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Targeting of MKRN1 for Identifying Cancer Treatment Agents

Background

Telomeres are essential and functional components of the physical ends of eukaryotic chromosomes. Most normal human somatic cells show a progressive loss of telomeric DNA during successive rounds of cell division due to a DNA end replication problem. In most human cancer cells, telomere shortening is alleviated by telomerase, a ribonucleoprotein enzyme that is composed of a catalytic subunit, hTERT. Several lines of evidence have suggested a post-translational regulation of telomerase activity. For example, the molecular chaperone Hsp90 binds specifically to hTERT to promote the assembly of active telomerase both in a cell-free system and in intact cells. Disruption of Hsp90 function by geldanamycin (GA) promotes ubiquitination and proteasome-mediated degradation of hTERT. The inventors have recently identified a novel hTERT-binding protein, Makorin RING finger protein 1 (encoded by the MKRN1 gene, a member of an ancient gene family). MKRN1 functions as an E3 ligase and mediates ubiquitination of hTERT. Overexpression of MKRN1 in telomerase-positive cells decreases telomerase activity and telomere length. These observations suggest that MKRN-1, a post-translational modifier of hTERT, plays a negative role in telomere length homeostasis. The current invention is a screening method based on identifying agents that up-regulate activity or expression of MKRN1 polypeptides or polynucleotides. Such compounds can serve as cancer therapeutic agents.

Invention

The current invention introduces novel methods to screen for compounds useful in treating telomerase positive cancers.

Application

The current invention allows for the identification of various MKRN1 binding compounds to be used as potential cancer therapeutic agents.

Advantages

Binding assays can be developed that utilize the MKRN1 protein
Enzyme assays can be developed to test compounds for their ability to increase or decrease MKRN1 activity and be developed into a potential cancer therapeutic agent
Pharmaceutical compositions could be developed based on their ability to bind to MKRN1 which are identified from the above assays

Lead Inventor

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Selected References

Kim JH, Park SM, Kang MR, Oh SY, Lee TH, Muller MT, Chung IK.. Ubiquitin ligase MKRN1 modulates telomere length homeostasis through a proteolysis of hTERT. *Genes Dev.* 2005; 19(7): 776-81.

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