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Mini-review

Computational pathology: Exploring the spatial dimension of tumor ecology

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ABSTRACT

Tumors are evolving ecosystems where cancer subclones and the microenvironment interact. This is analogous to interaction dynamics between species in their natural habitats, which is a prime area of study in ecology. Spatial statistics are frequently used in ecological studies to infer complex relations including predator–prey, resource dependency and co-evolution. Recently, the emerging field of computational pathology has enabled high-throughput spatial analysis by using image processing to identify different cell types and their locations within histological tumor samples. We discuss how these data may be analyzed with spatial statistics used in ecology to reveal patterns and advance our understanding of ecological interactions occurring among cancer cells and their microenvironment.

Introduction

The interaction between cancer and surrounding normal tissue plays a vital role in the progression of malignant disease [1–7]. Obtaining a continuous and sufficient supply of nutrients and oxygen [8] and the threat of destruction by the adaptive immune response of the host [9] are two of the major microenvironmental selection pressures faced by cancer cells. Due to genetic heterogeneity within a tumor some malignant cells are able to survive under these pressures, thus becoming 'naturally selected' [10–15]. The fitness advantages these cells have may include their ability to survive in hypoxic conditions [12,16,17], stimulate new vessel growth [18–20] and modulate the host immune response [2,21–23]. Such cells are adapted for a harsh microenvironment and have been linked with poor prognosis [17,24,25]. Pioneering research has revealed genetic changes in cancer cells during their evolution [26–28], but there is developing interest in studying this process from a novel perspective: ecology [29–31].

The synergy between cancer and normal cells is analogous to relationships between species in a given habitat, which is a prime area of study in ecology. These relationships have been systematically studied in four categories: (i) predation, where one species benefits by consuming another, (ii) mutualism, where two species interact in a way that is of benefit to both, (iii) commensalism, where one species benefits without any effect on the other, and (iv) parasitism, where one species benefits at the expense of the other [32–34]. In cancer, all four of these relationships have been observed or proposed to exist [5,30,35]. We propose that studies of cell–cell interactions in the tumor ecosystem can substantially benefit from applying these ecological concepts and accompanying analysis tools that have been developed over many decades.

Ecological studies often begin with examining the spatial distribution of species in their habitats, which is a key determinant in access to resources, predator evasion and interaction with other organisms and the environment [36–39]. In tumors, spatial mapping of cancer cells in their microenvironment can be achieved by analysis of histology samples [40–48]. However such specimen may contain hundreds of thousands of cells that would be prohibitively difficult to count by eye, and estimates may vary between observers [49]. In recent years, a new way of analyzing tumor specimen has emerged in response to this challenge. Computer vision techniques have been applied to pathology for automated identification and classification of various cell types and tumor regions [41,50–57] (Table 1), and can enable rapid mapping of their spatial locations. For example, just as large areas of land can be mapped for population density variation, a tumor sample may be processed to map changes in density of its constituent cells, as shown in Fig. 1 [58]. Such methods thus offer a new opportunity for studying interactions between cancer and normal cells.

Although the notion of ecological interactions occurring in cancer has been reviewed in great detail before [5,59], the application of computational pathology to study these interactions is a novel approach in the field of tumor microenvironment research. This review brings together three developing concepts with examples and applications: (i) ecological interactions among cancer cells and between

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Table 1
Computer vision tools developed for analysis of tumor histology images.

Authors, year	Description	Tissue	Stain	Accuracy	Limitations
Basavanhally et al., 2010 [51]	Lymphocytic infiltration detection and grading. Support vector machine classifier differentiates between samples with high and low grade infiltration.	Breast biopsy	H&E	>90%	Derived from 42 images from 12 patients. Does not provide lymphocyte locations for spatial analysis, but could be adapted for this.
Beck et al., 2011 [52]	C-Path: categorizes regions in a histology image to epithelial and stromal areas using 31 image-based features. Further classification of objects within these areas using morphological and contextual features. Can provide relational descriptors such as mean distance between epithelial and stromal nuclei.	Breast TMA	H&E	89%	Individual cells not detected. Classifier may need re-training before application to datasets from other institutions.
Doyle et al., 2012 [53]	Identification of cancerous regions in an image using a Bayesian classifier that operates at multiple resolution levels.	Prostate needle biopsy	H&E	ROC: 0.76-0.84	Patch-based rather than pixel-based classification recommended for a high resolutions. Spatial data cannot currently be obtained.
Holmes et al., 2009 [54]	GemIdent: identification of multiple phenotypes in a microscopic image. Uses supervised machine learning algorithms for automated detection and classification of objects. Locations of objects are also reported. Not limited to a particular stain or tissue type.	Various	Various	Dependent on classifier training	User is required to train the program to enable automated identification. The algorithm is best suited to images with few colors. Detection of centroids of small and large objects to identify their location may be less reliable and require retraining of the classifier.
Lu et al., 2014 [55]	ASH: automated selection of hotspots of Ki67+ stain. Region-based detection of high Ki67+ in an image using ImmunoRatio. User is provided with a ranked list of 10 hotspots. These areas are labeled on the original image.	Various	Ki67	Not stated	Does not detect single nuclei. No comparison to Ki67 hotspot scores by a pathologist provided.
Tuominen et al., 2010 [56]	ImmunoRatio: ratio of positive nuclear stain to total nuclear area for an IHC marker. Each nucleus is segmented and color deconvolution applied to identify it as positive or negative.	Breast tissue sections	ER, PR, Ki67, hematoxylin counter-stain	Correlation coefficient with visual scoring = 0.98	Spatial data not provided but could but algorithm could be adapted for this. Web-based application may hinder high-throughput analyses.
Yuan et al., 2012 [57]	CRImage: identification of cancer, lymphocyte and stromal cells as well as their locations within the tissue. Support vector machine classifier uses morphological and contextual features and operates at multiple resolutions. Can be used to obtain cellularity and lymphocytic abundance scores, and cell location data enables spatial pattern analysis.	Breast whole-tissue sections	H&E	>90%	Only three types of cells detected: cancer, lymphocyte and stromal. May suffer from variability in staining and batch effects. Potential application to other tissue types but will require re-training.

This is a non-comprehensive list of some of the non-commercial methods available for automated detection of objects of interest in a tumor sample. Given also are the specific tissue and stain for which each method was developed, the accuracy of the method reported by its authors and known limitations. H&E: hematoxylin and eosin; TMA: tissue microarray; ROC: receiver operating characteristic; ER: estrogen receptor; PR: progesterone receptor.

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