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Co-regulation of pluripotency and enhanced genetic integrity at the genomic level

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One important but poorly characterized aspect of stem cells is their ability to maintain genetic integrity while pluripotent, when induced to differentiate and or when derived from differentiated cells by reprogramming. We tested the hypothesis that pluripotency and enhanced genetic integrity are mechanistically linked at the genomic level. We used computational methods to mine previously published databases describing gene expression in human and mouse ES, iPS and differentiated cells and found that 40-44% of DNA repair genes are up-regulated in ES and iPS cells while only 1-13% are down-regulated. Cell death genes showed overall differential expression between pluripotent and differentiated cells with 14-24% of genes downregulated and 12-23% up-regulated in pluripotent cells. We then used Ingenuity Pathway Analysis (IPA) to examine direct interactions between three pluripotency factors, SOX2, OCT4 and NANOG and these differentially expressed genes. In addition, we examined interactions between pluripotency factors and intermediary transcription factors that are themselves, regulated by pluripotency factors and which in turn regulate downstream genetic integrity genes. The combination of direct and indirect interactions we detected accounted for regulation of 22-50% of differentially expressed genetic integrity genes by the three pluripotency factors investigated. Several of the pluripotency-genetic integrity network interactions predicted by computational methods were subsequently validated by ChIP-qPCR. Taken together, our data support our hypothesis that enhanced maintenance of genetic integrity is mechanistically linked to the epigenetic state of pluripotency at the genomic level. In addition, these findings demonstrate how a small number of key factors can regulate large numbers of downstream genes.

Biography

Daniel J Cooper has completed his PhD in Cell and Molecular Biology at the University of Texas at San Antonio in May of 2015, focusing on mechanisms maintaining genetic integrity in pluripotent stem cells. He is currently a Postdoctoral Associate at the University of Miami Miller School of Medicine's Project to Cure Paralysis.

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