Institut Européen de Chimie et Biologie

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Transcriptionally active chromatin recruits homologous recombination at DNA Double Strand breaks.

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Cells have developed homologous recombination (HR) and non-homologous end-joining (NHEJ) to repair highly toxic DNA double-strand breaks (DSBs). While these pathways coexist, the mechanisms by which one or other of these pathways is chosen to repair a particular DSB remain unclear. We have shown that the chromatin context in which a break occurs participates in this choice, and that transcriptionally active chromatin is preferentially repaired by HR. By using a human cell line expressing a restriction enzyme fused to the oestrogen receptor ligand binding domain (AsiSI-ER) together with genome wide chromatin immunoprecipitation-sequencing (ChIP-seq), we established that distinct DSBs induced across the genome are not necessarily repaired by the same pathway. Indeed, we identified an "HR-prone" subset of DSBs that recruit the HR protein RAD51, undergo resection, rely on RAD51 for efficient repair and are located in actively transcribed genes. Moreover, we established that repair at such DSBs can be switched to a RAD51-independent repair pathway upon transcriptional inhibition, and vice versa that transcriptional activation promotes RAD51 recruitment. Accordingly, we showed that HR is targeted to transcribed loci via the transcription-elongation associated H3K36me3 histone mark, with depletion of SETD2, the main H3K36 tri-methyltransferase, severely impeding HR at such DSBs. Our study thereby demonstrated a primary role for chromatin in DSB repair pathway choice in human cells.