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Integrative Omics-Portrayal Disentangles Molecular Heterogeneity and Progression Mechanisms of Cancer

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Abstract : Cancer is no longer seen as solely a genetic disease where genetic defects such as mutations and copy number variations affect gene regulation and eventually lead to aberrant cell functioning which can be monitored by transcriptome analysis. It has become obvious that epigenetic alterations represent a further important layer of (de-)regulation of gene activity. For example, aberrant DNA methylation is a hallmark of many cancer types, and methylation patterns were successfully used to subtype cancer heterogeneity. Hence, unraveling the interplay between different omics levels such as genome, transcriptome and epigenome is inevitable for a mechanistic understanding of molecular deregulation causing complex diseases such as cancer. This objective requires powerful downstream integrative bioinformatics methods as an essential prerequisite to discover the whole genome mutational, transcriptome and epigenome landscapes of cancer specimen and to discover cancer genesis, progression and heterogeneity. Basic challenges and tasks arise 'beyond sequencing' because of the big size of the data, their complexity, the need to search for hidden structures in the data, for knowledge mining to discover biological function and also systems biology conceptual models to deduce developmental interrelations between different cancer states. These tasks are tightly related to cancer biology as an (epi-)genetic disease giving rise to aberrant genomic regulation under micro-environmental control and clonal evolution which leads to heterogeneous cellular states. Machine learning algorithms such as self organizing maps (SOM) represent one interesting option to tackle these bioinformatics tasks. The SOMmethod enables recognizing complex patterns in large-scale data generated by highthroughput omics technologies. It portrays molecular phenotypes by generating individualized, easy to interpret images of the data landscape in combination with comprehensive analysis options. Our image-based, reductionist machine learning methods provide one interesting perspective how to deal with massive data in the discovery of complex diseases, gliomas, melanomas and colon cancer on molecular level. As an important new challenge, we address the combined portrayal of different omics data such as genome-wide genomic, transcriptomic and methylomic ones. The integrative-omics portrayal approach is based on the joint training of the data and it provides separate personalized data portraits for each patient and data type which can be analyzed by visual inspection as one option. The new method enables an integrative genome-wide view on the omics data types and the underlying regulatory modes. It is applied to high and low-grade gliomas and to melanomas where it disentangles transversal and longitudinal molecular heterogeneity in terms of distinct molecular subtypes and progression paths with prognostic impact.

Keywords : integrative bioinformatics, machine learning, molecular mechanisms of cancer, gliomas and melanomas
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