EXPRESSION AND SUBCELLULAR LOCALIZATION OF P53 PROTEIN ISOFORMS IN ACUTE MYELOID LEUKAEMIA

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The p53 tumour suppressor also known under the name "Guardian of the Genome" is a highly complex regulatory protein involved in the proliferative suppression of damaged cells. p53 is activated by cellular stress signals, causing transcriptional activation of genes involved in many cellular functions, most importantly cell cycle arrest and apoptosis. p53 is mutated in over 50 of all cancers; however, p53 is likely to be affected in most cancers through mutations which affect the p53 signalling pathway, causing it to malfunction. Due to alternative promoters and splice sites, the TP53 gene can be transcribed into ten different protein isoforms with significant variations in structure. The isoforms consist of different combinations of the structural and functional domains and their distinct functionality and interplay is only partly elucidated. We have chosen acute myeloid leukaemia (AML) as our disease model, as 95% of the cases have wt p53. In previous studies we have found p53 protein isoform expression to correlate with cancer type (acute myeloid leukaemia versus acute lymphoblastic leukaemia) and differentiation stage in AML, and observed a modulation of p53 isoforms in AML patients during chemotherapy. This proposes a role for p53 isoform expression both in diagnosis and in monitoring response to therapy.

Due to the structural variation among the isoforms, many of the isoforms lack the C-terminal nuclear export signal (NES) and/or the N-terminal nuclear localization signal (NLS). We will examine if they localize in different regions of the cell and the functional implications of their subcellular localization. Most importantly the differences in structure among the isoforms cause them to have functional differences and to be the subjects of different kinds of post-translational modifications. We aim to map the functional differences between the p53 isoforms, and how their functions are regulated through post-translational modifications. Furthermore, we will investigate how the isoforms interact with each other, especially in acute myeloid leukaemia.