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Mini Review

Detection of chromosomal aberrations: Past and future

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Introduction

To overcome cell death malignant (B)-cells acquire different strategies like numerical and structural chromosomal changes, gene amplifications, silencing, deletions or mutations resulting in constitutive activation of prosurvival pathways by activation or inactivation of genes involved in survival and/or apoptosis, which are strongly controlled in healthy cells. These functional changes are assumed to contribute to lymphomagenesis by owing the malignant clone advantages in proliferation and survival. With a focus on B-cells V(D)J recombination, class switch recombination (CSR) and somatic hypermutation (SHM) make possible to access an enormous antibody repertoire with high antigen affinity, whereas these natural processes are believed to be the reason of chromosomal aberrations like translocations and oncogenic mutations resulting in B-cell lymphomas and leukemias [1]. It is assumed that the high proliferation rate of the B-cells in germinal centers and immunoglobulin rearrangements in form of SHM and CSR, when showing an aberrant activity, may the reason of chromosomal translocations [2]. Especially translocations involving the IGH locus with its powerful enhancers may result in dysregulated expression of the genes resident on different partner chromosomes [3]. Chromosomal translocations involving the Ig loci are recurrently observed and useful diagnostic marker in B-cell malignancies [4-6].

The analysis of the Mitelman database (https://cgap.nci.nih.gov/Chromosomes/Mitelman) for IGH associated translocations showed that most of them are detected by fluorescence in situ hybridization (FISH) resulting in a gross overview about chromosomal regions containing millions of nucleotides and hundreds of genes. Even in a few molecular genetically analyzed publications the breakpoint is shown for only one of the derivative chromosomes, usually der (14) [7-13]. Now in the era of next generation sequencing, which has an enormous potential and is getting standard in most institutes, there are still some limitations to recognize rare translocations e.g. low sequencing coverage associated with whole genome sequencing (25-30x), or if the translocation is in a small subset of cells or if the translocation is seldom and the involving sequences are not represented in the reference genome [14]. Also using RNA sequencing only those translocations resulting in a fusion protein can be captured whereas when they arise or are associated with non-coding regions of the genome they won't be recognized. Thus molecular genetic analysis of chromosomal aberrations at the breakpoint regions not only reveals the involved genes and sequences, contributes also to the development of capture-based probes allowing the enrichment and easier detection of the translocation product and to the improvement of the search algorithms and NGS reference databases. Altogether molecular genetic characterization of translocations involving especially the rare entities contribute to a precise, fast, easier and cost-effective disease characterization resulting in the development of diagnostic and prognostic markers and personalized treatment strategies. To summarize in the past chromosomal translocation partner were analyzed by FISH, which allowed a gross overview to the associated partner. Future will be predicted by next generation sequencing. Molecular genetic

breakpoint analysis is the fine tuning by the connection of both methods from past and future.

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Conflict of interest

The authors declare no potential conflict of interest.

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