Integrated analysis of epigenetic and transcriptional circuits in gliomagenesis

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Motivations

Next Generation Sequencing (NGS) technologies have conceptually changed the planning of a molecular biology experiment, modifying the balance between the 'wet-lab' and the 'dry' aspects of the research in favor of the latter. Better and reliable results could be gained with the new technologies when adequate bioinformatics resources are allocated. In the last couple of years new and refined methods and algorithms have been developed to fully exploit this new data generation. Good results have been achieved especially for mRNA-Seq and ChIP-Seq experiments, taking advantage of the publicly available bioinformatics pipelines and of the robust analytical tools [1, 2]. In particular, combined analysis at both the transcriptomic and epigenomic level affords the opportunity of a much deeper characterization of biological samples, enabling the elucidation of the interlaced connections between genotypes and phenotypes. The development of ever more effective methods to integrate high-throughput data is thus a major challenge in the life sciences, as captured by Venkatesh and Harlow in 2002 [3] in their reframing of the concept of "integration" in molecular biology, also referred to as "Integromics", as the bioinformatic integration of high throughput 'omics' data [4, 5].

Methods

Here we advance in this integration effort and present new results obtained with a defined protocol of analysis, which combines the most recent NGS bioinformatic tools into an integrated pipeline aimed at investigating the transcriptional and epigenetic deregulation that underlies gliomagenesis. Malignant gliomas represent the most common form of primary brain tumor, comprising a pathologically and genetically heterogeneous set of tumor types, whose extremely poor prognosis has not significant improved in the last decades, with Glioblastoma multiforme (GBM), the most malignant glioma subtype, characterized by an average prognosis of less than one year [6, 7]. While genetic lesions and transcriptional profiles have been widely investigated in GBM [8], the chromatin-wide deregulation that mediates transcriptional changes, and whose effectors may constitute rational therapeutic targets, has not been uncovered. Specifically, despite convergent lines of evidence pointing to profound epigenome aberrations at the level of DNA methylation [9-11] and histonee modifications [12], we still do not understand the role that epigenetic alterations play in the initiation, progression and the recurrence of disease, which in turn prevents the definition of epigenetic pathways suitable as prognostic signatures or rational interventions.

Results

Here we employed a murine model that faithfully recapitulates the most common genetic lesions (Ink4a/Arf inactivation; constitutive EGFR signaling) and pathological hallmarks of human GBM [13]. We used ChIPseq for Histone 3 Lysine 27 trimethylation (K27Me3) and mRNA-seq in order to integrate the analysis of the transcriptomic and epigenomic aberrations in tumorigenic astrocytes and glioma initiating cells (GICs) at, respectively, the onset and end of gliomagenesis.

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