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Cancer treatment: A FRET assay for identifying antagonists of the LIN28-pre-let-7 interaction

Keywords

Cancer, LIN28, Let-7, Fluorescence Resonance Energy Transfer (FRET) assay, Oncology, Small molecule inhibitors

Summary

Screening compounds for inhibitors of oncogenes is a key step in the discovery and development of anti-cancer drugs. Oncogenic LIN28 suppresses levels of let-7 microRNAs by binding a guanine-containing motif in precursors of pre-let-7. A FRET assay (fig. 1) using a LIN28-Green Fluorescent Protein (GFP) fusion protein and labeled pre-let-7 suitable for high-throughput screening has been developed to identify small-molecule antagonists of the interaction. LIN28-let-7 antagonists will restore let-7 tumor-suppressor activity in LIN28-driven tumors.

Background

MicroRNAs play important roles in initiation and progression of many human cancers. For example, the LIN28-let-7 interaction is a well-characterized interaction with a proven role in several cancers. The development of agonists or antagonists of microRNAs provides opportunity to establish new therapeutics for cancer treatment. The invention deals specifically with the let-7 family of microRNAs, their processing and regulation by the RNA binding proteins (RBPs) Lin28/Lin28B and a novel means of targeting these interactions for modulating let-7 and Lin28 functions for therapeutic applications.

Patent Status

Patent pending

Invention

Let-7 microRNAs have important roles in cancer acting as tumor suppressors (fig 1A). The level of functional mature let-7 microRNAs depends largely on LIN28 proteins, which are upregulated and act as oncogenes in several human cancers. Libraries of small molecules are screened to identify antagonists of the interaction between the LIN28 zinc-finger domain and the terminal loop region of pre-let-7 (fig 1B). A cell line constitutively expressing the LIN28-GFP fusion protein is used as a source of the FRET donor and pre-let-7's conjugated with FRET acceptor. Compounds which antagonize the interaction reduce the FRET and are profiled for their effects on cancer cells.

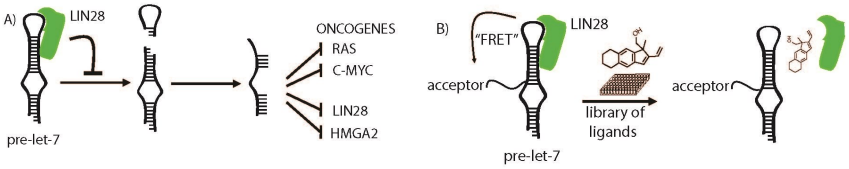

Fig. 1A: Regulation of let-7 biogenesis by Lin28; control of oncogene expression; B: Concept for the discovery of small molecule antagonists of Lin28-pre-let-7.

Features & Benefits

- The high efficiency of the FRET assay offers a unique opportunity to identify antagonists of a RNA-binding protein (RBP)-RNA interaction, generally-considered to be undrugable
- Secondary binding assays[3] and functional assays[4] are well-established to characterize antagonists
- The FRET assay provides technological entry into targeting disease-linked non-coding RNAs with conventional ligand classes

Field of Application

- Human cancers dependent on increased LIN28 activity

References & Institute

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- Group of Prof. Jonathan Hall. Institute of Pharmaceutical Sciences, ETH Zurich, Wolfgang-Pauli-Str. 10, CH-8093 Zurich, Switzerland

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ETH Zurich
ETH transfer
Zurich, Switzerland

+41 44 632 23 82
transfer@sl.ethz.ch
www.transfer.ethz.ch

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich