MODELING OF THE MDM4 AND P53 INTERACTION

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The p53 is one of the most important antineoplastic proteins in cells and controls cell cycle arrest, DNA repair and apoptosis. Its inhibition plays important role in progressing of cancer. Therefore, reactivation of p53 contribute to the death of cancer cells. The most studied inhibitor of both p53 activity and its protein stability is human E3-ligase HDM2 or its murine analogue MDM2. To fully suppress p53, HDM2 requires a partner protein MDM4 (MDMX).

MDM2 and MDM4 are essential for preventing p53 activity in the same cells, regardless of the proliferation/differentiation status of the cells [1]. Moreover MDM4 was identify as a key determinant in the dysfunction of p53 in human melanoma and designate it as a promising target for anti-melanoma combination therapy [2].

MDM4 is able to heterodimerize with MDM2. Although it is MDM2 that prevents accumulation of the p53 protein, MDM4 contributes to the overall inhibition of p53 activity independently of MDM2 [1]. MDM4 has 90% homology with MDM2, largely in its p53-binding and RING domains. However, a well-known inhibitor of the MDM2-p53 interaction, Nutlin-3, is much less effective against MDM4-p53 interaction [3]. The importance of the MDM4-p53 interaction is obvious, but mechanism of their interaction is still not clear.

The aim of this work was to analyze the interacting regions in MDM4 and p53 to define the location of binding sites and the binding energy of MDM4-p53 complex for subsequent virtual screening of small molecule inhibitors of this interaction. In addition, these data will be used for cross-screening of the multi-target MDM4-p53 and MDM2-p53 inhibitors. The transactivation domain of p53 was built by an ab initio structure prediction modeling. The interaction ability and binding energies of the complex between MDM4 and p53 were investigated by the macromolecular (protein-protein) docking method [4].

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References

1. *Francoz S., Froment P., Bogaerts S.* Mdm4 and Mdm2 cooperate to inhibit p53 activity in proliferating and quiescent cells in vivo // PNAS **Vol. 103**, № 9, 2006, Pp. 3232-3237.
2. *Gembarska A., Luciani F., Fedele C.* MDM4 is a key therapeutic target in cutaneous melanoma // Nature Medicine **Vol. 18**, 2012, Pp. 1239–1247.
3. *Shadfan M., Lopez-Pajares V., Yuan ZM.* MDM2 and MDMX: Alone and together in regulation of p53 // Transl. Cancer Res. **Vol. 1**, № 2, 2012, Pp. 88-89.
4. *Davidovich P., Tribulovich V., Melino G.* E3 ligase and the p53 family proteins interaction modeling // Abstracts of the Eight International Conference on Bioinformatics of Genome Regulations and Structure. Systems Biology, 2012, P. 78.