J Clin Cell Immunol 2014, 5:5
http://dx.doi.org/10.4172/2155-9899.S1.019

OMICS Group Conferences
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3rd International Conference and Exhibition on
Clinical & Cellular Immunology
September 29-October 01, 2014 DoubleTree by Hilton Baltimore-BWI Airport, USA

3D Chromatin structure of the immunoglobulin heavy chain gene

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Immunoglobulin heavy chain (IgH) genes are assembled by rearrangement of variable (V_H), diversity (D_H) and joining (J_H) gene segments spread over more than 2.5 Mb of the genome. The order of recombination is precisely determined, with DH to JH recombination occurring first, followed by VH recombination to newly-created DJH junctions. One key mechanism involves folding of the IgH locus into conformations that minimize hazardous translocation events during V(D)J recombination. In a previous study we proposed a two-step model for generating IgH locus conformation. The first step, which is Eμ-independent, permits pro-B-specific CTCF binding to the Ig_H locus and generates multiple 250-400 kb sub-domains. The second step involves Eμ-dependent interactions with distant sites in the V_H region that juxtapose sub-domains in the V_H part of the locus to the 3' end of the IgH locus, thereby leading to locus compaction. Here we verify that Eμ-dependent interactions with the V_H regions are involved in locus compaction and demonstrate that integrity of Eμ-dependent loops requires YY1 protein. We also provide evidence that YY1-dependent locus compaction is mediated by the condensin components Smc 2 and 4. In contrast, sub-domains in the VH are CTCF dependent but YY1- independent. Furthermore, these CTCF-dependent sub-domains are B lineage-specific and Pax5-independent. These observations strongly substantiate the hypothesis that IgH locus compaction occurs by two independently-regulated steps that first fold the entire locus into sub-domains followed by juxtaposition of sub-domains to accomplish full contraction. Using novel multi-probe FISH technique we also demonstrated a great variability and diversity of chromatin conformation even inside one genotype using IgH mouse locus. We suggest that these folding principles may apply more generally in folding megabase-sized chunks of the genome.

Biography

Tatiana Gerasimova received her education, PhD and Doctorate degree in Moscow, Russia. She worked in the Biology Department of Johns Hopkins University, USA, where she made significant contributions in molecular genetics of Drosophila melanogaster, in characterization of Insulators elements. During 15 years she was an Associate Editor of journal "Genetica" ((The International Journal of Genetics, Springer, Netherlands). She has published more than 100 papers in peer-reviewed journals, including Nature, Cell, Molecular Cell, Genes and Development, etc. Since 2007, she is a Staff Scientist of the National Institute of Aging, Laboratory of Molecular Biology and Immunology. During these years she dedicated herself to investigate chromatin structure and nuclear architecture of the murine immunoglobulin heavy chain (IgH) gene using 3D-multicolor FISH technique.

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