and DNA methylation data, we have studied the ITH of pRCC by looking at 10 different specimens, collected from the periphery to the center, of each of 29 pRCC. We found specific and congruent patterns of genomic and epigenomic evolution and, surprisingly enough, phylogenetic analysis has revealed features of linear clonal expansion in pRCC, demonstrating that ITH is not necessarily linked to polyclonal expansion [5]. These findings suggest that a single biopsy would be sufficient to identify the important genetic drivers and that targeting largescale SCNAs may improve pRCC treatment, which is currently poor. This work has gemmed from a collaboration with the NIH, National Cancer Institute, Cancer Epidemiology and Genetics, Bethesda, MD, USA and with the IRCCS "Regina Elena", National Cancer Institute, Rome.

Thus, ITH is complex and represents a shifting paradigm: our aim is to dissect ITH to find new therapeutic modalities and exploring the potential of combinatorial therapies, which tackle specific fragilities of the tumor in a time- and stage- specific manner.
References:


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