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EMT does not work regular shifts

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Metastasis is a complex mechanism – that accounts for the majority of cancer related-deaths. The ability of primary tumors to develop metastases represents a major roadblock against the action anti-tumor therapeutics. Metastatic cells, on their journey to colonize distant tissues, rely on coordinated and timely molecular programs to adapt to constantly changing environments. High-throughput 'omics' methods for profiling DNA, RNA or other analytes are invaluable tools to highlight underlying mechanisms driving cancer progression and to single out potential targets for drug design. From these technologies, both academia and the pharmaceutical industry expected quick breakthroughs in the development of antitumor therapies. Unfortunately, translational research efforts remain too often dampened by drug resistance [1]. The lesson learned through success and failure is that the most significant attribute that works against anti-tumor therapeutics is undoubtedly the acquired capacity of primary tumors to show extraordinary plasticity.

Each cell is unique – at any given time and as the tumor progresses, it occupies an exclusive spatiotemporal position consistent with its own molecular program. Tumor cells harbor distinct phenotypes and susceptibility to drugs [2]. These distinct features are regulated through complex biological processes that are orchestrated by transcriptional and post-transcriptional mechanisms. Single-cell sequencing technologies are currently providing significant insights in tumor biology at unprecedented resolution. These analyses allow the dissection of tumor cell heterogeneity by overcoming biases inherent to the analysis of whole tissue samples or cell populations and permit refinement of molecular mechanisms mediating tumor progression. However, to appreciate the extent of tumor cell heterogeneity and fully grasp its clinical relevance, time also has to be considered. Numerous studies have underscored the critical role of the transforming growth factor beta (TGF-ß) during tumor progression [3]. From the existing literature, and our own experimental observations, it is readily appreciated that the overall cellular reprograming induced by TGF-ß is built around a succession of interrelated regulatory mechanisms that are gradually set in place and dismantled over time.

Time frames of TGF-ß biological activities vary from minutes to months. Capturing all these steps requires careful and often challenging experimental design. A straightforward illustration of the importance of time as a significant variable is the so-called dichotomous nature of TGF-ß during tumorigenesis, a phenomenon now well known as the "TGF-beta paradox" and described by Roberts et al. some 30 years ago [4]. During the early phase of carcinoma progression, TGF-ß inhibits primary tumor development by inducing cell cycle arrest and apoptosis. In later stages, TGF-ß exerts a pro-tumor effect by stimulating invasion and migration. On a time scale in the order of several days, numerous studies have demonstrated its role as a transcriptional regulator of both epithelial and mesenchymal markers and, ultimately as an effector of cell plasticity. A few years ago, in our laboratory, Chaudhury et al. uncovered a mechanism operating on a time scale in the order of only a few hours in which TGF-ß quickly initiates the translation of a cohort of mesenchymal transcripts including Dab2 and ILEI [5]. Such activation occurs within three to six hours of TGF-ß signaling and results directly from the Akt2-dependent phosphorylation of hnRNP E1 happening within 30 minutes after TGF-ß treatment. More recently, we identified an alternative splicing mechanism activated by TGF-ß and mediated by hnRNP E1, which regulates EMT and metastasis through the generation of a lncRNA acting as a decoy for miRNA-205 [6]. This mechanism occurs within minutes after cytokine addition and persists for only a few hours. Despite its transient nature, the lncRNA-PNUTS induces EMT. Its expression allows for the translation of ZEB proteins which in turn maintain their own expression over time by transcriptionally repressing members of the miRNA-200 family in a feedback loop as previously proposed by Brabletz et al. [7]. This elaborate mechanism illustrates the temporal connection between molecular processes such as transcription, translation and splicing and places ZEB as the central molecular switch of EMT. Such model of regulation allows the cell to respond to immediate and sudden environmental changes.

Contrary to the classical model of differentiation in which cell commit to a particular fate in response to regulation of

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gene expression in a preprogrammed and unidirectional manner, tumor cell plasticity is more likely a reversible spatio-temporal mechanism that is constantly counterbalanced by opposing forces. As Jacques Monod famously wrote in his essay *Le Hasard et la Nécessité*, "*Le destin s'écrit à mesure qu'il s'accomplit, pas avant*. – Destiny is written concurrently with the event, not prior to it".

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