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Computational approach to epiallele profiling

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DNA methylation is one of the most studied epigenetic modifications, with an established role in regulating gene expression and genome stability. It consists of enzyme mediated addition of a methyl-group to DNA bases. By acting in concert with other epigenetic marks, DNA methylation shapes the fate and engraves the identity of a cell. Its dysregulation has been linked to pathological conditions, both as an epiphenomenon and as a driver event.

The methylation status of a cytosine residue is usually represented as the proportion of molecules in which the residue is methylated (average methylation), and differential analysis are concerned at finding residues whose methylation status shifts among conditions. As an alternative approach, the methylation status of a locus can be explored in terms of epialleles, i.e., the possible arrangements of methylated and unmethylated cytosines in individual DNA molecules. Epiallele profiling (the assessment of the frequency of the possible epialleles) enables to dissect methylation heterogeneity of a locus.

In recent years, our group developed bioinformatic tools and computational methods to analyze epiallele profiles in ultra-deep (UD) amplicon bisulfite sequencing data, a targeted sequencing assay in which one or few loci are sequenced at high depth, thus enabling a robust estimate of epialleles [1,2,3,4]. In this way, we were able to gain insights on DNA methylation dynamics, showing that 1) DNA methylation is highly heterogeneous among cells; 2) DNA methylation is mostly a non-stochastic phenomenon, with epiallele profiles being stable across different individuals; 3) According to mathematical models, the observed heterogeneity is compatible with a dynamic equilibrium between DNA methylation and demethylation; 4) Epiallele profiles can be a cell-specific signature. Studying epiallele profiles can aid to track the spatiotemporal evolution of cell-to-cell methylation differences in a cell population.

In the last two years, our group was concerned at applying the analysis of epiallele profiles to genome-wide data. To this aim, in collaboration with the group of Dr. Giovanni Scala, we developed a bioinformatic tool, EpistatProfiler. Currently, we are applying this approach to track the dynamic of epiallele profiles upon neuronal differentiation. We are also investigating how this dynamic can be disrupted in epigenetically dysregulated contexts, as enzymatic machinery knock-out and cancer.

References

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