Identification of Compounds That Overcome Cancer Drug Resistance and Compounds for Treating Huntington's Disease

Technology #m06-021

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Small molecules for treating or preventing multi-drug resistant cancer: The ability of tumor cells to survive after treatment with any of numerous anti-cancer drugs is known as multidrug resistance. For example, the tumor-suppressor protein p53 is mutated in more than 50% of human cancers, which enables resistance to apoptosis-inducing drugs. In addition, viral oncogenes, such as HPV E6, are capable of interfering with p53 function and increasing the resistance of tumor cells to chemotherapeutic agents. Small molecules are more easily adaptable for therapeutic use than peptide or nucleic acid reagents, but few examples of small molecules that overcome E6-induced drug resistance have been described and the reported examples lack specificity. Huntington’s disease, HD, is a neurodegenerative disease that involves neuronal loss in the striatum and cortex and is caused by polyQ expansion in the htt protein. Numerous efforts to develop therapies have been initiated; however, currently there is no cure for this fatal disease.

Compounds induce doxorubicin-resistant cancer cell death: Using synthetic lethal, high-throughput screening, known and novel compounds have been identified that potentiate doxorubicin’s lethality in E6-expressing colon cancer cells, as well as rescue disease-state lethality. Such compounds include two novel classes of compounds – analogs of a thiourea compound and acylated secondary amones named as indoxins. These compounds and related analogs can induce doxorubicin-resistant cancer cell death and are active at low micro-molar concentrations. A photolabeling strategy has also been developed to identify targets of indoxin. The research group has also identified a primary hit for Huntington’s disease using high-throughput screening, and confirmed cell death rescue by two analogs of this natural product.

Applications: • These small molecules can be developed into adjuvant treatments for treating or preventing multi-drug resistant cancer, e.g. enable cells to overcome E6-oncoprotein-mediated drug resistance. Multi-drug resistant cancer can be leukemia, breast, ovarian, and bladder cancers; small cell lung cancer; gastric cancer; sarcoma; Wilms' tumor; neuroblastoma; or thyroid cancer. • These compounds can be developed into drugs for treating a neurodegenerative disorder (such as HD) associated with polyglutamine (polyQ) expansion and inhibiting neuronal cell death. • These compounds can also be used to reveal mechanisms for overcoming resistance of tumor cells to anti-cancer drugs. • This technology also provides a method for identifying compounds that bind a motor protein.

Advantages: • Provide novel approach to cancer drug resistance problem


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