Modulating FOXO3 Transcriptional Activity by Small, DBD-binding Molecules

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FOXO3 is a member of Forkhead Transcription Factor family. Forkhead proteins share an evolutionarily conserved winged-helix DNA-binding domain (DBD), which recognizes specific DNA sequence. Through interaction with target DNA, FOXO proteins modulate various biological processes, such as cell death, cell-cycle arrest, DNA repair and energy homeostasis [1]. Due to FOXO3 ability to induce cell cycle arrest, it is considered a tumour suppressor. However, in certain cases, it has been shown that FOXO3 can promote tumour development and angiogenesis via maintaining cancer cell energy homeostasis. Moreover it also enhances tumour cell resistance to chemotherapeutic agents [2]. Therefore, targeting FOXO3 transcriptional activities by specific inhibitors can help to prevent drug resistance in cancer therapy.
A pharmacophore screening identified a low-molecular compound, named S9, that interacts with FOXO3-DBD and modulates FOXO3 transcriptional programme in human cells. The mode of interaction between S9 compound and FOXO3-DBD was characterized using NMR spectroscopy and docking studies [3]. This compound was further modified to increase its inhibitory potency. In this work we tested a group of newly designed S9 derivatives. Their inhibitory potency and interaction with FOXO3-DBD was tested using NMR spectroscopy and native electrophoresis. Furthermore, the effect of these compounds on FOXO3 transcriptional activity was evaluated in cell cultures. We have shown that these new derivatives are able not only to bind to FOXO3-DBD but also to inhibit its interaction with the target DNA.

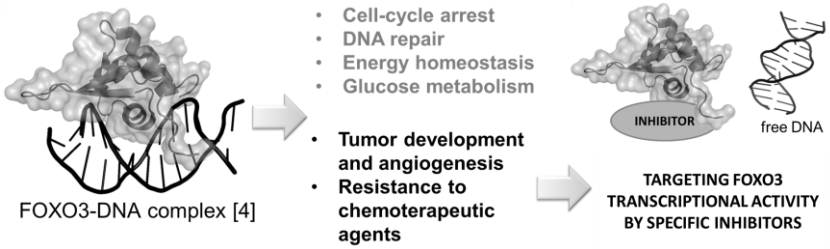

Figure 1 – Graphical scheme of abstract

[1] M. Hornsveld *et al*., *Seminars in Cancer Biology*, **50**, (2018), 90–100.
[2] S. Salcher *et al.*, *Mol. Cancer*, **13**, (2014).
[3] J. Hagenbuchner, V. Obsilova, T. Kaserer, N. Kaiser, B. Rass, K. Psenakova, V. Docekal, M. Alblova, K. Kohoutova, D. Schuster, T. Aneichyk, J. Vesely, P. Obexer, T. Obsil, M. J. Ausserlechner, *eLife*, **8**, (2019), e48876.
[4] K. L. Tsai *et al.*, *Nucleic Acids Res.*, **35**, (2007), 6984–6994.

This work was supported by the Czech Science Foundation (reg. No 21-02080S).