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Review

Regulation of cell signaling pathways by Wogonin in different cancers: Mechanistic review

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Abstract: Natural products have historically been invaluable as a premium source of therapeutic agents. Recent advancements in genomics and structural biology have portrayed a high-resolution landscape of the diversity of proteins targeted by pharmacologically active products from natural sources. Natural product research has generated valuable wealth of information and cutting-edge research-works have leveraged our conceptual knowledge altogether to a new level. Wogonin (5,7-dihydroxy-8-methoxyflavone) is an O-methylated flavone and has attracted noteworthy appreciation because of its ability to pharmacologically target plethora of cell signaling pathways in different cancers. In this mini-review, we have gathered scattered pieces of available scientific evidence to summarize how wogonin pharmaceutically targeted Wnt/β-catenin, JAK/STAT, VEGF/VEGFR and TRAIL-driven apoptotic pathways in wide variety of cancers. We have also critically analyzed how wogonin prevented carcinogenesis and metastasis in tumor-bearing mice. Although researchers have uncovered pleiotropic role of wogonin in the regulation of different oncogenic signaling cascades but there are visible knowledge gaps in our understanding related to regulation of non-coding RNAs by wogonin. Future studies must converge on the unraveling of additional drug targets for wogonin to achieve a fuller and realistic understanding of the chemopreventive properties of wogonin.

Key words: Cancer; Apoptosis; Signaling.

Introductory overview of Wogonin

Accumulating evidence from epidemiological studies has suggested that the consumption of various phytochemicals can not only reduce the incidence of cancer but can significantly enhance the sensitivity of chemotherapies (1,2). Carcinogenesis is a complicated process that involves multiple pathways and phytochemicals have pleiotropic effects that make them an ideal candidate to target tumors. However, the true anticancer potential of phytochemicals cannot be harnessed without understanding the underlying mechanism (2,3). This review aims to provide a mechanistic insight on the molecular pathways modulated by a phytochemical, wogonin that can help to utilize its chemopreventive and therapeutic effects.

Flavonoids are bioactive secondary metabolites synthesized by a plant that provides protection against environmental stress and possess several pharmacological activities (4). A number of in-vitro and in-vivo studies have shown that flavonoids possess potent anti-inflammatory, anti-oxidative and anti-tumorigenic effects (4). Wogonin is an active constituent extracted from the roots of *Scutellaria* baicalensis and is chemically 5,7-dihydroxy-8-methoxyflavon. It is also found as wogonoside in four different species of Scutellaria genus (5). *S. baicalensis* is one of the most widely used herb in traditional therapies and has shown potential therapeutic effects against a number of pathological disorders as cardiovascular, diabetes, bacterial and viral infections. Its anticancer activities have also been extensively studied (5). Among a number of active constituents found in *S. baicalensis,* wogonin displays remarkable pharmacological activities *i.e* anti-inflammatory (6,7), anti-oxidative/anti-radical (8) , neuroprotective (9,10,11), cardioprotective (12,13), induction of autophagy, apoptosis, cellular senescence in cancer cells (9), antiproliferative effect on tumor cells (14) and increasing in the sensitivity of various chemotherapeutic agents (15,16). However, the use of wogonin is limited by its poor bioavailability and poor solubility (17,18).

In this review we have provided an overview of the pharmacological properties of wogonin. We have partitioned this review into various sub-sections. We will exclusively discuss how wogonin regulated Wnt/β-catenin and JAK/STAT pathways in different cancers. We have also discussed how wogonin modulated HIF proteins and VEGF/VEGFR signaling axis. In the last section, we will conclude with a discussion of areas of current interest and challenges in the field, and opinions about how progress may be made to deepen our understanding about the pleiotropic roles of wogonin in different

cancers.

Regulation of Wnt/β-catenin Pathway

WNT ligands interacted with Frizzled receptors and the co-receptors to induce β-catenin-mediated canonical WNT transduction cascade. β-catenin interacted with the T-cell factor (TCF)-LEF complex in WNT-mediated regulation of gene networks.

Wogonin caused marked reduction in the phosphorylated levels of GSK-3β (Serine residue 9) and downregulated β-catenin levels (19). Activation of GSK-3β is mainly because of inhibition of AKT by wogonin. Importantly, inhibition of GSK-3β activity by LiCl (activator of β-catenin signaling) abolished wogonin mediated repressive effects on β-catenin (19).

Wogonoside effectively suppressed the levels of p-PI3K, p-AKT and p-β-catenin in the SCL-1 and SCC12 cells (20). Wogonoside notably reduced p-β-catenin levels in the tumor tissues of the mice subcutaneously injected with SCL-1 cells (20).

Moreover, LW-213 not only reduced phosphorylated levels of AKT and GSK-3β but also restricted the accumulation of β-catenin in the nucleus in breast cancer cells (21).

Levels of p-GSK-3β at Serine 9 were noted to be reduced in wogonin-treated ER-negative cancer cells (22).

Unquestionably, there are missing parts of the puzzle that remain to be solved. However, these important research works have given us a better understanding of the underlying mechanisms.

Regulation of JAK/STAT Pathway

JAK/STAT pathway has been shown to play critical role in tumorigenesis. Pharmacological targeting of STAT proteins has been reported to be effective in cancer chemoprevention.

FV-429, a derivative of wogonin was found to be effective against STAT-driven oncogenic signaling (23). FV-429 not only reduced the levels of p-STAT3 but also inhibited its nuclear accumulation in ovarian cancer cells. Studies have shown that active STAT3 moved into the nucleus and transcriptionally upregulated HIF1α. However, paclitaxel and FV-429 worked with effective synergy and markedly reduced the levels of p-STAT3 and HIF1α in the tumor tissues of mice injected with A2780 cancer cells (23).

Inflammatory cells, particularly tumor-associated macrophages have been demonstrated to play dominant role in tumorigenesis. THP-1 conditioned media induced migration of A549 cancer cells. However, wogonin inhibited THP-1 conditioned media-mediated migration of A549 cancer cells (24). THP-1 conditioned media caused epithelial-to-mesenchymal transition in A549 cancer cells mainly through upregulation of N-cadherin and vimentin. However, wogonin induced upregulation of E-cadherin and repression of N-cadherin and vimentin. Interleukin-6 was present in the conditioned media which triggered STAT-driven signaling in A549 cancer cells. Wogonin also reduced the levels of p-JAK2. Wogonin induced regression of the tumors in mice transplanted with A549 cancer cells. Wogonin effectively reduced p-STAT3, N-cadherin and vimentin in the tumor tissues of xenografted mice (24).

IL-6 stimulated PDL1 (Programmed death Ligand-1) expression in SGC-7901 cancer cells, but wogonin significantly inhibited PDL1 (25). Moreover, wogonin efficiently reduced IL-6 mediated activation of STAT3 in SGC-7901 cancer cells. Wogonin enhanced infiltration of lymphocytes to retard tumor growth in tumor-bearing mice (25). PDL1/PD1 signaling has attracted noteworthy attention because of its ability to "switch-off" natural killer cells. Therefore, future studies must converge on a comprehensive analysis of the ability of wogonin to pharmaceutically target PDL1-driven signaling.

Wogonin also reduced p-STAT3 levels in colorectal cancer cells (26).

Seemingly, wogonin effectively modulates different STAT proteins for cancer chemoprevention, but there is still a need to comprehensively analyze how wogonin interferes with JAK/STAT signaling to inhibit or prevent cancer.

Regulation of HIF by Wogonin

HIFα (Hypoxia-inducible factor) subunits frequently undergo oxygen-dependent hydroxylation on specified proline residues (27). Hydroxylated HIFα subunits are recognized by VHL (von Hippel–Lindau) protein and degraded by the polyubiquitination/proteasomal pathway. Prolyl hydroxylase domain (PHD) proteins induced hydroxylation of HIF subunits. Wogonin increased the expression of PHD1, 2, and 3 under both hypoxic and normoxic conditions. Wogonin increased the levels of hydroxylated HIF1α. Wogonin stimulated the expression of VHL. Wogonin failed to reduce the levels of HIF1α in VHL-silenced-MCF-7 cells. Wogonin potentiated the interaction between VHL and HIF1α in MCF-7 cancer cells. Wogonin not only prevented the association between HSP90 and HIF1α but also inhibited nuclear translocation of HIF1α (27).

Importantly, c-MYC has been reported to enhance the stability of HIFα (28). However, wogonin notably reduced the levels of HIFα in c-MYC-overexpressing RPMI 8226 cells (28).

PI3K/AKT pathway was also found to be necessary for HIFα stabilization (29). Hypoxia induced an increase in levels of p-AKT and PI3K. However, wogonin reduced the levels of p-AKT and PI3K. There was a marked reduction in the expression levels of PI3K, AKT and HIFα in the tumor tissues of mice treated with wogonin (29).

Wogonin significantly decreased HIF1α and MCT4 (Monocarboxylate transporter-4) levels in SGC-7901 cells (30).

Regulation of VEGF/VEGFR Signaling

VEGF is the fundamental regulator of angiogenesis. VEGF has a pivotal role in the regulation of physiological and pathological growth of any type of blood vessels during vasculogenic and angiogenic processes. More importantly, studies had shown that VEGF played a central role in the neovascularization of tumors. Deprivation of oxygen in the interiors of rapidly-growing tumors generated hypoxic areas. Consequently, hypoxia

induced VEGF upregulation by increasing the transcriptional rates and/or the stability of VEGF mRNAs.

Choroiallantoic membrane (CAM) assay is useful for the assessment of anti-angiogenic effects of different natural products (31). Wogonin inhibited LPS-induced formation of the new vessels in the CAM model. Wogonin induced reduction in the protein levels of VEGF and VEGFR2 (31).

LW-215, a derivative of wogonin was found to be effective against angiogenesis (32). Sprouting of microvessels from rat aortic ring and CAM model also clearly indicated that LW-215 effectively suppressed angiogenesis. LW-215 markedly reduced VEGF-induced phosphorylation of VEGFR2 (32). Wogonin inhibited protein levels of VEGFR1 and suppressed angiogenesis (33).

Wogonin also exerted inhibitory effects on VEGF-induced migration and tube formation of HUVECs (34). Wogonin also blocked VEGF-induced phosphorylation of VEGFR2 (34).

Regulation of Matrix Metalloproteinases

Wogonin inhibited the mobility of $CD133^+$ osteosarcoma cells via downregulation of MMP9 (35).

Wogonin concentration-dependently inhibited the activities of MMP2 and MMP9 (36). Wogonin considerably inhibited phorbol 12-myristate 13-acetate (PMA)-induced expression and activity of MMP9 in MDA-MB-231 cancer cells (36).

ERK (Extracellular signal-regulated kinase) activation is involved in the TPA (12-O-tetradecanoylphorbol-13-acetate)-induced MMP9 activation and migration of GBM8401 cells (37). TPA enhanced migratory potential of GBM8401 cells through the activation of NFκB. However, wogonin was found to be effective against TPA-induced MMP9 activation (37).

Nicotine induced upregulation of MMP2 and MMP9 mRNA, whereas these effects were reversed by baicalin, baicalein or wogonin in lung cancer cells (38).

Wogonin also notably inhibited the activities of MMP2 and MMP9 in gallbladder cancer cells (39).

Interestingly, a study revealed that wogonin directly interacted with MMP9 and inhibited its activity (40).

Regulation of Cyclin-dependent Kinases

During the past two decades, emerging wealth of information has unraveled the instrumental role of cell cycle deregulation in a wide variety of human cancers. Cyclin-dependent kinases (CDKs) are a well-characterized family of serine/threonine kinases that play a fundamental role in the regulation of cell cycle progression. The integral part that CDKs and other kinases play in the regulation of the cell cycle and its checkpoints underscores the opportunity of the design and development of therapeutic strategies based on the druggability of these molecules.

Retinoblastoma protein Rb, a tumor suppressor has the ability to prevent cell cycle progression via binding to E2F transcriptional factors (41). Rb phosphorylation during G1 phase caused by cyclin D and E dependent kinases resulted in the de-repression and eventual release of E2F1. Wogonin reduced the levels of cyclin D1 and CDK4. However, wogonin did not exert inhibitory effects on cyclin E and CDK2. Furthermore, phosphorylation of Rb was also found to be reduced by wogonin. Wogonin also induced an increase in the levels of $p21^{Cip1}$ (41).

Wogonin markedly decreased the levels of p-RB, Cyclin D1 and CDK4 in renal cell carcinoma cells (42). Wogonin and sunitinib synergistically inhibited the levels of p-RB, Cyclin D1 and CDK4 in the tumor tissues of the mice injected with 786-O/ sunitinib-resistant cancer cells (42).

Wogonin concentration dependently reduced the levels of cyclin D1, cyclin E and CDK4/6 in hepatocellular carcinoma cells (43).

Wogonin directly binds to the ATP-binding pocket of CDK9 (44). One of the wogonin derivatives was also noticed to be effective against CDK9 (45).

Wogonin-based PROTACs have also shown notable efficacy against CDK9. Wogonin-based PROTACs markedly enhanced the degradation of CDK9 (46).

ROS-modulating role of Wogonin

Wogonin robustly induced H_2O_2 accumulation in A549 and HeLa cells (47). Wogonin sensitized A549 and HeLa cells to cisplatin by increasing the levels of ROS (47).

Wogonin induced apoptosis in $CD133^+$ Cal72 osteosarcoma stem cells by inhibition of survivin (48). Wogonin severely reduced the self-renewal capacity of $CD133^+$ Cal72 cells. Wogonin dose-dependently reduced stem cell markers CD133 and OCT3/4. Wogonin downregulated the levels of PRX5 and blocked PRX5-mediated elimination of ROS in cytosol and mitochondria. Wogonin caused significant inhibition of p-STAT3 and p-AKT. However, wogonin induced an increase in ERK phosphorylation in $CD133^+$ Cal72 cells (48).

Regulation of TRAIL-driven pathway

Irrespective of the underlying biology and the fascinating conceptual questions about apoptotic cell death, therapeutic manipulations of cell death pathways have tremendous potential. Excitingly, the development of effective therapeutics targeting cell death pathways is exceedingly complex and researchers have witnessed ground-breaking discoveries in the underlying mechanisms of apoptosis. Different molecular mediators of classical caspase-triggered apoptotic pathways were categorized extensively during the past three decades. More importantly, recent mechanistic findings have ushered in a new era in the field of molecular oncology. Death receptor signaling is activated by ligand-induced receptor trimerization (49-54). Particularly fascinating is how signals originating from the release of cytochrome c from the mitochondria are translated into the activation of the death cascades. Now there is growing understanding of how this critical mechanism is intricately handled by a cytosolically located signaling platform known as the apoptosome. Importantly, formation of the apoptosome and the consequent activation of caspase-9 revealed a sophisticated mechanism for the initiation of apoptotic cell death.

Levels of c-$FLIP_L$, XIAP, cIAP1/2 were found to be

considerably reduced in A549 cancer cells combinatorially treated with TRAIL and wogonin (55). Wogonin reduced antiapoptotic proteins through proteasomal degradation and sensitized resistant cancer cells to TRAIL-induced apoptotic cell death. Furthermore, wogonin and TRAIL synergistically induced regression of the tumors in the mice subcutaneously injected with A549 cancer cells (55).

PUMA (p53 upregulated modulator of apoptosis) is transcriptionally controlled by p53 (56). High levels of PUMA and p53 are essential to maximize TRAIL-mediated apoptotic cell death. Wogonin synergized with TRAIL and induced an increase in the levels of p53 and PARP1 cleavage in $p53^{+/+}$ colorectal cancer cells, but not in $p53^{-/-}$ colorectal cancer cells. Wogonin potentiated TRAIL-mediated cell death and PARP1 cleavage in $PUMA^{+/+}$ cancer cells, but not in $PUMA^{-/-}$ cancer cells (56).

TRAIL-resistant human T cell leukemia virus type 1 (HTLV-1)-associated adult T cell leukemia/lymphoma (ATL) cells regained TRAIL sensitivity upon treatment with wogonin, chrysin and apigenin (57). Wogonin chrysin and apigenin displayed remarkable potential to cause transcriptional downregulation of c-FLIP. Wogonin chrysin and apigenin also enhanced p53 mediated upregulation of TRAIL-R2 (57).

AML cells isolated from AML patients were used to analyze if wogonin and TRAIL combinatorially induced apoptotic cell death. Results clearly indicated that wogonin and TRAIL worked with effective synergy and potently induced apoptotic cell death (58).

Regulation of Protein networks

RAP1 has a central role in the integrity of the glioma perivascular niche and aggressiveness of glioma (59). Baicalein, baicalin and wogonin considerably increased RAP1-GTP binding. RAP1 is regulated by α7nAChR. a7nAChR enhanced the phosphorylation of Src and AKT and also inhibited Rap1 activation. Whereas, a7nAChR inhibition not only effectively promoted Rap1 activation but also simultaneously reduced phosphorylated levels of Src and AKT. Id1 is a member of helix-loop-helix (HLH) transcriptional factors. Baicalein, baicalin and wogonin dose-dependently inhibited Id1 protein expression. Invasive potential of Id1-silenced H1299 and A549 cancer cells was found to be notably reduced. However, invasive and migratory capacity of Id1-overexpressing-H1299 and A549 cancer cells was noted to be significantly enhanced (59).

Carcinogenesis and Metastasis in Mice

Wogonin enhanced GSK3β-mediated phosphorylation and degradation of Cyclin D1 in MHCC97L and HepG2 cells (60). Wogonin and sorafenib induced regression of the tumors in mice orthotopically transplanted with MHCC97L cancer cells (60).

Wogonoside is an important metabolite of wogonin (61). Wogonoside reduced the levels of TNFα, TRAF2 and TRAF4. Wogonoside reduced the expression of MMP2, MMP9, CD44v6 and vimentin in MDA-MB-231 and MDA-MB-435 cells. TNFα-induced TWIST1 in breast cancer cells. Moreover, TWIST1 overexpression promoted metastasis and increased the expression of MMP9, MMP2, CD44v6 and vimentin in cancer cells. Wogonoside reduced the levels of TWIST1. Wogonoside inhibited TNFα-induced NF-κB cascade through suppression of TRAF2/4. Wogonoside inhibited TWIST1 through suppression of TRAF2/4 in MCF7 cells. Wogonoside suppressed the formation of metastases in brain, lung, liver and bone. Wogonoside increased the levels of E-cadherin and simultaneously reduced MMP9, vimentin and TWIST1 (61).

Wogonin inhibited the VEGFC-mediated phosphorylation of VEGFR3 (62). The chemokine MCP-1 (monocyte chemoattractant protein-1) and cytokine IL-1 are key agonists that attract macrophages to the tumors. Accordingly, tumor-associated macrophages promoted the growth of tumors and metastasis through angiogenesis and lymphangiogenesis. Wogonin inhibited the levels of IL-1β production and COX-2 expression induced by lipopolysaccharides in THP-1 macrophages. Pulmonary metastatic nodules were noted to be reduced in mice transplanted with LM8 osteosarcoma cells (62).

Wogonin has been shown to induce senescence in breast cancer cells (63). Interestingly, accumulating evidence has revealed that senescence is often accompanied by discrete alterations of the chromatin structure, commonly known as senescence-associated heterochromatic foci (SAHF). Some senescent cells formed SAHF in the nuclei. Likewise, H3K9Me3 foci were noted in wogonin-treated cancer cells. Levels of TXNRD2 (Thioredoxin reductase-2) were noted to be reduced in MDA-MB-231 cells treated with wogonin. Wogonin caused reduction in the enrichment of histone-3 lysine-9 acetylation (H3K9ac) within the regulatory regions of TXNRD2. Wogonin efficiently reduced the volume and weight of the tumors derived from 4T1 and MDA-MB-231 cancer cells in xenografted mice. Conditioned media from wogonin-treated MDA-MB-231 cancer cells potently enhanced M1 polarization of macrophages. Conditioned media from wogonin-treated MDA-MB-231 cancer cells enhanced the migratory potential of THP-1-derived macrophages. Wogonin-induced senescent breast cancer cells triggered the polarization of M1 macrophages and increased the recruitment of M1-like macrophages and natural killer cells (63).

Wogonin induced apoptosis in HCT-116 cell through increased endoplasmic reticulum stress (64). Importantly, ER stress induced an increase in the cytoplasmic accumulation of p53 by increasing the phosphorylation at 315^{th} serine and 376^{th} serine. Wogonin was highly effective against azoxymethane (AOM)/dextran sodium sulfate (DSS) animal model. Wogonin effectively reduced tumor multiplicity in animal models (64).

Wogonin inhibited the invasive capacity of MDA-MB-231 cancer cells by downregulation of IL-8 and MMP9 (65). Wogonin caused repression of leukotriene B4 receptor 2 (BLT2). Wogonin also exerted inhibitory effects on the synthesis of its ligand mainly through inhibition of 5-lipoxygenase in LPS-stimulated MDA-MB-231 cancer cells. BLT2 depletion reduced LPS-induced invasive potential of MDA-MB-231 cancer cells. Moreover, BLT2 depletion suppressed mRNA and protein levels of IL-8 and MMP9 in MDA-MB-231 cancer cells. Wogonin inhibited the production of IL-8/

MMP9 in LPS-stimulated MDA-MB-231 cells mainly through the activation of ERK. Metastatic nodules were noted to be significantly reduced in the mice transplanted with wogonin pre-treated MDA-MB-231 cancer cells (65).

Concluding remarks

The inventory of natural molecules remains incomplete and full of exciting questions. Therefore, groundbreaking discoveries of novel pharmacologically active structures and functions are likely to continue as underexplored and untapped sources of natural products are evaluated more scientifically and systematically. In this review, we have summarized most recent updates related to wogonin-mediated targeting of oncogenic signaling cascades. However, we still have incomplete understanding about regulation of SHH/Gli, Notch and Hippo pathways by wogonin in different cancers. Similarly, wogonin-mediated regulation of non-coding RNAs in wider variety of cancers has also been incompletely understood. SPI1 (Spleen focus forming virus proviral integration oncogene) can be directly targeted by miR-155. NF-κB-mediated upregulation of miR-155 and blocked apoptosis. Wogonin impaired NF-κB-driven upregulation of miR-155 and induced apoptotic cell death[66].

Therefore, there is a need to drill down deep into the underlying mechanisms utilized by wogonin to inhibit/prevent carcinogenesis and metastasis.

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