Biology and Pathology

Cancer Biology

Tumor Heterogeneity

Kevin M. Brindle
Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge, United Kingdom

Learning Objectives:

- Understanding of the origins of tumor heterogeneity
- Awareness of the imaging methods that can be used to assess tumor heterogeneity
- Awareness of the how tumor genomic heterogeneity is being assessed from sequencing of tumor DNA in biopsies and in the plasma

Multi-region DNA sequencing has demonstrated the genomic heterogeneity of tumors [1], which can be regarded as a collection of ecosystems harboring diverse clones, each adapted to their specific microenvironment. Such heterogeneity may foster tumor evolution, by Darwinian selection of those clones that are best adapted to their environment, and will hinder the application of targeted therapies that rely on specific gene mutations identified by exome sequencing of single tumor biopsies. For example, identification of activating mutations in the EGFR kinase domain can be used to select non-small cell lung cancer patients that will respond to gefitinib and erlotinib [2]. Tumor images are intrinsically heterogeneous, reflecting the metabolic, perfusion and morphological heterogeneity of the tissue. Functional and morphological imaging, whether it is with CT, MRI, PET, or indeed any imaging modality, is well placed to map this heterogeneity and, by implication, the underlying genomic heterogeneity [3]. This has already been demonstrated in a landmark study where features in CT images of hepatocellular carcinoma were related to underlying gene expression patterns [4]. In principle, we may be able to use non-invasive imaging techniques like MRI, PET and CT in the clinic to monitor tumor evolution in response to therapy and to detect the emergence of drug-resistant clones. However, imaging is not the only way in which this can be done. A potential solution to the sampling bias introduced by single tumour biopsies is to sequence circulating cell-free tumour DNA released into plasma in a so-called 'liquid biopsy'. Recent studies suggest that this DNA represents the entire tumour genome [5-7]. This is a powerful approach since it allows repeat and minimally invasive sampling that could be used to follow tumour evolution and the development of treatment resistance; the technique has already been used to track genomic evolution of metastatic cancers in response to therapy [8]. This approach of assessing tumour heterogeneity through genomic analysis of circulating tumour DNA is in the longer term likely to be cheaper than imaging and already offers the opportunity, through multiple sampling, of providing more detailed kinetic information about clonal evolution. This talk will assess the potential of non-invasive imaging for assessing genomic evolution of tumours in comparison with sequencing of cell free tumour DNA and discuss how the two techniques might be used in conjunction with each other in the future.

References:

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