Mini Review

CLINICAL INVESTIGATION

Oncology drugs and anticancer herbs: Target *GT198*

Abstract

Angiogenesis in tumours is a characteristic of cancer. There are clinically effective therapeutic pharmacological inhibitors of angiogenesis. Previously, we discovered that the oncoprotein *GT198* (gene symbol PSMC3IP, commonly known as Hop2) causes tumour angiogenesis in human malignancies, including oral cancer. In this study, we demonstrate that numerous oncology medications and several clinically effective anticancer medicines directly target the *GT198* protein. A DNA repair protein that binds to DNA is called *GT198*. We examined the 129 cancer medications in the National Cancer Institute's approved oncology drug set VII using an in vitro DNA-binding assay. Known inhibitors of *GT198* include mitoxantrone, doxorubicin, paclitaxel, etoposide, dactinomycin, and imatinib, among others. Higher binding affinities are shared by paclitaxel and etoposide, but higher binding efficacy is shared by doxorubicin due to competitive inhibition. As DNA topoisomerases are known drug targets and GT198 shares protein sequence homology with them, it is possible that *GT198* represents a novel therapeutic target that has not yet been identified. We investigated more anticancer plant extracts in our search for more potent *GT198* inhibitors. Clinically effective anticancer herbs include allspice from Jamaica; Gleditsia sinensis, or honey locust, from China; and BIRM from Ecuador. These herbs also have high affinity and efficacy. When the activity is observed by the in vitro DNA-binding assay utilising *GT198* as a target, partial purification of allspice employing an organic chemical technique indicates excellent feasibility of natural product purification. Our research as a whole identifies *GT198* as a brand-new targeting mechanism for oncology medications. The study also provides a great pharmacological target that can be used for purifying natural products and identifying compounds. This study offers a unique chance to quickly identify natural medicines with high efficacy and minimal toxicity.

Keywords: Angiogenesis

Received: 5-Oct-2022, Manuscript No. fmci-22-81870; **Editor assigned:** 7-Oct-2022, PreQC No. fmci-22-81870 (PQ); **Reviewed:** 15-Oct -2022, QC No. fmci-22-81870 (Q); **Revised:** 20-Oct-2022, Manuscript No. fmci-22-81870 (R); **Published:** 28-Oct-2022; DOI: 10.37532/2041-6792.2022.12(10).217-220

Hawra Johnson*

Editorial Office, Journal of Clinical Investigation, London

*Author for correspondence: Dr. Hawra Johnson, E-mail: hawraj5@hotmail.com

Introduction

A common feature of many different forms of human solid tumours is angiogenesis. It has been demonstrated that drugs that target tumour angiogenesis offer excellent therapeutic benefits. According to growing evidence, angiogenic blood arteries in tumour tissues are not their normal counterparts; rather, they act as the tumor's growth centres. Angiogenic blood vessels in tumour tissues may be cancerous in and of themselves.

The pericyte is essential to the regulation of angiogenesis. In response to stimuli, perivascular cells called pericytes start angiogenesis. Pericytes are progenitor or stem cells that can differentiate into numerous types of cell lineages. During the development of an embryo or the repair of adult tissue, normal pericytes may differentiate into new tissues. However, in tumours with angiogenic and malignant pericytes, this process is hijacked, endangering the development of the pericytes. The angiogenic pericytes separate, move, and proliferate excessively to become undifferentiated tumour cell. Previous studies have discovered migratory pericyte behaviour in tumour cells. Vascular mimicry is another term for tumour cells formed from pericytes that surround blood arteries. Multiple lines of evidence suggest that malignant stem cells, which would include angiogenic pericytes, replenish sustained tumour cell proliferation [1, 2].

Numerous angiogenesis medication inhibitors have been created to target tumour angiogenesis. Many affect the development of blood vessels by acting as kinase inhibitors or VEGF pathway inhibitors. When angiogenic pericytes are targeted, drug resistance may be overcome and tumour angiogenesis is particularly suppressed. Drug resistance may emerge when tumour vascular mimicry lacks endothelial cells. A DNA repair oncoprotein termed *GT198* has been found by us and others in the past (gene symbol PSMC3IP, alias Hop2) Angiogenic pericytes in malignancies overexpress the *GT198* protein, although typical quiescent pericytes do not. In this study, we demonstrate that the *GT198* protein is a

potent pharmacological target that is inhibited by a panel of licenced chemotherapeutic medications for oncology as well as by a number of anticancer herbs that have been successfully used to treat cancer in people.

Initially identified as a transcriptional coactivator, the *GT198* protein Early-onset breast and ovarian cancer families, families with familial ovarian illness, and insufficiencies are all affected by germline mutations in the human *GT198* gene. Sporadic malignancies have frequent and recurring somatic mutations in *GT198* in the tumour microenvironment. Importantly, *GT198* mutations result in the overexpression of its protein, which can be found in angiogenic pericytes and the vascular smooth muscle cells that develop from them, including myoepithelial and adipocytes in breast cancer, theca cells in ovarian cancer, and myofibroblasts in prostate and bladder cancer. Oral malignancies, a variety of different solid tumours, and murine tumours have all been associated with pericytes that express the gene for *GT198*. Human cancer development appears to have its roots in abnormal angiogenic pericytes seen in the microenvironment [3].

The expression and activity of *GT198* in stem cells may be related to its function in pericytes. *GT198* expression generally mimics cancer-testis antigens with high levels in the embryo, testis, and cancer and low levels in healthy adult tissues. Transitioning from the functionally antagonistic te *GT198* splice variant to its wild form is necessary for normal stem cell development. Somatic mutations in human cancers produce variations that are similar to the typical splice variants, putting stem cell differentiation at risk. Undifferentiated cells are really produced by the angiogenic pericytes in the stroma of oral tumours. A little DNA-binding protein dimer called *GT198* has 217 amino acids in its monomer. An N-terminal domain, a leucine zipper dimerization domain, a DNA-binding domain that may bind to either single-stranded or double-stranded DNA, and a C-terminal auto-inhibitory domain are all present in the *GT198* protein. Numerous biochemical investigations using the pseudonym Hop2 for *GT198* show that mammalian *GT198* is an essential DNA repair factor that promotes homologous DNA recombination and controls meiosis. The accumulating data positions *GT198* as a master nuclear controller of primary significance. Opening and binding of DNA strands is necessary for the processes of transcriptional activation, recombination in DNA repair, and pairing of homologous chromosomes in meiosis. So, DNA binding is a crucial function of *GT198*. *GT198* inhibitors are subjected to DNA-binding activity assays [4].

In this article, we expand on our earlier findings and demonstrate additional evidence of angiogenicpericytes expressing *GT198* in human oral cancer. We examined 129 clinical oncology medications obtained from the National Cancer Institute (NCI) using an in vitro DNA-binding assay of *GT198* to see if it would be a target of angiogenesis inhibitors. Unexpectedly, we discovered that some chemotherapeutic medications, including angiogenesis inhibitors like doxorubicin, mitoxantrone, paclitaxel, etoposide, and gleevec, are also *GT198* inhibitors. It's conceivable that *GT198* is a previously unknown, hidden pharmacological target. In this study, we investigated several anticancer herbs that have historically been effective in treating human cancer in order to enhance our search for potent *GT198* inhibitors. We have discovered a number of effective herbs, such as Chinese Gleditsia Sinensis, Ecuadorian BIRM, and Jamaican allspice, which directly inhibit *GT198* with high affinity and efficiency. Allspice was partially purified using organic chemistry techniques, which demonstrated the great viability of natural product purification as tracked by blocking *GT198* activity [5].

Discussions

In an endeavour to identify breast cancer genes in the 17q21 region, the *GT198* cDNA was initially described in 1995. Today, *GT198* has come out of BRCA1's shadow to become a crucial cancer gene. HUMGT198A was the gene's initial NCBI symbol; years later, it was changed to PSMC3IP. The full-length human *GT198* and its mouse counterpart were first described as transcriptional coactivators and TBP-interacting proteins, respectively. Due to functional similarities to the yeast Hop2 protein, it was later reported under the alias name Hop2 in meiosis and in DNA repair. For example, Hop2 or TBPIP in biochemical investigations, *GT198* in cancer studies, and PSMC3IP in genetic studies, are some of the alias names now used in the literature. The various study areas reflect the complicated roles of *GT198,* which are challenging to understand in the early stages of discovery. The roles of *GT198* become more unified as the evidence mounts. *GT198* binds to DNA to promote transcription, recombination, DNA repair, and meiosis as part of the nuclear biochemical processes. Several nuclear proteins, including DNA repair factors and steroid hormone receptors, interact with *GT198*. From the perspective of cancer biology, *GT198* controls stem cells, promotes angiogenesis, and causes apoptosis. From a genetic perspective, ovarian illnesses and malignancies are caused by germline and somatic mutations in the *GT198* gene. Our latest research adds to the evidence supporting the involvement of *GT198* in oncogenesis by expanding its utility as a multidrug target.

The discovery of numerous clinically effective oncology medicines that target *GT198* calls into question many of the medications' earlier modes of action. We discovered that a lot of historical data is, in fact, compatible with a mechanism that targets *GT198*.

GT198. Given that DNA topoisomerases I and II and their homologs are homologous to the *GT198* protein, this directly explains why doxorubicin, etoposide, and camptothecin, as well as their homologs, are *GT198* inhibitors. Consistently, doxorubicin, etoposide, and camptothecin have also been demonstrated to decrease angiogenesis. Doxorubicin's clinically significant cardiovascular adverse effects could potentially be linked to the drug's ability to block blood vessel pericytes. Dactinomycin is cytotoxic and controls DNA processes, which explains why it acts as a *GT198* inhibitor. Paclitaxel and docetaxel are frequently used chemotherapeutic medications for treating oral cancer in humans, which is consistent with their roles as angiogenesis inhibitors. Angiogenesis inhibition is also demonstrated to be a function of Gleevec aminolevulinic acid, and Celastrol Platinum DNA inhibitors did not directly block *GT198*, probably as a result of their DNA crosslinking rather than DNA intercalating property. Collectively, the aforementioned data shows that *GT198* is a master oncoprotein that hasn't been equaled by many others yet. Because many medications have not been thoroughly examined, it's possible that more *GT198* inhibitors will be discovered in the future.

In the majority of developing nations, herbs are still used today as a primary source of medicine. Numerous medical texts have detailed the increasing sophistication of the uses of herbs, and over 70,000 plant species have historically been employed as remedies. Because people and plants co-evolved in the same habitat, many natural substances have been adapted by people with lower toxicity than chemically fabricated non-natural molecules. Many effective clinical oncology medications have their roots in plants, including paclitaxel from the Pacific yew tree and etoposide from the mayapple.

We hypothesised that more effective *GT198* inhibitors would exist in anticancer herbs after finding *GT198* inhibitors among currently available oncology medications and understanding that none of them are perfect in terms of both *GT198* binding affinity and efficacy. This conclusion was drawn as a result of growing historical evidence that anticancerherbs include the protein *GT198*, which is a druggable target and plays a significant role in the start of cancer. After that, we chose and tested herbal remedies for cancer treatment in humans.

GSL (*Gleditsia sinensis L.*) was chosen by an old herbalist named Li Shi-texts Zhen in the Chinese medicinal book Ben Cao Gang Mu, a UNESCO-recognized asset. Only GSL stands out among the more than 1200 plants identified as having an effect on all sex organs, including the breast, ovary, testis, and uterus, which is linked to the functional properties of *GT198*. The book claims that GSL is incredibly helpful at treating women's abdominal tumour masses. In Asia nowadays, GSL is widely used as an anticancer herb, and the tree is heavily cultivated for medicinal purposes. In Asia nowadays, GSL is widely used as an anticancer herb, and the tree is heavily cultivated for medicinal purposes. About 100 publications in PubMed discuss the research on Gleditsia sinensis, including its anticancer properties in tumour angiogenesis and breast and prostate malignancies. Additionally, a previous summary of GSL biological activities.

References

1. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med. 285(21):1182-1186(1971).
2. Carmeliet P and Jain RK. Molecular mechanisms and clinical applications of angiogenesis. Nature. 473(7347):298-307(2011)
3. Plate KH. Tumor angiogenesis and anti-angiogenic therapy in malignant gliomas revisited. Acta Neuropathol. 124:763-75(2012).
4. Sennino B and McDonald DM. Controlling escape from angiogenesis inhibitors. Nat Rev Cancer. (10):699-709(2012).
5. Sandler A. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. N Engl J Med.355(24):2542-2550(2006).