DNA REPAIR AND GENOMIC INSTABILITY IN HEMATOPOIETIC STEM CELLS AND ACUTE MYELOID LEUKEMIA

Principal investigator Dr. Margherita Bignami

DNA mismatch repair (MMR) is an important replication error avoidance mechanism that prevents mutations. It has recently become apparent that MMR defects are common among acute myeloid leukemia myelodysplastic syndrome (AML/MDS) that follows successful chemotherapy for a primary malignancy. The frequency of these secondary AML/MDS (s-AML/MDS) cases is increasing and they now account for at least 10% of all AML/MDS. MMR defective sAML/MDS is particularly associated with alkylating agent therapy. Recent experimental evidence suggests that s-AML/MDS may also be associated with defects in other DNA repair/DNA damage signalling pathways (particularly the recombinational DNA repair pathway). The aims of this project are to investigate the contributions of defective MMR and recombinational DNA repair to the development of AML. This will be achieved by several complementary approaches. We will perform a detailed examination of the DNA repair capacities of myeloid precursor cells. Firstly, the efficiency of DNA repair in haematopoietic cells undergoing a normal differentiation programme will be compared in CD34+ and CD34- cells derived from individual cord blood donors. Secondly, an expanding CD34+ stem cell population will be used to verify whether proliferation modulates the efficacy and/or mode of DNA repair. Finally, DNA repair will be analysed following differentiation of myeloid progenitors along the granulocyte or monocytes/macrophages lineages. Several repair pathways will be investigated. These include MMR, recombinational repair of DNA double strand breaks, base, and nucleotide excision repair.

Global cellular responses of hematopoietic cells to DNA damage will also be investigated by microarray analysis. In particular we will compare the effects of ionizing radiation on gene expression in hematopoietic cells of various lineages. Parallel analysis by whole genome expression profiling and DNA repair assays following induction of DNA damage will help to clarify whether variations in gene expression of DNA repair genes influence the efficiency of repair. Studies of gene expression in differentiating CD34+ stem cells will be complemented by expression profiling of s-AML/MDS of different FAB subtypes (including Acute Promyelocytic Leukemias).

s-AML/MDS is particularly associated with treatment for a primary malignancy of the reproductive tract and with a trend towards early-onset primary breast cancer. This suggests that there might be common predisposing factors for these cancers and for tAML/MDS. To examine this hypothesis we plan to examine s-AML/MDS for mutations in acknowledged breast cancer susceptibility genes that are also implicated in homologous recombinational repair and/or DNA damage signalling (BRCA1/BRCA2/ FANCD2).