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Genomic instability, chromothripsis and cancer progression

Jeremy Andrew Squire PhD[1,2]; Alexandra Galvão Gomes MSc[1]

Abstract/Resumo

One of the biggest surprises to emerge from the cancer genome sequencing project has been the discovery of massively re-arranged genomes that have been detected within various types of human cancers caused by a novel mechanism called “chromothripsis”. This phenomenon generates up to thousands of clustered chromosomal rearrangements as a single event in localised and confined genomic regions in one or a few chromosomes. To describe the various interpretations of how these fragmented and stitched chromosomes are generated, other names have been given including “chromoplexy”, “chromoanasynthesis”, “chromoanagenesis” or collectively as “chromothripsis-like” rearrangements. These recent studies reflect a developing interest in chromothripsis-like alterations, as they may offer new insights into mechanism of cancer formation that are different to the traditional stepwise accumulation of gene mutations.

This presentation will review the classical linear models of tumor progression, in which DNA instability generates the genomic variation that then provides a selective advantage during cancer progresssion. The presentation will illustrate how analysis of chromosomal diversity, identified by classical cytogenetics, FISH and array comparative genomic hybridization, has provided strong support for clonal models of cancer progression. Examples from leukemia, osteosarcoma (where chromothripsis is very common) and prostate cancer will be used to illustrate this process.

The role of bioinformatic analysis of public domain datasets will be presented to illustrate how the frequency of chromothripsis-like events can be determined using osteosarcoma and prostate cancer as examples. Some tumors that illustrate how chaotic alterations may have led to the inactivation of tumor suppressor genes will be shown. A summary will be presented of data from international exome cancer sequencing studies, in which a surprisingly high level of both intratumour heterogeneity and overall genomic chaos has been found. Finally, some general considerations about how tumour heterogeneity could affect tumour progression, metastasis and may also influence the anti-tumour immune response will be presented.

Keyword/Palavras-chave: Chromothripsis; Cancer Progression; Genomic Instability

1 Department of Genetics, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil - *jsquireinsp@gmail.com*
2 Department of Pathology and Legal Medicine, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil