Investigation of active peptides from natural products that induce ER-stress-mediated apoptosis in cancer as potential therapeutics for kidney cancer, common in some genetic diseases: An in silico approach

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Article Info:

Article History:
Received 08 Sep 2023
Reviewed 16 Oct 2023
Accepted 03 Nov 2023
Published 15 Nov 2023

Cite this article as:
DOI: http://dx.doi.org/10.22270/jddt.v13i11.6307

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Abstract

Background: The endoplasmic reticulum (ER) stress initiates unfolded protein response (UPR) to re-establish ER homeostasis as an adaptive pathway in cancer. However, persistent ER stress triggers the apoptotic pathway usually observed in kidney cancer (KC). The term KC actually refers to a number of distinct cancers. Kidney cancer is generally observed in a number of genetic diseases. Treatment options for KC have changed greatly over the years. The most commonly used (tyrosine kinase inhibitors) TKI show conflicting results regarding the beneficial effect on patients, as demonstrated in different KC patient cohort studies, indicating that the underlying molecular mechanisms involved in KC are complex and likely need combined therapies able to modulate the activity of ENDOPLOSMIC RETICULUM. Methods: The purpose of this research was to generate peptides from natural product in silico that might be used as kidney cancer potentials modulators. For this aim, several methods were used: Target prediction, protein hydrolysis, and protein-peptide molecular docking have all been used as technics Results: The network of critical KC gene is constituted of C3AR1, CSNK2A2, ACE, DPP4, CAPN1, FPR2, HLA-A and MMP2 together with predicted kinases such as RPS6KA5, MAPK14, CSNK2A1, PRKCD, CDK1 and HIPK2 in addition to transcription factors such as IRF8, TCF3, ERG, CREB1, EZH2, SPI1, IRF1 and SUZ12. The identified molecular target of isolated peptides HLA class I histocompatibility antigen A-3, Lipoxin A4, Dipeptidyl peptidase IV, Angiotensin-converting enzyme, Cyclooxygenase-2, C3a anaphylatoxin chemotactic receptor, Melanocortin receptor 4, Neurotensin receptor 1, Mu opioid receptor, Delta opioid receptor and Calpain 1. Conclusion: Overall, the results showed that GVSK, FOP, WQR, YGGF and IP peptides are promising candidates for further study. Future work would be needed to test the therapeutic properties of these hydrolysate peptides by in vitro and in vivo approaches.

Keywords: Genetic diseases, Kidney cancer, peptide treatment, molecular docking.

INTRODUCTION

The endoplasmic reticulum (ER) is an essential site for the synthesis and maturation of plasma membrane proteins, this organella plays critical roles in cell signaling, metabolism homeostasis, and protein synthesis. He can be subjected to stress because of an overabundance of incorrect proteins setting up a situation of “endoplasmic reticulum stress” for the cells, this situation can induce the UPR response (unfolded protein response). The UPR response is designed to increase the cell’s capacity to eliminate incorrect proteins, to resolve cell injury or activate cell death by apoptosis, if the stress is too intense or too long-lasting 1. Overall, endoplasmic reticulum stress is a cellular mechanism that allows damaged cells to repair cellular lesions or activate their death, depending on the extent of the damage. In the context of kidney cancer, cancer cells stimulate this stress mechanism at an intermediate level, which helps them to survive but does not trigger the death process 2. Despite a number of studies being conducted on cancer, it remain the second biggest cause of death worldwide, the effective mechanism for treating cancer has not yet been fully understood 3. KC, also known as renal cell carcinoma, affects close to 300,000 people worldwide each year and is the cause of more than 100,000 fatalities. Patients with metastatic disease have a 5-year survival rate of 0% to 10%, whereas patients with localized or locally advanced disease have a 5-year survival rate of 20% to 95% depending on the extent of the disease 4. Over 400,000 new cases, or 2% of all cancer diagnoses, were reported in 2020, with a higher prevalence in male patients 5. RCC is divided into various subtypes based on the histology and genetics of the tumors, so it is not a single disease. Ten different types of RCC are depicted in these histology images, along with the genes that have been altered in each of these histologies. Both germline and somatic mutations of VHL, BAP1, MET, FH, TSC1, TSC2, and PTEN can result in inherited diseases and sporadic diseases, respectively. Specific inherited disease syndromes result in germline mutations of FLCN, SDHB, SDHC, and SDHD 6. The study of patients with inherited RCC susceptibility syndromes, such as von Hippel-Lindau (VHL; VHL gene), hereditary papillary RCC (HPRC; MET gene), Birt-Hogg-Dubé (BHD; FLCN gene), and hereditary leiomyomatosis and RCC (HLMRC; FH gene), has contributed significantly to our understanding of the genetic.
and metabolic basis of RCC. Studies of sporadic (nonfamilial) and familial disease have laid the groundwork for the creation of therapeutic strategies that target the metabolic basis of RCC.

Clear-Cell Renal Carcinoma: VHL/HIF Oxygen-Sensing Pathway

Familial ccRCC: von Hippel–Lindau

Clear-cell renal cell carcinoma (ccRCC) occurs in both a sporadic (nonfamilial) and a familial form. Patients affected with VHL disease are at risk for the development of tumors in a number of organs, including the kidneys.

VHL Gene

VHL families underwent genetic linkage analysis to pinpoint the VHL gene's location on the short arm of chromosome 3. Nearly all VHL families have been found to have a germline alteration of the VHL gene, including point mutations, splice-site mutations, and partial or complete gene deletions. 7

Birt–Hogg–Dubé RCC: FLCN Nutrient Sensing

BHD Syndrome

Affected people who have BHD syndrome are at an increased risk of developing benign cutaneous tumors (fibrofolliculomas), pulmonary cysts (which are frequently linked to pneumothorax), and kidney tumors. More than 85% of BHD patients over the age of 25 have cutaneous fibrofolliculomas, and between 70% and 84% of BHD patients have pulmonary cysts. 8

FLCN Gene

The BHD disease gene was discovered to be located on chromosome 17p11 by genetic linkage analysis in BHD families, and germline mutations in the novel gene folliculin (FLCN) were discovered in affected people 9

Cowden Syndrome

An increased risk of developing tumors in a number of organs, such as the breast, thyroid, endometrium, and kidney, characterizes Cowden syndrome, an autosomal dominant disorder. Numerous germline gene mutations, including the PTEN gene mutation on chromosome 10q22, are linked to Cowden syndrome 10

It is known that at least 17 different genes can cause KC and that mutation of these genes can affect the cell's ability to respond to changes in oxygen, iron, nutrients, most notably in the case of mutations of some genes especially in genes for the tricarboxylic acid (TCA) cycle enzymes fumarate hydratase and succinate dehydrogenase (SDH). Energy. Finding potential therapeutic targets to block the actions of Trans-regulatory factors and kinases involved in the carcinogenesis process could result from studying the interactions between particular molecules and peptides in these pathologies. Cancer treatment is difficult to diagnose early and to treat effectively. Fundamental innovations in conventional diagnosis and therapy are required to effectively diagnose and treat cancer. Most conventional chemotherapies are administered systemically in the majority of the world, and after a while, they are discontinued due to unfavourable side effects like systemic manifestations or drug resistance, and in the majority of cases, there are no suitable alternatives 11. Because of their versatility, peptides can be very helpful in this regard. These peptide-based cancer treatments have employed more than two distinct methods: These peptides have the potential to cross the membrane and deliver therapeutic agents and they have been used as mimics of natural peptides involved in cancer-related signaling pathways; in the field of therapeutic agent delivery, they have thus been studied and employed 12. For this study, peptides used can be consider as modulators able to interact

with specifics protein targets involved in carcinogenesis process in order to control potential genetics and epigenetic modifications and consolidate the re-establishment of ER homeostasis. This study adopts a different perspective on the use of peptides in cancer therapy.

MATERIALS AND METHODS

Preparation of kidney cancer-related genes

The genes involved in kidney cancer-related genes have been identified in the literature - a total of 50 genes have been identified: ASPSCR1, FH, FLCN, PRCC, TFE3, AMER1, CD274, DCRB1, DROSHA, EPAS1, ETV6, IGFL2, IL2, MET, MTR, NTRK3, SETD2, TP53, VEGFA, VHL, WT1, ZCCHC6, AMACR, ATF6B, B3GAT1, CA9, KRT7, NUTM2B, POUF2, UKP3A, CTNNB1, CTR9, OSCAR, PRBM1, P1050, SMARCAD4, SMARCBI, SSI8, SXX2, B3GAT1, NUTM2E, SAA1, SAA2, PRBM1, BAP1, TCEB1, MITF, TSC2, TSC2, FIM2P.

Gene network analysis

For network analysis to determine transcription factor and kinase enrichment and protein-protein interaction, 50 published genes linked to kidney cancer were used. This part of the work was carried out using the X2K Web server (https://maayanlab.cloud/X2K/). With the help of the signatures of genes with differential expression, it determines upstream regulatory networks. X2K Web generates inferred networks of transcription factors, proteins, and kinases thought to regulate expression of the captured gene list by combining transcription factor enrichment analysis, protein-protein interaction network expansion, and kinase enrichment analysis.

Interaction of proteins

The protein-protein interaction profile of the 50 genes identified as being involved in kidney cancer. These outcomes were attained by utilizing the WEB STRING (https://string-db.org/).

Protein hydrolysis and bioactivity testing

For these analyses, a number of peptides that have been identified as having appropriate biological activity as anti-cancer and anti-apoptotic in studies on kidney cancer were chosen, especially bioactive compounds from natural products that induce ER-stress-mediated apoptosis in cancer and the peptides to be hydrolysed were obtained from the server (https://www.uniprot.org/): Paris polyphylla (Polyphyllin D, MEGALLLILT) 11, Sausurea lappa (Dehydrocactuslac tone, ATYKVLITTP) 12, Orzya officinalis (a-Hydroxyundec-9-enolic acid, MSKMISLELY) 13, Curcuma longa (Curcumin, MEANGRITY) 14, Mylabris phalerata Pallas (Cantharidin, TLYLFGAWA) 16, Curcumae Rhizoma (Furaniode, LVGVDPPVDG) 16, Tanacetum parthenium L (Parthenolide, MFSSFETLL) 17, Anacardium occidentale (Anacard acid, LSCVFILFFH) 18. These molecules were all found in various online databases and books. The sequences were uploaded to the BIOPEP-UWM web server to encourage enzymatic hydrolysis, using the digestive enzyme mixture of trypsin (EC 3.4.21.4), chymotrypsin (EC 3.4.21.1), pepsin, and pH 1.3 (EC 3.4.23.1) [118]. Prior to further analysis, as previously described, peptide sequences from the hydrolysate were converted to the simplified format of molecular input line specification (SMILES) on the BIOPEP-UWM web server.

Reconstruction of the gene network and target prediction

On SwissTargetPrediction (http://www.swisstargetprediction.ch), the hydrolysate peptide sequence obtained from in silico enzymatic hydrolysis was used for target prediction analysis, with human (Homo sapiens) designated as the target organism and a probability threshold of 20% used as a selection criterion. The enrichment
of transcription factors, kinases, and protein-protein interactions were then determined using further network analyses using the predicted gene identifiers. Man (Homo sapiens) was chosen as the target organism, and the experiment was conducted on the eXpression2Kinases (X2K) web server, which is accessible at https://maayanlab.cloud/X2K/.

**Allergenicity prediction using ADME in silico**

Functional hydrolysate peptides were searched for using in silico ADME (absorption, distribution, metabolism, and excretion) screening on the SwissADME server (www.swissadme.ch), which was run with the default settings and the SMILE format. The AllerTOP v.2.0 web server (http://www.ddg-pharmfac.net/AllerTOP) was used to estimate allergenicity.

**Molecular docking studies**

The criteria used for molecular docking studies are peptides with no more than four amino acid residues are non-allergenic and have a minimum 50% probability of targeting at least one molecular target protein. On the basis of the predicted obtained in the previous step, peptide-protein docking was carried out on the SERVER SwissDock (http://www.swissdock.ch/). The molecules were drawn using ChemDraw Professional 16 software and visualised using Chem3D.

**RESULTS**

**Gene network analysis**

Figure 1 below shows the involvement of the kinases and the number of substrates enriched by each of these kinases during the actions of the genes employed: HIPK2 (11 substrates), CDC2 (15 substrates), CDK1 (33 substrates), MAPK14 (26 substrates), GSK3B (30 substrates), CK2ALPHA (13 substrates). Numerous transcription factors were also implicated in the interactions of genes generally mutated in kidney cancer: TAF1, TRIM28, RCOR1, CHD1, UBTB, TCF3, ERG, SP1.

**Protein-protein interaction**

The figure 2 below shows all the genes identified as being associated with kidney cancer visualised with K-mean clustering in 7 groups: group 1: red (B3GAT1, ETV6, KRT7, POU6F2, SSX2, WT1); group 2: brown: ATF6B, CTR9, EPAS1, NUTM2B, NUTM2E, TCEB1, VHL); group 3: olive green (AMACR, ASPSCR1, FH, FLCN, FNIP2, MTF, PRCC, TFE3, TSC2); group 4 green: (B3GNT1, OSCAR, SAA1, SAA2); group 5 blue: (DGCR8, DROSHA, TP53, UPK3A, ZCCHC6); group 6 light blue: (AMER1, CA9, CD274, CTNNB1, IGF2, IL2, MET, Mtor, NTRK3, SMARCA4, VEGFA) and group 7: (BAP1, PBRM1, SETD2, SMARCB1, SS18).
Protein Hydrolysis and Bioactivity Testing

Table 1 below shows the 13 peptides isolated and the proteins with which they may associate, as well as the predicted probability between them.

Table 1: Molecular target of peptide hydrolysed

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### TABLE 2: predicted pharmacokinetic properties of the hydrolysate peptide

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**SN:** Serial number. **Legend:** Physicochemical properties: molecular weight (MW), molar refractivity (MR), total polar surface area (TPSA). Lipophilicity: log P (consensus). Water solubility: ESOL log S, ESOL class. Pharmacokinetics: gastrointestinal absorption (GIA), blood-brain barrier (BBB), P-glycoprotein (P-gp) substrate, inhibition of cytochrome P450 (CYPs) type CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, skin permeation; (Log Kp). Drug-likeness: bioavailability score (BS). Medicinal chemistry: synthetic accessibility (SA).

The figure 3 below shows the interaction between kinase, intermediate proteins and transcription factors.

![Figure 3: KC predicted target gene network](image-url)
The figure 4 below presents different clusters generated after gene identification presented as follows:

**Cluster 1**: C3AR1, CDK1, CSNK2A1, CSNK2A2, ERG, EZH2, IRF1, IRF8, PRKCD, SPI1, SUZ12, TCF3

**Cluster 2**: ACE, CAPN1, CASP8, CREB1, DPP4, FPR2, HLA-A, HMGCR, MAPK14, MMP2, PTGS2, RPS6KA5, SLC5A1, XIAP

**Cluster 3**: CCKBR, DLG4, HIPK2, MC4R, NTSR1, OPRD1, OPRK1, OPRM1, PDYN, TACR1

**Molecular docking**

The image 5 below shows the various potential interactions that may exist between certain peptides and targets. On the whole, we observed fairly polar compounds, showing mesomerism and hydrogen bonds between hydrogen and oxygen atoms. Also between the nitrogen and iron-3 doublets (5-c). In some interactions, SO4 serves as a ligand (5-d) and are all visible on UV.
DISCUSSION

The traditional approach to studying cancer was primarily concerned with identifying and figuring out the patterns of genetic anomalies that are caused by mutational or other chromosomal aberration events; however, only a small number of cancer-related genetic mutations have been found in patients, which in no way explains the vast genetic deviation that ultimately manifests in the malignant phenotype of cancer.

Kidney cancer is the 14th most common cancer worldwide, with renal cell carcinoma (RCC) making up the majority of cases. In the last few years, immuno-oncology and targeting actionable alterations in oncogene-driven cancers have both revolutionized cancer treatment paradigms. Despite these therapeutic advances, cancer treatment remains a real problem. The findings of this study, which sought to pinpoint...
molecules able to interact with genes, kinases and transcription factors in kidney cancer, demonstrate that; the kidney cancer has been linked to a network of kinases and transcription factors that can communicate with transcription factors through specific proteins.

Among the identified kinases, HIPK2 kinase is more involved in several case of cancer, fang and collaborators showed that HIPK2 restrains NF-kB activation through phosphorylating HDAC3 at serine 374 to inactive HDAC3 deacetylase activity, thus reducing the p65 deacetylation and suppressing inflammation during the associated colorectal carcinoma and sepsis 23. Study on colorectal cancer showed that Prostate cancer-associated SPOP mutations lead to genomic instability through disruption of the SPOP–HIPK2 axis 24. These observations can be due to the fact that kinase HIPK2 who is a conserved serine/threonine kinase from the family of homeodomain-interacting protein kinases is produced by this gene. Depending on the transcription factor and its subcellular localization, the encoded protein can act as a coressor or a coactivator. It interacts with many other transcription factors, including p53 25. The cell division control gene 2 (CDC2) was also among kinase involved in kidney cancer development; CDC2 can be more phosphorylated in case of osteosarcoma 26 and overexpressed in breast cancer. The CDC2 serves as a beneficial regulator of cell proliferation while the main gametophyte, embryo, and endosperm are developing. CDK1 kinase has presented an interest during this study among kinase identified; these genes is generally involved in phosphorylation and dephosphorylation of proteins and also play important regulatory roles in cell cycle control. Alternatively spliced transcript variants encoding different isoforms have been found for this gene. Many study present CDK1 that overexpression of CDK1 has been associated with cancer; CDK1 inhibitors may restore equilibrium to the skewed cell cycle system and operate as an effective therapeutic drug 25, and CDK1 serves as a therapeutic target of adenocortical carcinoma via regulating epithelial–mesenchymal transition, G2/M phase transition, and PANoptosis 28. MAPK14 is known as Mitogen-activated protein kinase 14 (MAPK14), which plays an important role in DNA damage and repair, is activated by various environmental stress and proinflammatory cytokines. Although it is very active in a variety of tumors and can either promote or suppress tumor growth 30. GSK3β gene identified is known to reduce tumor growth and improves survival in an ovarian cancer mouse model in association with HDACs 31. This gene could be involved in modulating epigenetic activity in kidney cancer. In addition, Overexpression of YBX1 Promotes Pancreatic Ductal Adenocarcinoma Growth via the GSK3β/Cyclin D1/Cyclin E1 Pathway (Liu et al., 2020). High Expression of Casein Kinase 2 Alpha (CK2α) can enhance phosphorylation of DNA and increase tumor mutation rates in Colorectal Cancer. The identification of this gene could explain why several alterations can be identified in kidney cancer. In addition to the identified kinases, several genes coding for transcription factors are also part of the network. Proteins like TAF1 identified acts as a flexible scaffold that drives the co-translational recruitment of TFIIH submodules preassembled in the cytoplasm 33; TFIIID is crucial for recognizing promoter DNA and putting together the pre-initiation complex. RCOR1 is a known transcription repressor that recruits and positions LSD1 and HDAC1/2 on chromatin to erase histone methylation and acetylation 34; the presence of RCOR1, CHD1 shows the involvement of the epigenetic system in kidney cancer carcinogenesis. The same observations are also done with the transcription factor TRIM28 who is generally involved in upregulation of cancer expression in tissues whereas correlate with worse overall patient survival 35, so TRIM28 could supports kidney cancer progression. Most transcriptional factor as TFCF3 36, ERG 37, SP1 38,39 contribute to the pathogenesis of human cancers. Several peptides have been identified with high target prediction probabilities, notably 13. The EILDV peptide, which showed affinity with caspase 8 and disk large homolog 4, is a serious candidate for a modulating inter-action with the molecules involved in the carcinogenesis of kidney cancer in particular and for the fight against cancers in general. Cancer cells are known to use nuclear caspase-8 to overcome the p53-dependent G2/M checkpoint by cleaving USP28 40, caspase 8 globally regulates cell life and death 41. The GYSK peptide has been shown to interact with the HLA class I histocompatibility antigen A-3 protein, which is one of the metabolites derived from arachidonic acid and is catalysed by 15-lipoxygenase (15-LOX), and has recently been reported to have anticancer effects. 42. The isolated PGP peptide shows affinity with Dipetidyl peptidase IV, an enzyme expressed on the surface of most cell types and associated with immune regulation, signal transduction and apoptosis. This shows that this small molecule could significantly regulate the apoptotic action of cancer cells by accelerating their programmed death. By interacting with the enzyme, this peptide could reduce its activity 43. The isolated PGP peptide shows affinity with Dipetidyl peptidase IV, an enzyme expressed on the surface of most cell types and associated with immune regulation, signal transduction and apoptosis. This shows that this small molecule could significantly regulate the apoptotic action of cancer cells by accelerating their programmed death. By interacting with the enzyme, this peptide could reduce its activity 43. In addition, the WQR peptide, which has the ability to bind with C3a, could prevent C3a-C3AR signalling in CAPs, which generally facilitates breast cancer metastasis 46; This shows that targeting C3aR signalling could be a potential anti-metastasis strategy for the treatment of cancer. The peptide YGGF showed a high affinity with the opioid complex; this peptide could induce the targeted re-expression of the mu-opioid receptor on cancer cells, thereby inhibiting mechanical and thermal hypersensitivity and preventing tolerance to opioids, which are psychoactive substances that can act in the areas of the brain responsible for pain control by producing an analgesic effect and can induce euphoria 46. The IF peptide had an affinity for calpain, which plays an important role in cell apoptosis 47. Molecular docking predicts ligand binding sites (active and allosteric/regulatory sites) on the surfaces of biological macromolecules (proteins, RNA or DNA) and predictively calculates the binding affinities of their interaction, or DNA) and predictively calculates the binding affinities of their interaction; the binding energy score ≤-5.00 kcal.mol indicates good affinity between the target protein and the ligand. The non-allergenic peptides obtained in this study showed binding energy scores ≤-5.00 kcal.mol, with all these peptides showing real promise as modulators of carcinogenic reactions leading to kidney cancer.

CONCLUSION

Cancer in general is a real public health problem for persons affected, and it is even more aggressive for those who contract it as a side-effect of a genetic disease, a phenomenon that is very much in evidence in kidney cancer. Despite technological and scientific advances, the treatment of cancer remains difficult and very costly, with many side effects; different approaches must therefore be adopted in the search for a therapeutic solution, which is why we have been working on peptides that could have potential in modulating the expression of the activity of proteins involved in carcinogenesis. It turns out that this line of therapy offers a great deal of hope, since most of the peptides isolated are active and can interact with the other molecules involved in kidney cancer. The current problem with
these peptides are their ability to negatively modulate the evolution of cancer dynamics by participating in the support of the apoptotic pathway during stress of the endoplasmic reticulum.

REFERENCES


