

Immunotherapy with Oncolytic Virus and its Modulation by Use of Statins

Cancer is one of the leading causes of mortality in the US as well as around the world. According to the National Cancer Institute, it is estimated that in 2018, about 1.7 million people will be diagnosed with cancer and it will cause over 600 thousands death. Over the past decades, several new cancer drugs have been developed and the mortality from this disease has decreased but more work needs to be done in this space. Although there are multiple approved therapies of cancer, one of the major drawbacks is the non-specific effects and/or toxic effects of cancer drugs on normal cells. This necessitates an urgent need for developing innovative oncology therapies that are more specific and efficient. One innovative strategy that has the potential to be implemented as highly specific cancer therapy is the growing field of oncolytic virotherapy. This therapeutic method utilizes the specific cancer-killing properties of certain oncolytic virus and uses live viruses as therapeutic agents. The method developed by researchers at NSU, combines oncolytic Vesicular Stomatitis Virus (VSV) with a known statin drug, Simvastatin, to develop a specific and efficient therapy for cancer. The uniqueness of this method is the ability to modulate the effect of the VSV virus using the statin drug. The field of oncolytic viral therapy is still in its infancy and more work needs to be done to ensure safety and efficacy of this strategy. However, it is obvious that novel oncolytic virotherapy, such as the invention mentioned here offers higher specificity in targeting cancer cells, less toxicity towards healthy cells. Therefore, they have the potential to be developed into more efficient cancer therapies than currently existing cancer drugs.

Technology

Cancer patients may be treated by administering Vesicular Stomatitis Virus (VSV) and simvastatin (Sim) to modulate oncolytic viral therapy and synergistically enhance cancer cell death. By this method, two major barriers of using oncolytic viruses for cancer immunotherapy can be overcome: 1) clearance by the innate immune system, which can rapidly destroy oncolytic viruses, and 2) minimizing the risk of uncontrollable systemic viral infections to normal cells. Sim is protective to normal cells and has dual mode of action towards the virus, depending on the dosage. Low dosages allow for fast viral growth in cancer cells and higher dosages kills the virus. Initially, a low concentration of Sim is administered to increase replication of oncolytic VSV. After this initial priming (at least 2 hours later), the VSV itself is administered. The pretreatment with Sim allows for natural antiviral proteins present at the nuclear pore complex, namely Rae1 and Nup98, to be upregulated in host cells. After an overnight period of viral incubation, Sim is administered at a second, higher dosage level, causing the statin to exhibit an antiviral effect on the VSV, an enhanced rate of cancer cell death and further protection of normal cells. At least 4 hours after the second Sim administration, a different anticancer therapeutic substance (PLX4032, or vemurafenib) is administered. PLX4032, is an inhibitor of the RAS/Raf/ERK pathway. The invention has been demonstrated in HeLa cells to date.

Application

- This technology has the potential to be an efficient novel therapy for different types of cancers.
- Applying a combination of simvastatin and oncolytic virus can be implemented to increase the anticancer properties and more efficiently modulate oncolytic virus that are being currently used for cancer treatment.

Advantages/Benefits

- This method can be developed into a therapeutic procedure where the viral infectivity to normal/healthy cells are minimized and the oncolytic potency of the viral particles is enhanced
- It combines an approved drug, Simvastatin, with VSV to produce a combination therapy more efficient in killing cancer cells and less toxic to normal cells

Status of Development

A combination of statin and oncolytic virus was tested in *in vitro* experiments on HeLa cells. This combined treatment resulted in significant reduction in viability of cancer cells.

Patent Status

US Patent 9,289,456 issued 22 Mar, 2016.

Information on Inventors

Dr. Ana Maria Castejon—Dr. Castejon is an Associate Professor and Interim Chairperson at Nova Southeastern University's College of Pharmacy. Her research focus includes oxidative stress, autism, pharmacist intervention in minority populations of diabetics and effects of statins in vascular smooth muscle cells.

Dr. Cubbedo—Luigi Cubeddo, M.D., Ph.D. is Professor of Pharmaceutical Sciences at Nova Southeastern University's College of Pharmacy. Areas of research Dr. Cubeddo is interested in are, mechanisms and treatment of hypertension associated with obesity, detection of insulin resistance and abnormalities in glucose metabolism, Statin withdrawal syndrome and antiviral actions of statins.

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