A Novel Method to use tRNA Manipulation to Treat Tumors and Viral Infections

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Technology description

Researchers at UC San Diego have an invention that provides a novel method of treating a cancer in a subject by administering a therapeutically effective amount of an inhibitor of DNA damage response and repair pathways. Moreover, when using SLFN11-deficient cancer cells, it was shown that they can be re-sensitized to DNA damaging agent therapy by specifically reducing or inactivating the function of tRNA-Leu-TAA, which is rarely used by highly expressed housekeeping genes for their protein syntheses (e.g. GAPDH or actin), but are abundantly used by most genes in DNA damage repair pathways including ATR and ATM, as well as genes from viruses including HIV and Ebola.

DNA damaging agents (DDA) have been successfully used therapeutically to treat an extensive range of solid tumors and blood cancers including lymphomas and leukemias. Despite its broad use,many tumors become resistant to DDA therapies over the course of the treatment. One strategy to overcome this shortcoming is the ability to reverse the resistance to DDAs.The Schlafen (SLFN) gene family members encode a diverse group of proteins, which play important roles in regulating biological functions including cellular proliferation, immune responses and suppression of viral replication. Some SLFN family members have been reported to inhibit growth in cancer cells and promote cancer cell sensitivity to chemotherapeutics.

Human SLFN11 (Schlafen 11) is one such member whose expression deficiency has been observed to cause chemotherapeutics resistance in a vast collection of tumor cells. SLFN11 sensitizes tumor cells to DNA damaging agents (DDA) by preferentially inhibiting protein syntheses of multiple components of the DNA damage response and repair pathways (e.g. ATR and ATM).Alternatively, tumor cells might not only acquire drug resistance from loss of Slfn11duringtreatment, but might already be drug-resistant and Slfn11-deficient a priori.Unlike those highly expressed housekeeping genes, the proteins syntheses of most genes involved in DNA damage response and repair heavily rely on tRNA-Leu-TAA (for leucine), which is cleaved by SLFN11 upon DNA damages. The inventors also have shown previously that SLFN11 inhibits HIV replication by inhibiting syntheses of viral proteins through a similar mechanism. As such, the destruction of tRNA-Leu-TAA (e.g. by antisense oligonucleotides Gapmer) or their inactivation (e.g. via leucine tRNA synthase inhibition) inhibits DNA damage repair and restores the sensitivity of DDA-resistant tumor cells to these chemotherapeutic agents, and can also be used as a novel approach to target viruses that rely on tRNA-Leu-TAA for their replication.

Application area

SLFN11 is required for tumor cell sensitivity to DNA damaging agents because it inhibits expression of most components of the DNA damage response and repair pathways (e.g. ATR and ATM), which rely heavily on tRNA-Leu-TAA for their proteins syntheses. When administering an inhibitor of tRNA-Leu-TAA, itrestores the sensitivity of DDA-resistant tumor cells to these chemotherapeutic agents. The direct alteration of tRNA-Leu-TAA offers a novel strategy to overcome tumor cell resistance to DDAs, and can also be used as a novel approach to target viruses that require those tRNAs for their replication.

Advantages

This method allows for reverse of a tumor’ s non-sensitivity toDNA damagingagents. As compared to the traditional strategy of inhibiting individual component of the DNA damage response and repair pathways, the direct targeting of tRNA-Leu-TAA inhibits multiple components of the pathways simultaneously and prevents the development of drug-resistant tumor cells. The same benefit also applies to the development of novel antiviral treatments.

Institution

University of California, San Diego

Inventors

Michael David
Manqing Li

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com