P012 Direct visualization of DSB induction and repair in gene dense (RIDGE) and gene poor (anti-RIDGE) chromatin domains

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Induction and repair of DNA double-strand breaks (DSB) were for the first time directly visualized in functionally and structurally different chromatin domains of human cells. Our results show that genetically inactive condensed chromatin is much less susceptible to DSB induction by gamma-rays than expressed, decondensed chromatin. These findings were obtained by comparing two structurally homogenous but distinct 11-Mbp-long chromatin regions of HSA11: One containing clusters of highly expressed genes and decondensed chromatin (RIDGE) and the other, gene-poor, mainly with genes having only low expression (ANTI-RIDGE) and chromatin compaction of 41 % higher than RIDGE. The same conclusions result from comparison of DSB induction in whole chromosome territories, differing in gene density and consequently in the content of condensed chromatin. Furthermore, our results show that DSB repair in condensed chromatin requires extensive local chromatin decondensation, which probably contributes to significant retardation of DSB repair compared to open chromatin. Hyperosmotic-induced chromatin hypercondensation did not influence DSB induction and thus indicates that rather than simple chromatin compaction, heterochromatic proteins protect DNA from damage by γ-radiation. Some agents potentially used in cancer therapy (TSA, hypotonic, hypertonic) influence cell survival of irradiated cells via changes in chromatin structure and efficiency of DSB repair.