Study of Chromatin Remodeling in Colorectal Cancer Progression

Simone Nantes de Aquino, Nicole M. Scherer, Mariana Boroni

Laboratório de Bioinformática e Biologia Computacional, Instituto Nacional de Câncer

Colorectal cancer (CRC) it is the result of an accumulation of genetic and epigenetic changes in colon epithelial cells, which converts them into adenocarcinomas. Many of these tumors start from polyps, benign lesions that may occur on the inner wall of the large intestine and if untreated, can develop to an invasive cancer. Epigenetic changes play an important role in cellular differentiation process, allowing cells to be phenotypically diverse despite containing the same genetic content. Selective modifications of histones have been shown to act together with DNA methylation, both resulting in the modification of the chromatin conformation, which therefore influences the expression of genes. These alterations influence the nucleosome positioning along the DNA, and it is a crucial factor of chromatin accessibility. Like gene mutations, these alterations can also contribute to the pathogenesis and molecular heterogeneity of tumors. Thus, increased understanding of the gene expression regulation from epigenetic context during the CRC progression may contribute to the development of new epigenetic markers that can be applied to diagnostic, tissue invasion tendency and metastasis, prognosis or response to chemotherapy agents. In order to study the chromatin structure of CRC genomes, we have downloaded data from the public database SRA of six paired samples, normal and tumor, of the study SRP065259: SRR2810481 to SRR2810486. This data were generated by using MNase-Seq followed by enrichment of transcription start sites (TSS) regions. This approach leads to the mapping of nucleosome positions in TSS regions by treating chromatin with micrococcal nuclease (MNase), which preferentially digests linker DNA, followed by paired-end sequencing of undigested DNA fragments (MNase-seq) that came from TSS regions. After the download, the quality of the reads were analyzed using FastQC tool. Low quality reads were removed using Trimmomatic algorithm. Them, reads were aligned to the human genome (GRCh37 version) with BWA program. The RSeQC package was used to evaluate the quality of alignments and only reads with single alignment were accepted for subsequent analysis. The positioning of nucleosomes was determined using MACs2 tool, generating the following numbers of peaks per sample: 51804 (SRR2810481); 53275 (SRR2810482); 52550 (SRR2810483); 58018 (SRR2810484); 55919 (SRR2810485) and 57404 (SRR2810486). All changes found in primary metabolic pathways and related tumor signaling will be further characterized using the tools KEGG, GO and Reactome, in order to determine the impact of chromatin remodeling in the progression of the CRC.

Financial support: Ministério da Saúde