Abstract

This work deals with the study of human transcription factors FOXO4 and p53. FOXO4 is a member of the "O" subfamily of FOX transcription factors. Genes encoding FOXO proteins are evolutionarily conserved across species. FOXO transcription factors regulate the expression of genes involved in the control of metabolism, cell cycle and cell proliferation, cell survival and stress resistance. They are considered tumour suppressors because of their ability to arrest the cell cycle and induce apoptosis. However, their function in tumorigenesis appears to be more complicated, as recent studies indicate a poorer prognosis for the development of tumours that express higher levels of FOXO4. The p53 protein is a thoroughly studied naturally occurring tumour suppressor. The cellular response after its activation is somewhat similar to that of FOXO4, it can also block cell cycle progression or induce apoptosis depending on the cell type and severity/type of cellular stress. Both FOXO4 and p53 appear to be key molecules affecting aging. Under stress conditions, p53 and FOXO4 interact with each other and together increase the expression of p21 protein, thereby inducing the transition of cells to a senescent state. The accumulation of senescent cells is recognised as one of the main causes of ageing and the development of age-related diseases. This bachelor thesis is part of a larger project that aims to characterize the binding interface of the protein complex between FOXO4 and p53. For this purpose, truncated constructs of the human transcription factors FOXO4 and p53 (FOXO4-DBD$_{(86-211)}$) and p53-TAD$_{(1-93)}$) were expressed and purified. Using the paramagnetic enhancement relaxation NMR (PRE NMR) method, it was found that the C-terminal region of helix H2 of the FOXO4 forkhead domain interacts primarily with residues 20–26 and 50–58 of the N-terminal transactivation domain of p53. This thesis also discusses the current strategies used to develop drugs, so-called senolytics, that are able to selectively kill senescent cells. The preliminary studies show that reducing the number of senescent cells reduces chronic inflammation and improves the body's fitness.

Keywords: FOXO, p53, celluar senescence, senolytics, protein-protein interaction