

BIO_19 - Screening system development for HDAC1/Sp1 complex inhibitors

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Introduction: The members of the Sp1 transcription factor family have critical roles as gene expression regulators. This protein has become a new therapeutic target for cancer due to its role in gene expression associated with stage, invasiveness and metastatic potential. Considering that the mechanisms of Sp1 activation and function are still an obstacle for an effective anticancer drug development based on this protein, an alternative way is to target the elements that interact with Sp1 such as histone deacetylase 1 (HDAC1). The interaction of its non-catalytic domain and the C-terminal region of Sp1 inhibits the connection of HDAC1 with the promoter region of genes and repress gene expression.

Objective: Considering the role of post-translational modifications in determining the transcriptional activity of Sp1 and the interaction with other proteins such as HDAC1, we report a system for the development of inhibitors of the HDAC1/Sp1 complex using mammalian two-hybrid system.

Methodology: In this strategic approach, the DNA-binding domain and the transcriptional activation domain are produced by separate plasmids and become closely associated when the protein HDAC1 fused to a DNA-binding domain, interacts with the protein Sp1 fused to a transcriptional activation domain. The interaction between the proteins results in transcription of the firefly luciferase reporter gene.

Results: With this experimental system we can select substances that inhibit the HDAC1/Sp1 interaction and use them in the development of anticancer drugs based on the activation of tumor suppressor genes regulated by Sp1/HDAC1 complex.

Conclusion: Our system is applicable to the screening of HDAC1/Sp1 binding inhibitors to assess their antitumor and toxicity activity, but due to the complexity of histone modifications and transcriptional initiation, we cannot rule out the involvement of other epigenetic enzymes or transcription factors.

Keywords: HDAC1/Sp1 interaction; Therapeutic target; Post-translational modifications