Molecular Modeling Of Twist1 – A Metastasis Biomarker

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Approximately 90% of cancer-related death is due to tumour metastasis complications and treatment. Epithelial-mesenchymal transition (EMT) has been studied for developmental biology and has also an important role in tumour metastasis. For EMT to occur epithelial cells undergo a transitory transformation into mesenchymal cells. For that, they change the gene expression program and epithelial markers such as E-cadherin and a-catenin are suppressed along with the expression of mesenchymal markers, as N-cadherin and vimentin, changing the cell phenotype. The transcription factors TWIST1, Snail and SIP are involved in EMT switch program. In breast cancer (BC) metastasis TWIST1 seems to be the key protein responsible for changing the tumour phenotype to an aggressive and metastatic carcinoma. In a BC animal model, TWIST1 siRNA completely abolish lung metastasis, and its ectopic expression in normal mammary cells is capable of turning them into metastatic cells. The objective of this work is to resolve by computational modeling the TWIST1 3D structure. This knowledge can improve the understanding of its characteristics, functions and, most importantly, the possibility of rational drug design to block metastasis. The protein was divided in 3 structural domains: N-terminal, basic-Helix-Loop-Helix, C-terminal. For bHLH domain we performed comparative modeling with atomic coordinate information from homologous proteins which share sequence similarity with TWIST1 and with available structures in the PDB. For the other domains *ab initio* technique was applied. Each part was properly evaluated and corrected. The 3D structures for the three domains of TWIST1 were obtained. The HLH domain has a good resolution to start the analysis of TWIST1-DNA binding affinity in order to find a way to block metastasis. Afterwards, the three domains will be linked and its dynamical behavior in solution will be monitored by molecular dynamics simulations.

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