Chromosomal rearrangements in myelodysplastic syndromes

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Myelodysplastic syndromes (MDS) are group of clonal hematologic disorders. The molecular basis are deletions and/or rearrangements of chromosomes 5, 7 and 8. Large interstitial deletions of the chromosome 5 (5q) appear most frequently.

Since the breakpoints are variable but still clustered in specific chromosomal regions, the instability of 5q-arms could not be simply explained by the presence of DNA fragile sites. We hypothesize that the higher-order chromatin (HOC) structure may cause 5q fragility. Chromosomal regions encompassing frequent MDS deletions might adopt specific HOC structure, potentially in MDS precursor cells or some individuals only, which facilitates their damage.

We addressed this question by reconstructing 3D HOC structure of the 5q31.1 - 5q32 chromosomal region, which we identified to be deleted with the highest frequency. Using 3D-FISH and high-resolution confocal microscopy, we determined unclear and mutual positions of 5 BAC probes, hybridizing to individual G-bands between 5q23.3 and 5q32 (in human G0-lymphocytes isolated from healthy donors, CD34+ cells isolated from patients and healthy donors, and human skin fibroblasts).

Centromeric, telomeric, and whole chromosome probes were used in combinations with the BAC probes to reveal the arrangement of the affected locus inside the chr. 5 territory. Our results indicate the formation of a large chromatin loop between the 5q23.3 and 5q32 loci that sometimes protrudes out of the chromosome 5 territories. This substantial level of chromatin decondensation and protrusion of the loop into the interchromatin channels might contribute to the region fragility. The flexibility of the loop structure we observed might then explain the variability of MDS deletion breakpoints. In accordance with these results, we suggest that HOC organization of the affected region could contribute to formation of chromosomal aberrations in MDS.

Acknowledgement

The work was supported by the following projects: the Ministry of Health of CR (16-29835A), The Ministry of Education, Youth and Sports of CR the Czech Science Foundation (P302/12/G157 and 16-12454S).