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Genome-wide studies on the interaction of anti-tumor drug Bleomycin (and analogues) at the transcription start sites of actively transcribed human genes

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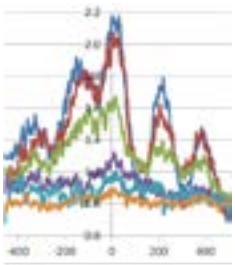
Bleomycin is a glycopeptide that is utilized as a cancer chemotherapeutic agent to treat Hodgkin's lymphoma, squamous cell carcinoma and testicular cancer. It is thought that DNA damage is the main mechanism for the anti-tumor activity of bleomycin. In this study, next-generation DNA sequencing was utilized to investigate the effect of transcriptional activity on bleomycin cleavage. The main outcome of this study was that bleomycin preferentially cleaved at the transcription start sites (TSSs) of actively transcribed genes compared with non-transcribed genes in human cells. The enhanced bleomycin cleavage at TSSs correlated with the level of transcriptional activity. The pattern of bleomycin enhanced cleavage had peaks that were approximately 200 bp apart, and this indicated that bleomycin was identifying the presence of phased nucleosomes at TSSs. Hence bleomycin can be utilized to detect chromatin structures that are present at actively transcribed genes. The genome-wide cleavage of DNA by bleomycin analogues was also determined in human cells and it was ascertained that 6′ -deoxy-BLM Z and ZBM preferentially cleaved at the transcription start sites of actively transcribed genes in human cells. The degree of preferential cleavage at the transcription start sites was quantified and an inverse correlation with the IC50 values was observed. This indicated that the degree of preferential cleavage at transcription start sites is an important component in determining the cytotoxicity of BLM analogues. This study provided insight into the mechanism of action of this anti-tumor drug where actively transcribed genes were preferentially targeted. This information could be used to enhance the cancer chemotherapeutic activity of bleomycin. For example, down-regulation of the highly expressed genes that are targeted by bleomycin could enhance the anti-tumor activity of bleomycin.



Enhanced bleomycin cleavage at the transcription start site

Recent Publications

1. V Murray, J K Chen and A M Galea (2014) The anti-tumor drug, bleomycin, preferentially cleaves at the transcription start sites of actively transcribed genes in human cells. Cellular and Molecular Life Sciences 71(8):1505-1512.
2. V Murray, J K Chen and A M Galea (2014) Enhanced repair of bleomycin DNA damage at the transcription start sites of actively transcribed genes in human cells. Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis, 769:93-99.
3. V Murray, J K Chen and M M Tanaka (2016) The genome-wide DNA sequence specificity of the anti-tumor drug bleomycin in human cells. Molecular Biology Reports, 43(7): 639-651.

4. V Murray, J K Chen and L H Chung (2018) The interaction of the metallo-glycopeptide anti-tumor drug bleomycin with DNA. International Journal of Molecular Sciences, 19(5):1372.
5. V Murray, J K Chen, D Yang and B Shen (2018) The genome-wide sequence specificity of DNA cleavage by bleomycin analogues in human cells. Bioorganic & Medicinal Chemistry 26(14):4168-4178.

Biography

Vincent Murray has been an Academic at the University of NSW since 1990. He has obtained his BSc (Hons) at Glasgow University, U K and his PhD at the National Institute for Medical Research, London, UK. He carried out Post-Doctoral Research at Princeton University, USA and at the Cancer Institute, Melbourne, Australia. He has been an active researcher in the field of molecular biology and cancer and his lab has concentrated on investigating the interaction of anti-tumor drugs with DNA. He has focused his research on several cancer chemotherapeuticagents including bleomycin, cisplatin and cisplatin analogues. Murray has published over 100 peer-reviewed papers.

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