CDB SEMINAR

Stephen Pettitt

Institute of Cancer Research, London, UK

Monday, December 17, 2012

16:00~17:00 A7F Seminar Room

Genetic screens in haploid mouse ES cells to determine mechanisms of drug toxicity and resistance

Abstract

The recent isolation of haploid mouse embryonic stem cells (ES cells) greatly expands the scope of genetic screens in cultured cells. We have used the piggyBac transposon to mutagenise haploid cells and identified genetic mechanisms of resistance to drugs, including 6-thioguanine, the toxic antiviral fialuridine and the clinical poly (ADP-ribose) polymerase (PARP) inhibitor olaparib. We identified Parp1 as the major requirement for olaparib toxicity to normal cells. This supports the hypothesis that inhibited PARP1 is a component of the toxic DNA damage lesion. Our results suggest that toxicity to normal cells in patients treated with PARP inhibitors is likely to be an on-target effect mediated via PARP1, and also identify PARP1 mutation as a possible route of resistance to PARP inhibitors in tumours. Haploid screening will be a powerful way of identifying genetic determinants of toxicity and resistance to other drugs, and investigating other phenotypes in ES cells.

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