Evaluating the efficacy of Tigecycline to target multiple cancer-types: A Review

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Abstract

Tigecycline (TIG) is a Food and Drug Administration (FDA)-approved antibiotic that has recently demonstrated its anti-cancer properties in diverse tumour types. This review will discuss current research findings and future directions pertaining to the use of TIG in mitigating acute myeloid leukemia (AML), non-small cell lung cancer (NSCLC), gastric cancer, hepatocellular carcinoma (HCC), breast cancer, melanoma, cervical squamous cell carcinoma (CSCC), and glioblastoma (GM). TIG exerts its therapeutic effects via inhibition of mitochondrial functionality, interference of various signal transduction pathways, and acting synergistically with pre-existing chemotherapy drugs, all of which contribute to cell death. In comparison to conventional treatments such as chemotherapy, TIG may result in less severe and reduced side effects; this may be attributed to its selectivity and non-invasiveness. Upon evaluation of TIG's efficacy in targeting multiple cancer-types, future efforts should aim to validate findings through human trials, broadening the scope of cancers targeted, establishing novel TIG derivatives, and assessing its performance when used in combination with other treatments.

Key Words

Tigecycline, cancer, treatment, antibiotics

Introduction

Cancer is the first leading cause of death in Canada, affecting about 40% of the population [1]. Characterized by uncontrolled proliferation of malignant cells, cancer is a complex disease that may result in a myriad of health ramifications. An accelerated rate of progression further contributes to the limited number of effective treatment regimes. Current treatment methods for cancer mainly consist of chemotherapy, surgery, immunotherapy, hormonal ther-

apy, as well as radiation therapies [2]. The success of such therapies are coupled with several drawbacks. For instance, many of these treatment options are nonspecific, thereby targeting both healthy and cancer stem cells [3]. Chemotherapy resistance may render pre-existing drug-based interventions ineffective [4,5]. Treatment related mortality (TRM) is also a plausible and increasingly prevalent concern [6,7]. Furthermore, the aforementioned treatment options have multiple long-term side effects ranging from hypoplasia to secondary malignancies [8].

Currently, antibiotics are used as post-cancer treatment to alleviate and/or prevent bacterial infections that may result as a side effect of cancer treatments [9]. In addition to their conventional indication, specific antibiotics are now presenting their multi-faceted characteristics by targeting cancer at its roots.

A recent independent study conducted by researchers from the University of Manchester demonstrated anti-tumor therapeutic properties of common antibiotics [10]. Particularly, there are five known classes of antibiotics that effectively target cancerous cells: erythromycins, tetracyclines, glycylicyclines, anti-parasitic drugs, and chloramphenicols [10].

Scientific literature shows that cancer cells undergo increased mitochondrial biogenesis and mitochondrial protein translation in order to respond to the high energy, metabolic, and signaling demands of the cell [11]. Cancer cells are highly dependent on oxidative phosphorylation; consequently, the inhibition of mitochondrial translation leads to the malfunctioning of the electron transport chain (ETC) [12]. Additional research findings have demonstrated alternate mechanisms of action, providing further evidence for the viability of such antibiotics [13].

Several studies have established the strong anti-tumor therapeutic properties of tigecycline (TIG), a type of broad-spectrum glycylicycline [14]. Currently used for skin infections and pneumonia, TIG is known to treat both gram negative and gram positive bacteria [14].

Within tumour environments, TIG selectively targets cancerous cells, without altering the activity of healthy cells [13]. Furthermore, TIG surpasses required safety regulations and adheres to the recommended tolerability profile for chemotherapy drugs [13]. Its pre-existing FDA approval would prevent further time and costs associated with the drug development process [13].

This literature review will address current research and findings pertaining to the use of TIG as an emerging antibiotic targeting cancer. The biological mechanisms and pathophysiological processes which TIG exerts its anti-cancer properties will be analyzed with respect to several cancer types including acute myeloid leukemia (AML), non-small cell lung cancer (NSCLC), gastric cancer, hepatocellular carcinoma (HCC), breast cancer, melanoma, cervical squamous cell carcinoma (CSCC), and glioblastoma (GM). This review will also evaluate novel lines of investigation regarding the advancement of cancer care and research.

Acute Myeloid Leukemia

AML is a type of blood cancer characterized by the accumulation of abnormal myeloblasts, red blood cells, and platelets in the bone marrow. This hinders the functional growth of healthy hematocytes [15]. Incidence of AML increases with age and the disease progresses very quickly if not diagnosed and treated within a few weeks of onset [16]. Originating in the bone marrow, malfunctioning stem cells may metastasize via the bloodstream to induce negative repercussions in other parts of the body such as the central nervous system, the skin, and the gums [15]. Similar to other cancers, a hallmark of AML cells is the preference for glycolysis as a means of adenosine triphosphate (ATP) production to thrive in the lower oxygen levels within tumors [17]. In fact, AML cells have evolved greater mitochondrial mass and DNA copy number to maximize oxygen consumption required for their increased rates of growth and proliferation [17].

TIG has proven to be an effective antibiotic for treating infections as it inhibits polypeptide elongation by binding to the 30S subunit of bacterial ribosomes, preventing aminoacyl-tRNA from accessing the acceptor site [18]. However, mitochondrial ribosomes differ from those found in the bacteria due to their physical and chemical characteristics [18]. In addition, mitochondrial ribosomes possess distinct protein translation machinery, including elongation and initiation factors [18]. In a previous study, Reed et al. [18] observed that knock-down of an elongation factor, Eftu, caused a decline in the levels of Cox-1 and Cox-2 proteins. These proteins are essential units of the respiratory complex IV in the mitochondrial electron transport chain [18]. Collectively, these

results mimicked those observed when TIG was administered in AML cells [18]. Furthermore, this decreased respiratory chain activity and oxygen consumption [18]. TIG was found to be selective as it caused cell death of AML blast cells and leukemic stem cells, both which have increased mitochondrial mass and greater reliance on oxidative phosphorylation; however, TIG did not target normal hematopoietic cells [18].

Hence, TIG exhibited safety as an antimicrobial and demonstrated preclinical efficacy in AML cells through successful inhibition of proteins crucial in the mitochondrial respiratory chain. TIG also interrupted energy production via aerobic glycolysis. Nonetheless, upon conducting an in vivo phase I dose-escalation study of intravenous TIG in patients with relapsed and refractory AML, the researchers did not observe a clinical or pharmacodynamic response, arresting the study after administering TIG to 27 patients for 42 cycles. This may be attributed to the fact that the drug was unable to inhibit mitochondrial protein translation because it was not on-target for an adequate amount of time due to its short half-life of 9.5 hours [18]. The study also predicted that TIG may act as a reversible inhibitor in AML mitochondrial ribosomes, arresting the synthesis of 13 mitochondrial DNA (mt-DNA) encoded proteins [18]. Such proteins play an integral role in the maintenance of the mitochondrial respiratory chain, which is essential for the transport of electrons produced by fatty acid oxidation [12]. Specifically, this inhibition restricts AML cells from generating energy required for cellular processes and hinders their survival [12].

Non-Small Cell Lung Cancer

NSCLC is one of the most prevalent forms of cancer, constituting about 80% of the total lung cancer cases [19]. Smoking, air pollution, alcohol consumption, and lack of physical activity may predispose individuals to NSCLC [20]. Current treatment methods, which encompass platinum-based and adjuvant cisplatin-based chemotherapies present inadequate results due to “driver mutations,” which contribute to the advancement of the disease [19]. TIG offers therapeutic potential via mitochondrial dysfunction and apoptosis [19].

A recent study showed that TIG inhibits proliferation and anchorage-independent colony formation upon introduction to NSCLC cell lines A549, PC9, H157, and EBC-1 when used at a concentration of 50µm [19]. The NSCLC cell lines were treated with TIG or dimethyl sulfoxide (DMSO) for 24 hours. Using an MTS assay, concentrations of 1µm, 5µm, 10µm, 25µm, 50µm of TIG and DMSO were used to exhibit cell proliferation [19]. It was shown that while TIG dose-dependently inhibited proliferation in

all tested cell lines, NSCLC cell lines, A52 and PC9, derived from squamous cell carcinoma subtype were more sensitive to TIG than cell lines from adenocarcinoma subtype, H157 and EBC-1 [19].

The four NSCLC cell lines showed that TIG dose-dependently and preferentially induces apoptosis, a natural form of cell death, in contrast to necrosis [19]. Administration of A549 cells with TIG at 50 mg/kg twice a day in mice also demonstrated that TIG caused a statistically significant decrease in tumour weight of the experimental mice compared to the control mice [19].

Additionally, according to the *in vivo* and *in vitro* studies, TIG demonstrates selectivity as normal fibroblast cells remain unaffected at low TIG concentrations [19]. When administered in doses less than 10 μ M, TIG did not inhibit proliferation in normal fibroblast cells, and in concentrations less than 25 μ M, no apoptosis was observed in these cells [19]. TIG also downregulates the expression of B-cell lymphoma 2 (Bcl-2), an inhibitor of apoptosis, in NSCLC cells [19]. Bcl-2 corresponds to chemoresistance and is vital for maintenance of increased mitochondrial function in NSCLC cells [19].

TIG was also observed to reduce ATP levels by decreasing the mitochondrial respiration rate, lowering the mitochondrial membrane potential, and heightening reactive oxygen species (ROS) levels [19]. Specifically, mtDNA regulates the synthesis of proteins essential for the ETC; consequently, impeding mitochondrial translation of such proteins disrupts respiration [19]. The mitochondrial respiratory chain is responsible for generating the electrochemical gradient that drives the mitochondrial membrane potential [19]. TIG inhibits mitochondrial respiration, thereby disrupting the mitochondrial membrane potential and lowering ATP levels [19]. TIG also elevates ROS levels, which may contribute to apoptosis [19]. The lack of harmful effects in murine models further conveys TIG's compliance to human safety guidelines [19].

Gastric Cancer

Gastric cancer originates from gastric mucosa, neuroendocrine tissue, lymphoid tissue, or connective tissue of the gastric wall [21]. Current treatments for gastric cancer include gastrectomy, chemotherapy, and radio-chemotherapy [22,23].

Tang et al. [22] report TIG's ability to counteract gastric cancer growth via inhibition of mitochondrial protein synthesis. TIG or DMSO was administered to human primary gastric cancer cells and cell line MKN-45 in concentrations of 1 μ M, 5 μ M, or 10 μ M for 72 hours [22]. Specifically, the study found that TIG binds to the mitochondrial ribosomal subunit, hindering the entry of the aminoacyl transfer RNAs into the acceptor site, and preventing polypep-

tide elongation. This prevents the proliferation of gastric cancer cells [22]. Nonetheless, MDC staining revealed acidic vesicular organelles, a biomarker for autophagy [22]. This indicates that TIG did not induce cell death through apoptosis, but rather autophagy, a mechanism responsible for the degradation of non-functional organelles and proteins [22,24]. Treatment of MKN-45 or GAM-016 cells with 5 μ M and 10 μ M of TIG decreased cell proliferation [22]. Particularly, it was confirmed that a 10 μ M concentration increased phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) at amino acid residue threonine at position 172 [22]. AMPK is a stress-sensing enzyme, which is responsible for controlling metabolism and cell growth under stressful conditions [22]. Normally, AMPK activation is driven by increasing levels of adenosine monophosphate (AMP) bound to AMPK, along with low levels of adenosine triphosphate (ATP), which is accomplished by mechanisms that inhibit mitochondrial ATP synthesis or by increasing concentration of AMP and adenosine diphosphate (ADP) [22,25]. Under stressful conditions, AMPK/mTOR control cell autophagy by activating autophagy-initiating kinase, further resulting in cell death [22]. Specifically, phosphorylation of AMPK represses the mammalian target of rapamycin (mTOR) and its downstream target, P70 S6 serine/threonine kinase (p70S6K) [22,26]. mTOR can activate p70S6K, which is essential for cell growth and the G1 phase of the cell cycle [26]. Thus, phosphorylation of AMPK prevents cell proliferation by promoting autophagy [26]. Hence, Tang et al. [22] showed that TIG can activate AMPK and therefore suppress mTOR and P70S6K.

Additionally, Tang et al. [22] found that TIG was able to reduce tumour growth in a xenograft model by lowering protein expression without changing the appearance or behaviour of SCID mice model organisms. Taken together, TIG was proven to mitigate gastric cancer, specifically by targeting mitochondrial protein synthesis [22].

Hepatocellular Carcinoma

Originating from hepatocytes, HCC is the most recurrent type of liver cancer and can metastasize to various other organs to induce cellular damage [27].

Despite its heterogeneous phenotype and variability in different individuals, Tan et al. [28] recently demonstrated the effectiveness of TIG as a therapeutic strategy in HCC through inhibition of mitochondrial translation. Mechanistically, a decrease in mitochondrial membrane potential, activities of complex I and IV of the ETC, oxygen consumption rate (OCR), and ATP levels lead to the observed mitochondrial dysfunction [28]. Specifically, Tan et al.

[28] monitored expression of mitochondrial respiratory complex IV subunits, cytochrome c oxidase-1, 2, and 4, as well as grp78 for 48 hours after administration with TIG. An increase in Cox-1 and Cox-2 mRNA levels confirmed TIG's ability to decrease protein expression levels of the subunits [28]. Furthermore, TIG increases oxidative stress within HCC cells, leading to cellular damage [28]. This was due to increased levels of mitochondrial superoxide, hydrogen peroxide, and ROS levels, which are major hallmarks of oxidative stress in cancerous cells [28]. Interestingly, treatment with the antioxidant N-acetyl-L-cysteine (NAC) reversed the anti-cancer effects of TIG, portraying that oxidative stress is required for TIG to exert its effects pertaining to cellular damage in HCC cells [28]. This finding further highlights the selective nature of TIG and its ability to differentiate between normal and cancerous cells [28]. Increased mitochondrial biogenesis in HCC cells was observed in comparison to normal liver cells [28]. Differences in levels of glycolysis were not observed, and it was concluded that the mechanism of mitochondrial biogenesis differed among normal and HCC cells [28]. Consequently, the heightened sensitivity towards TIG in HCC cells was observed [28].

Moreover, using an *in vivo* model consisting of HepG2 and HuH6 human HCC cell lines, TIG was shown to inhibit further proliferation and induce significant apoptosis via a dose-dependent manner when administered in 5 μ m and 10 μ m concentrations [28]. Upon treatment with similar conditions, the same effect was not observed in normal liver cell lines, suggesting the selectivity of TIG towards HCC cells [28]. Also, when treated with a combination of TIG and cisplatin, HCC cells showed a greater decrease in proliferation, in comparison to treatment with either drug alone [28]. Synergism between antibiotics and pre-existing chemotherapy is also evident in literature, which validates this finding [29].

Breast Cancer

A majority of cancer-related deaths in women worldwide can be attributed to breast cancer [30]. An effective treatment regime for several subtypes of breast cancer has yet to be elucidated [30]. Lamb et al. [10] demonstrated that TIG arrested tumour-sphere formation in two commonly explored breast cancer lines, MCF7 and T47D [10]. Specifically, this was observed when TIG was administered in a concentration range from 10 μ m to 50 μ m [10]. In contrast to other chemotherapeutics, this glycylcycline was able to inhibit mitochondrial protein translation by binding to the 28S subunit of the small mitochondrial ribosome [10].

Jones et al. [30] observed the effects of TIG in triple-negative breast cancer, which is comprised of basal-like and claudin-low

subtypes. These tumors exhibited decreased expression of hormone receptors for estrogen and progesterone, as well as the HER2 receptor, which plays a crucial role in the onset of breast cancers [30]. Moreover, the genes corresponding to the tumour suppressors, p53 and retinoblastoma protein (pRB), are mutated in triple-negative breast cancers [30]. When bound to activating transcription factors such as E2Fs, pRB controls cell proliferation by allowing progression through the cell cycle and targeting apoptotic genes [30]. Loss of RB1 results in increased mitochondrial protein translation; this is enhanced by insufficient p53, which prevents permeabilization of the mitochondria. This is counteracted by TIG, which inhibits mitochondrial protein translation [30]. As a result, expression of COX I and COX II nuclear-encoded proteins is suppressed in Rb-deficient tumour cells, which ultimately leads to lower ATP levels [30]. TIG is thus effective in arresting the growth of human RB1/TP53-deficient cells [30]. Furthermore, a proto-oncogene known as MET is expressed in p53-deficient tumors and Rb/p53 mutant tumors [30]. Therefore, TIG used in combination with crizotinib, an inhibitor of the MET, induced tumour cell death [30]. Nonetheless, MET inhibitors have been unsuccessful in clinical trials [30]. TIG's effect was also enhanced when administered with an FDA-approved antioxidant inhibitor known as sulfasalazine [30].

Melanoma

Melanoma is one of the most fatal cancer-type and originates from mutated melanocytes. These cells are vital for skin homeostasis as they express melanin, a pigment that is able to protect the body from harmful ultraviolet (UV) rays and provides colour [31,32]. UV light is a widely recognized carcinogen which induces the formation of pyrimidine dimers, resulting in mutations [31]. In addition, UV light is known to alter the activity of p53, a tumour suppressor gene involved in apoptosis as a mechanism of repairing DNA damage [31]. Although reducing exposure to UV light is an effective preventative measure, TIG is now emerging as a promising treatment method [31]. A study conducted by Hu et al. [33] found that TIG was successful in suppressing cell growth and proliferation of A375 and MV3 human melanoma cells when administered at concentrations of 5 μ m and 10 μ m. This was a consequence of cell cycle arrest in the G1 phase in combination with reduced expression of CDK2 and Cyclin E, which encourage progression through the G1/S checkpoint [33]. It was also established that TIG counteracts metastasis by preventing cell migration and invasion through inhibition of the epithelial-mesenchymal transition (EMT) [33].

The cyclin-dependent kinase inhibitor, p21CIP1/Waf, is an essential regulator of cell proliferation, differentiation, migration, senescence, as well as apoptosis [33]. When found in the nucleus, this protein restricts the functions of cyclin E-CDK2, arresting the cell cycle at the G1 phase [33]. In the cytoplasm, p21CIP1/Waf acts as an oncogene due to its role in activating the RhoA-pathway and inducing a variation in cofilin phosphorylation; this leads to increased migration, which contributes to metastasis [33]. Additionally, p21 exhibits oncogenic properties through increased induction of apoptosis and proliferation [33]. Expression of cytoplasmic p21 is increased in melanomas and prevents apoptosis via p53 [33]. Hu et al. [33] established that overexpression of p21CIP1/Waf reversed the effects of TIG in human melanoma cells and supported advancement of the cell cycle through activation of CDK4/6, and thus, CDK2 [33]. A previous study conducted by Šestáková et al. [34] demonstrated that p21CIP1/Waf is crucial for melanoma cell survival and lineage determination. Similarly, it also regulates the expression of genes for melanocytes owing to its capacity to control the microphthalmia-associated transcription factor (MITF) [34]. Although the exact biochemical mechanisms are yet to be elucidated, such findings show that TIG functions to prevent melanoma cell proliferation, cell cycle progression, and migration or invasion by means of downregulating p21CIP1/Waf [33].

Cervical Squamous Cell Carcinoma

Originating from the keratinocytes, CSCC is a commonly occurring cancer in women [35]. CSCC oncogenesis is mainly attributed to human papillomavirus (HPV) infections and upregulation of the canonical Wnt/B-catenin signal transduction pathway [35,36].

Using the human lung adenocarcinoma cell line, Hela, Li et al. [36] established that TIG counteracts CSCC cell proliferation via interference with the Wnt/B-catenin signalling pathway. Through an MTS assay, the metabolic activity of cells was measured, allowing for the detection of a dose-dependent decrease in proliferation; an EC50 of 0.35 mM was observed [36]. In particular, the Wnt/B-catenin signalling pathway functions to increase nuclear levels of B-catenin, an oncogenic transcription factor [36]. Upon activation of the frizzled-7 receptor (Fz) by the Wnt protein, a cascade of molecular events leads to the inactivation of the cytoplasmic destruction complex responsible for degrading B-catenin; hence, allowing for accumulation of B-catenin and the onset of tumor-specific characteristics [36]. Li et al. [36] demonstrated that TIG increases levels of Axin 1, which is a negative regulator of

the Wnt/B-catenin pathway and forms the destruction complex responsible for degrading the oncoprotein B-catenin. Moreover, the decrease of B-catenin as a result of the increase in Axin 1 levels was validated through the subsequent observed decrease in B-catenin levels upon treatment with Axin 1 [36]. Inhibitory effects on B-catenin transcription were further validated by the absence of luciferase-induced blue colouration, following transfection of a luciferase-based reporter gene in HeLa cells [36].

Additionally, high doses of TIG curtails CSCC via induction of mitochondrial dysfunction [36]. Experimentation conveyed the significant decrease in mitochondrial oxygen consumption rate (OSR) as a precursor to eventual CSCC cell death [36]. Although the exact mechanisms of action are subject to further elucidation, TIG also demonstrated anti-cancer activity via apoptosis, as determined through flow cytometry techniques. In addition, administration with TIG also promoted dysregulation of anchorage-dependent CSCC growth in highly invasive subpopulations of the cell line [36]. Moreover, TIG and paclitaxel dose-dependently act in synergy to exert an amalgamated anti-cancer effect tumor in CSCC, as observed through isobolographic analysis [36].

Glioblastoma

GM is one of the most aggressive types of human cancers and originates from astrocytes within connective tissues of the brain [13]. It is characterized by pervasive angiogenesis and resistance to pre-existing therapeutics [14]. Moreover, current effective therapies only yield a median survival rate of 15 months and mainly target palliative aspects of the individual's condition [13].

Recent in vitro studies have established the effectiveness of TIG as a therapeutic agent for GMs. Yang et al. [14] showed that the antibiotic inhibits cell proliferation dose-dependently by inducing cell cycle arrest via upregulation of the miRNA-199b-5p-HES1-AKT pathway. In general, miRNAs are widely recognized as key agents involved in cancer pathogenesis as they upregulate cell proliferation and tumour growth [14]. In fact, many in vitro studies reveal the differing levels of miRNA expression in poor and good survival GM groups [14]. miR-199b-5p is a type of miRNA that is known to downregulate the AKT signaling transduction pathway, resulting in decreased cyclin D1 expression [14]. Since inhibition of cyclin D1 prevents progression to the G1 phase of the cell cycle, GM cells exhibit cell cycle arrest and thus decreased proliferation [14]. One of the known mechanisms by which miR-199b-5p induces AKT dysfunction is via inhibition of the transcription factor HES1, a downstream target of the universal Notch pathway [14]. Many studies exploring multiple cancer types have attributed the

overexpression of HES1 with AKT activation and cell proliferation [14]. In the aforementioned study, TIG yielded significant up-regulation of miRNA-199b-5p levels, as detected via an miRNA assay [14]. To validate the results, treatment with miR-199b-5p antagomir decreased levels of miRNA-199b-5p; thus, blocking TIG's effects [14]. Interestingly, Zhong et al. [37] also observed cell cycle arrest at the G1 phase via AKT activation in neuroblastoma cells upon treatment with TIG.

Conclusion

Tigecycline (TIG) has recently surfaced as a potential candidate for cancer therapy. This review examined its pharmacodynamics for a cohort of cancer-types including acute myeloid leukemia (AML), non-small cell lung cancer (NSCLC), gastric cancer, hepatocellular carcinoma (HCC), breast cancer, melanoma, cervical squamous cell carcinoma (CSCC), and glioblastoma (GM). TIG's effects in AML cells suggested that future studies be geared towards the use of a stable form of the antibiotic, allowing for the increase of TIG's concentration in cells [18]. Further studies with CSCC should aim to identify the specific molecular targets and loci of interference of Axin 1 and the mechanism by

which TIG accesses the specific target site. Since several studies provide strong evidence portraying favorable outcomes, further investigations should consist of human clinical trials to leverage these findings, in addition to comparing TIG's efficacy with conventional therapeutics. Given TIG's unique ability to cross the blood-brain barrier, subsequent studies should aim to broaden the scope of the aforementioned cancers; especially in regards to brain tumors [10]. The current understanding of TIG's molecular underpinnings could be applied to the design of novel pharmaceuticals using high-throughput screening. Additionally, pre-existing literature analyzed in this review illustrates TIG's enhanced effect when used in conjunction with other Food and Drug Administration (FDA)-approved drugs. Future research should also explore TIG's synergistic effect when used with cancer interventions such as surgery and radiation techniques, as well as with other classes of antibiotics known to target cancer. Moreover, TIG serves as a plausible solution for combating cancer in developing countries as it is both readily available and cost-effective [10]. Overall, several studies have demonstrated TIG's promising role in cancer remediation; however, further research and clinical data are required to solidify its current standing.

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