Seminars in Cancer Biology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Network dynamics in the tumor microenvironment

Hamid Bolouri*

Division of Human Biology, Fred Hutchinson Cancer Research Center, USA

ARTICLE INFO

Keywords:
Tumor microenvironment
Modeling
Network biology
Big Data
Computational biology
Bioinformatics
Systems biology

ABSTRACT

The evolutionary path from tumor initiation to metastasis can only be fully understood by considering cancer cells as part of a multi-species ecosystem within the tumor microenvironment. This paper reviews and suggests two important recent trends. Firstly, I review arguments that interactions among diverse cells in the tumor microenvironment create a distinct cellular environment that can confer growth advantages, resist interventions, and allow tumors to remain dormant for long periods. Second, I review and highlight a trend toward data-rich, molecularly detailed, computational models of the tumor microenvironment. I argue that data-driven molecularly detailed tumor microenvironment models can now be built using data from multiple emerging high-throughput technologies, and that such models can pinpoint mechanisms of dysregulation and suggest specific drug targets and follow up experiments.

1. Introduction

Cancer is often portrayed as an evolutionary process involving somatic genetic and epigenetic changes and clonal selection among tumor cells. This tumor-centric approach has enabled much progress in cancer prevention and treatment [1]. However, the evolutionary path from tumor initiation to metastasis can only be fully understood by considering cancer cells as part of a multi-species ecosystem within the tumor microenvironment (TME) [2,3]. The evolutionary fitness of clonal tumor populations is determined not in isolation, but in the context of their mechanical and biochemical interactions with other clones, the Extracellular Matrix (ECM), hormones, soluble factors, and stromal tissues within the TME [4,5].

The relative importance of "rogue" cancer cells versus the inductive/repressive roles of the cancer microenvironment has been the subject of a polarized debate for decades (e.g. [6,7]). This paper reviews and suggests two important recent trends. Firstly, I highlight arguments in favor of a synthesis of the above positions, namely that interactions among cells in the TME create a distinct microenvironment that can confer growth advantages, resist interventions, and allow tumors to remain dormant for long periods. Second, I review and highlight a trend toward rich, molecularly detailed, computational models of the TME. I argue that data-driven molecularly detailed TME models can now be built using data from emerging high-throughput technologies, and that such models can pinpoint mechanisms of dysregulation and suggest specific drug targets and follow up experiments.

Structurally, this review is organized in four parts. Section 1 discusses the need for computational, mathematical, and statistical tools when exploring the TME. Considering the available biotechnologies, I argue that tumor evolution within the TME can be most effectively modeled as a dynamic, multi-cellular gene regulatory network [8] whose steady states correspond to different stages of cancer progression.

Section 2 reviews some exemplars of TME modeling efforts to date and highlights the maturation of TME computational modeling and analysis in recent years. To make the preceding discussions more concrete, Section 3 reviews a specific and tangible example of multicellular gene regulatory network dynamics in the TME. This example also highlights the surprising and complex behaviors that can arise from even the simplest inter-cellular interactions within the TME.

Finally, Section 4 considers the challenges and opportunities that we can look forward to in the next few years. In particular, I argue that the advent of high-throughput technologies and 'Big Data' has been accompanied by the maturing of computational algorithms and tools for analysis, modeling and visualization of large-scale, multi-cellular gene regulatory network dynamics in the TME.

Abbreviations: CPM, Cellular Potts Model; ECM, Extracellular Matrix; EOC, epithelial ovarian cancer; GBM, Glioblastoma Multiforme; GRN, gene regulatory network; MMP, matrix metalloproteinase; RTK, Receptor Tyrosine Kinase.

* Correspondence to: Mail Stop: C3-168, Division of Human Biology, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue N, PO Box 19024, Seattle, WA 98109, USA. Tel.: +1 206 667 2748; fax: +1 206 667 2917.
E-mail address: HBolouri@fhcrc.org

http://dx.doi.org/10.1016/j.semcancer.2014.02.007
1044-579X/

2. Why and how should we model the TME?

Over the past decade, the importance of the TME in molding tumor evolution has become increasingly clear [9]. However, multiple barriers have impeded better understanding of the TME at the molecular level. The TME is both complex (i.e. it has non-linear, hard-to-predict behavior) and complicated (i.e. it involves large numbers of irregularly interacting parts). It also encompasses interactions at multiple spatial and time scales.

Spatially, the TME is determined by molecular interactions within and across organelles (e.g. mitochondria [10]) as well as within and among tumor clonal populations, and stromal cells such as epithelial cells [11], fibroblasts [12], vascular endothelial cells [13], and multitudes of innate and adaptive immune cells [14]. These interactions are further complicated by the effects of cell polarity and tissue architecture [15,16]. Moreover, interactions occur across multiple time-scales ranging from milliseconds (as in protein–protein interactions), through minutes (e.g. transcription) to days (e.g. interactions with the immune system) and years (as in dormancy and recurrence).

In addition to spanning multiple scales of time and space, the study of cancers necessarily spans an enormous information-processing hierarchy from DNA, RNA and protein sequence to emergent systems properties such as aberrant molecular structure and function and dysregulated cellular and organ behavior and physiology.

Thus within the TME, emergent complex behaviors are especially hard to decipher because of the complicated, multi-scale organization of the TME. Underlying the various stages of tumor evolution are forbiddingly large, complex, multi-scale systems of interactions that can only be studied through the use of statistical, mathematical, and computational tools [17].

What type of modeling is most appropriate for understanding the TME? Historically, TME models have tended to compress and abstract molecular detail into a handful of key properties such as cellular deformability and adhesiveness [18]. However, molecularly detailed models are increasingly needed in order to identify causal mechanisms and pinpoint optimal molecular targets for intervention. Molecularly detailed models also suggest specific molecular and cell biological experiments that can be performed to test their predictions and gain further insights. In this way, models can drive a virtuous cycle of model development, testing, refinement, and validation.

To understand the usefulness of molecularly-detailed TME modeling better, it is helpful to divide the TME modeling process into three parts. First, we need to develop models of the regulatory state of the various cells of interest – what genes are expressed/repressed, what pathways and processes are active/inactive in each cell type (and evolutionary stage) in the TME? Second, we need to identify signaling and physical interactions between the various cell types (and between the cells and the ECM [19,20]). The third step is to develop an integrative multi-cellular model of intra- and inter-cellular interactions. Predictions made by the integrative model represent data-driven hypotheses that can be subjected to experimental testing. The results of the experimental tests enable the refinement of the model, and lead to a new iteration of modeling, prediction, and experimental testing.

Multiple new technologies are enabling integrative molecular modeling of the TME. Consider for example aberrant signaling, which is a common theme in the TME [21,22]. Reconstructions of signaling activity in cultured cells using quantitative phosphorylation-specific immunofluorescence microscopy are now well established [23–25]. Additionally, the latest technological advances in proteomics allow quantitative pathway-wide and multi-pathway measurement of abnormal phosphorylation in patient and animal samples [26]. These technologies are revealing emergent properties of the TME that arise specifically at the level of protein-modification interactions. A good example is presented in [27], where Kreeger et al. demonstrate that signal transduction kinetics lead to different cellular responses to NRAS and KRAS mutations.

In the past few years, sequencing-based high-throughput technologies such as RNA-seq, miRNA-seq, ChIP-seq, DNase1-seq, and ChIA-PET (reviewed in [28]) have become widely available, highly reliable, fast, and affordable. The NCI TARGET (http://target.nci.nih.gov) and TCGA (http://cancergenome.nih.gov/) projects have amply demonstrated the power of these technologies to characterize cancer tissues. Beyond characterizing tumor tissues, these technologies can also provide detailed, genome-wide molecular characterization of all TME cell types at various stages of tumor progression. Integrative analysis of such data can provide highly-detailed molecular snapshot models of the evolution of tumors within their microenvironments.

Returning to our question: 'What type of modeling is most appropriate for understanding the TME?', I note that sequencing-based high-throughput technologies provide genome-wide data at the level of DNA and RNA. Thus a natural way to interpret these data is in terms of gene regulatory network (GRN) models focused on the regulation of mRNA type and abundance.

Signal transduction models and post-translational modifications can be integrated into GRN models at different levels of abstraction depending on data availability. At a minimum, the known topology of signaling pathways describes how signaling interactions can drive GRN state transitions.

Because transcription and translation proceed at much slower rates than signal transduction, GRN models typically capture signaling activity as steady-state input-output relationships derived from more detailed models [8].

Signal transduction activity can usually be inferred from mRNA data by identification of up-regulated (replenished) receptor and signal transduction genes in tumor and stromal cells, and down-regulation of signaling repressors.

In addition to low cost and ease of adoption, sequencing-based multi-cellular GRN models capturing snapshots of TME evolution naturally fit current sample collection and handling practices. In particular, they do not require cells to be cultured, treated, modified, or assayed at a large number of short time intervals.

An important lingering barrier to the use of high-throughput data for multi-cellular modeling of the TME has been the difficulty of assaying individual cell types in situ within the TME. However, the latest advances in technologies for in vivo and ex vivo study of the TME (e.g. [29–33]) are rapidly changing this landscape. Molecularly detailed TME models can now be constructed by combining such in situ data with recently released large-scale datasets that characterize common tumors and cancer cell lines (e.g. from the TCGA, TARGET, ENCODE (http://encodeproject.org/), Roadmap Epigenomics (http://www.roadmapepigenomics.org/) and the Cancer Cell Line Encyclopedia (http://www.broadinstitute.org/ccle/) projects).

3. Key developments in TME modeling to date

Mathematical modeling of tumor evolution has a long and distinguished history dating back at least to Armitage and Doll's classic 1954 model [34] suggesting that "human cancer is the end-result of several successive cellular changes". More recently, such cellular evolution models have been applied to the TME, notably by Gatenby and Gillies [35] whose models suggested that "carcinogenesis requires tumor populations to surmount six distinct

Please cite this article in press as: Bolouri H. Network dynamics in the tumor microenvironment. Semin Cancer Biol (2014), http://dx.doi.org/10.1016/j.semcancer.2014.02.007