Recurrent DNA Break Cluster Genes in Neural Stem and Progenitor Cells

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We had shown that C-NHEJ DSB repair is required for both immune and nervous system development, leading us to propose, by analogy, that there could be recurrently breaking genes in neural progenitor cells that would be involved in neural functions. Consistent with this possibility we found that conditional inactivation of C-NHEJ in p53-deficient neural progenitors led to medulloblastomas that harbor recurrent translocations, reminiscent of our similar finding of recurrent translocations in B cell lymphomas that arise upon B cell-specific C-NHEJ inactivation in p53-deficient peripheral B cells. Recent studies by others have shown that brain cells frequently contain somatic genomic variations that might theoretically involve DSB intermediates. Based on these findings, we employed our unbiased, high-throughput LAM-HTGTS genomic DSB identification approach to identify genomic regions harboring recurrent DSBs in primary neural stem/progenitor cells (NSPCs). Strikingly these studies identified 27 recurrent DSB clusters (RDCs), most of which were found upon mild replication stress. Remarkably, all occurred within gene bodies. In addition, the vast majority of RDCs occur in long, transcribed, and late-replicating genes. Most striking, almost 90% of identified RDC-containing genes are involved in synapse function and/or neural cell adhesion, with a high fraction of these also being implicated in mental disorders. A substantial fraction are also implicated in various cancers including brain cancers. We will describe several additional NSPC RDC genes, including some in human stem and progenitor cells and additional new studies. Based on our findings, we will speculate on potential general overlaps, with respect to development and disease, of NSPC RDC gene DSBs and the programmed DSBs that occur in B cells. Finally, we will describe recent progress that we have made in establishing a rapid and efficient ES cell-based blastocyst complementation approach for generating complex mouse models for neurobiological studies.

References:

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