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The Cleavage of DNA by the Anti-Tumor Drug Bleomycin at the Transcription Start Sites of Human Genes Using Genome-Wide Techniques

Authors : Vincent Murray

Abstract : The glycopeptide bleomycin is used in the treatment of testicular cancer, Hodgkin's lymphoma, and squamous cell carcinoma. Bleomycin damages and cleaves DNA in human cells, and this is considered to be the main mode of action for bleomycin's anti-tumor activity. In particular, double-strand breaks are thought to be the main mechanism for the cellular toxicity of bleomycin. Using Illumina next-generation DNA sequencing techniques, the genome-wide sequence specificity of bleomycin-induced double-strand breaks was determined in human cells. The degree of bleomycin cleavage was also assessed at the transcription start sites (TSSs) of actively transcribed genes and compared with non-transcribed genes. It was observed that bleomycin preferentially cleaved at the TSSs of actively transcribed human genes. There was a correlation between the degree of this enhanced cleavage at TSSs and the level of transcriptional activity. Bleomycin cleavage is also affected by chromatin structure and at TSSs, the peaks of bleomycin cleavage were approximately 200 bp apart. This indicated that bleomycin was able to detect phased nucleosomes at the TSSs of actively transcribed human genes. The genome-wide cleavage pattern of the bleomycin analogues 6′-deoxy-BLM Z and zorbamycin was also investigated in human cells. As found for bleomycin, these bleomycin analogues also preferentially cleaved at the TSSs of actively transcribed human genes. The cytotoxicity (IC_{50} values) of these bleomycin analogues was determined. It was found that the degree of enhanced cleavage at TSSs was inversely correlated with the IC_{50} values of the bleomycin analogues. This suggested that the level of cleavage at the TSSs of actively transcribed human genes was important for the cytotoxicity of bleomycin and analogues. Hence this study provided a deeper understanding of the cellular processes involved in the cancer chemotherapeutic activity of bleomycin.

Keywords : anti-tumour activity, bleomycin analogues, chromatin structure, genome-wide study, Illumina DNA sequencing
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