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Review

Cooperation and competition in the dynamics of tissue architecture during homeostasis and tumorigenesis'

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ABSTRACT

The construction of a network of cell-to-cell contacts makes it possible to characterize the patterns and spatial organization of tissues. Such networks are highly dynamic, depending on the changes of the tissue architecture caused by cell division, death and migration. Local competitive and cooperative cell-to-cell interactions influence the choices cells make. We review the literature on quantitative data of epithelial tissue topology and present a dynamical network model that can be used to explore the evolutionary dynamics of a two dimensional tissue architecture with arbitrary cell-to-cell interactions. In particular, we show that various forms of experimentally observed types of interactions can be modelled using game theory. We discuss a model of cooperative and non-cooperative cell-to-cell communication that can capture the interplay between cellular competition and tissue dynamics. We conclude with an outlook on the possible uses of this approach in modelling tumorigenesis and tissue homeostasis.

1. Epithelial organization and cellular interaction networks

In a monolayer epithelium, apical cell surfaces appear polygonal in shape. In a normal tissue, these polygons fit perfectly together to form a tiled array that is free from gaps. Therefore, for each polygon the number of sides corresponds to the number of cell neighbours in the tissue. By using this information to construct an "epithelial network" of cell-to-cell contacts (or cellular interaction network) it is then possible to capture information about the patterns in the spatial organization of epithelial cells (Fig. 1). In such a network, the centroid of each cell in the epithelium is treated as a node and two nodes are linked if the two cells are neighbours (i.e., they are in physical contact). This approach can help us to understand the local interactions – also termed "cellular sociology" [1] – in tissues.

Conceptualizing the arrangement of cells as a network opens up new possibilities to investigate tissue organization and patterns using principles from graph and network theory [2]. For instance, when considering the cellular interaction network of the epithelial tissue of the developing *Drosophila* wing [3] one sees that while most cells have six direct neighbours, some have four or nine neighbours [4]. Remarkably, other multicellular tissues show very similar distribution of sidedness (number of neighbours per cell or 'degree' of nodes in the contacts networks) [4,5].

Several theoretical hypotheses have been proposed to explain how this observed distribution could emerge, using elasticity theory [6], mechanics [7,8], or stochastic models of cell replication [4,9]. However, while the degree distributions seem to follow a general principle [4] that can be captured by the proposed mathematical models, more specific topological measures of cellular contact networks, e.g. the degree or the cluster coefficient of nodes (a proxy of the connectedness density), can be used to distinguish both tissues and species [2,10]. Specifically, the quantitative signature of a tissue can be obtained by considering an appropriate set of statistics concerning the cellular contacts networks [10]. For instance, the analysis of muscle biopsies allows the evaluation of differences between normal and pathological muscle tissues.

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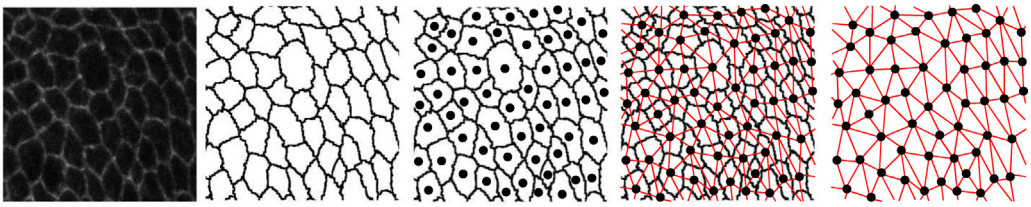

Fig. 1. From tissue topology to the cellular interaction network. The panels show the different processing step from left to right. The original image (*Drosophila* wing disc in this case) is segmented to obtain the outline of all cells. This allows the localization of the centroid (nodes) and the identification of the neighbours (links) of every cell, the basis of the cellular interaction network. The contacts network is called Delaunay graph, while the cell outline graph is called Voronoi diagram.

This method not only automates the work of the pathologist by capturing the geometrical information from the biopsy, but also captures the spatial organization of muscle fibres by constructing a "muscle network" of fibre-to-fibre contacts. Interestingly, using this approach some "network features" (among a list of 82 possible features) were found as key parameters to quantify the degree of pathology of muscular dystrophy patients [10]. One can therefore conclude that the topological organization of the epithelium differs between tissues and between species and can provide valuable information. On the other hand, the highly reproducible network structure of the same epithelia taken from different individuals hints at the presence of genetic controls that guide local and long-range tissue organization, such as force-dependent cell division and cell competition [11], suggesting multiple levels of control which shape the overall cellular interaction network of living tissue across multiple scales.

2. The forces that shape epithelial topology

The general phenomenon termed as cell competition can arise when two populations of cells, differing in their growth, coexist in a developing tissue. In a homotypic population, cells will proliferate and the tissue will develop normally. However, when two populations coexist in a tissue and must compete for space, the fitter (faster growing) of the population will proliferate at the expense of the less fit population. The "winner" cells can eventually take over the developmental compartment by inducing apoptosis in "loser" cells [12,13]. In addition, identical cells have been shown to compete for space in crowded epithelia in different model organisms so that 'loser' cells are lost by delamination [14,15]. Thus, mechanical interactions and molecular signalling (communication) between surrounding cells can drive localized cell death in epithelia. In healthy tissues the removal of loser cells and winner proliferation appear to be carefully balanced, such that the competition acts to return a tissue to the homeostatic condition. Conversely, it has been proposed that cancer cells, which lack the controls necessary to respond to tissue overcrowding, out-compete their neighbouring wild-type cells through a process known as field cancerization, leading to the growth of the early-stage hyperplastic tumour at the expense of the host tissue [16,17]. Specifically, epithelial pre-neoplastic lesions progress from normal homeostatic differentiated epithelium to undifferentiated carcinoma in situ through a complex accumulation of genetic mutations associated to loss of tissue architecture and modification of cellular interactions. It is therefore important to determine how tissue topology changes in different epithelial tissues such as mucosa, skin, lung or cervix.

Technically, the tissue topology can be obtained by analysing patient histological samples with algorithms from graph theory, such as Voronoi diagrams, Delaunay triangulations, Minimum Spanning Tree, or other neighbourhood-based distance algorithms, [18]; for instance, these approaches are used to assess the degree of epithelial differentiation, loss of order and homeostatic equilibrium in epithelial pre-neoplastic lesions [19] as well as loss of cell differentiation in carcinomas [20]. Statistical parameters of the cellular interaction networks combined with precise measurement of morphological changes in cell nuclei have shown promising potential as surrogate markers for malignancy grade and cancer progression [21,22]. Fig. 2 presents different examples of p16 immuno-stained cervical pre-neoplastic lesions and the corresponding obtained tissue topology network. Recent advances in imaging, microscopy, optical technologies, and digital pathology, make possible high-throughput analysis and simultaneous measurements of multiple proteins, and other molecules (miRNA, etc.) in histological specimens and tissue microarrays. This allows the segmentation and identification of subpopulations (clones) of genetically similar cells within tissue samples through measurement of loci-specific fluorescence in situ Hybridization (FISH) spot signals for each nucleus [23]. These new methodologies can then facilitate the construction of the global topology of an epithelial tissue and the quantitative analysis of the spatial distribution of clonal subpopulations.

3. Cellular interactions and game theory

Cell competition, cooperation and more general cellular interactions present in living tissues can be studied using game theory [24–27]. Game theoretical approaches are widely used to analyze interactions between individuals using different strategies. In evolutionary game theory one assumes that strategies ("phenotypes") are associated with genotypic variants, enabling one to analyze the emergence and spreading of specific successful strategies in a population [28]. Individuals using successful strategies will have higher fitness, reproduce faster and spread in the population. One of the most analyzed evolutionary games, known as the prisoner's dilemma, is used to capture the notion of cooperation and defection (cheating) (Fig. 3). In this game a cooperator pays a cost to distribute benefits to its interaction partners. Defectors (cheaters) do not pay any cost and do not yield benefits to their partners. If benefit and costs result in corresponding changes to fitness, then a well-mixed population of cooperators can be invaded by cheaters. The spreading of cheaters leads to a decrease in the average population fitness and can lead to population collapse if its sustainability depends on the presence of cooperators (in what is known as the "tragedy of the commons") [29].

Evolutionary game theory has been used to model the evolution of specific strategies in various complex networks [30–34] as well as in population of spatially structured cells [24,26,30,33,35–38]. This has been generally done by arranging cells on a static grid (e.g., cellular automaton) and following how their interactions influence their movement and proliferation [39]. This approach can be extended to study tissue topologies, but the fixed grid puts an unrealistic limit on the dynamical changes of the cellular interaction network. This is evident when the abstract notion of cooperation and cheating among cells is mechanistically explained by different types of cell-to-cell communication. Many distinct mechanisms are known to exist. For instance, direct membrane-bound signalling-receptor interactions can send information between cells to drive competition for cell fate [40] or to repel dissimilar cells [41].

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