

Research

Genomic Instability and Cancer

Exploiting mitosis for cancer therapy

Intratumour heterogeneity (genetic, epigenetic, phenotypic) is evident in human cancers and presents a formidable challenge for cancer therapy as tumour cells vary in their sensitivity to chemotherapeutics due to genotypic or phenotypic variation. Consequently, addressing the biological basis for how cells acquire intratumoural heterogeneity has important implications for diagnostic and therapeutic approaches in the clinic.

Genomic instability has been proposed as an enabling characteristic for tumour formation. A type of genomic instability that frequently occurs in cancer cells is chromosomal instability (CIN) which is defined as the elevated rate of gain or loss of chromosomes, causing aneuploidy. CIN may generate cellular heterogeneity and potentially underlies the basis of clonal diversity, disease progression and resistance to cancer therapy. Structures called micronuclei that arise from chromosome missegregation and occur commonly in preneoplastic lesions and cancers, are reflective of CIN. Micronuclear chromosomes can acquire breaks and potentially lead to chromosomal rearrangements, thus possessing tumourigenic potential (Crasta et al, 2012). Thus, one of our research aims is to characterize the functional role of micronuclear chromosomal aberrations in CIN and clonal diversity of cancer disease. Additionally, it has been proposed that low rates of chromosome missegregation during mitosis can promote tumourigenesis, whereas missegregation of high numbers of chromosomes leads to cell death and tumor suppression. We wish to extend this in the chemotherapeutic context, and determine whether one could exploit micronuclear acquisition of massive DNA damage by elevating micronuclei frequencies to induce cell death since cells with unrepaired DNA damage tend to be eliminated via programmed cell death or apoptosis. Since micronuclei are present in preneoplastic lesions and cancers, we will conduct studies to better define cell biological properties of micronuclei for utility as a candidate biomarker for risk prediction as well as carry out profiling to correlate type and frequencies of micronuclei with molecular grades of cancers for patient stratification. We are also working with a geriatrician to understand the genetic roots of the increased incidences of cancer and other metabolic diseases in older individuals since the single biggest risk factor for developing cancer today is aging.

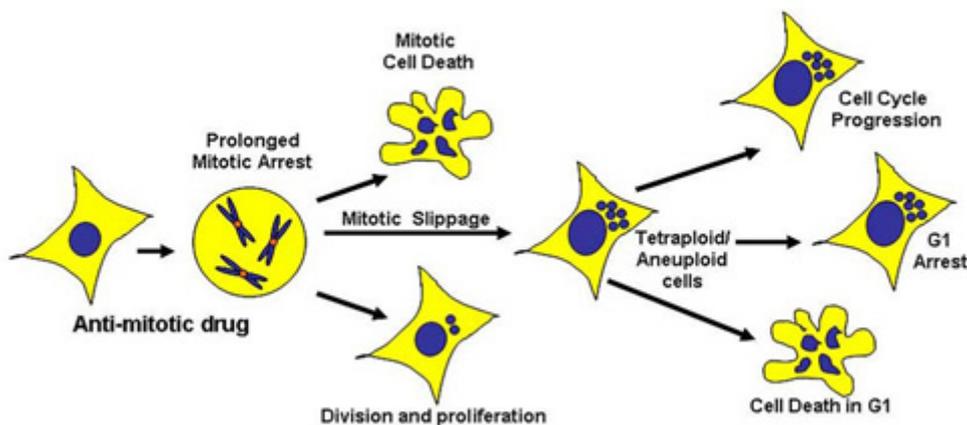


Figure 1. (Left panel). A micronuclei showing chromosomal breaks (shown in red). (Right panel) Spectral karyotyping showing fragmented chromosome 1 originating from a micronucleus.

To address these questions, we will be utilizing cell biology, biochemistry, high-resolution microscopy, chromosomal analyses, histochemistry, immunoFISH, spectral karyotyping, structural biology, functional genomics and bioinformatics.

Micronuclei formation is also one of the various outcomes following a prolonged mitotic arrest upon treatment with anti-mitotic drugs such as paclitaxel and vinblastine. Despite utilization of anti-mitotic drugs as front-line therapy for many cancers, very little is known about the mechanism behind how the prolonged mitotic arrest induced upon treatment culminates in cell death, as well as how and why some cancer cells escape the arrest and survive or die. Current research in our lab aims to have a deeper molecular understanding of drug response of cancer cells treated with these anti-mitotic drugs. To gain insight into these issues, we will be taking a multidisciplinary approach and will utilize parallel integrative experimental (cell biology, biochemistry, high-resolution microscopy, genome-wide RNAi screening, loss-of-function genetic screening in a human cell line with a largely haploid karyotype pioneered by Thijn Brummelkamp et al, small-molecule screening) and biocomputational approaches to understand the intracellular dynamics governing cell fate decisions. Our research hopes to identify novel cellular targets that could be of relevance to the development of combination therapies to improve sensitization of tumour cells, as well as provide insights into chemoresistance, a major setback in oncology.

Figure 2. Cell fate in response to anti-mitotic drug treatment.



Projects will be conducted in collaboration with groups at A*STAR (IMCB, GIS, IHPC, IMB), NTU, CSI, TTSH, NCC, Harvard Medical School and Imperial College London.