# Regulation of Cell Signaling Pathways by Genistein in Different Cancers: Progress, Prospects and Pitfalls

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## ABSTRACT

On the translational front, integrative genomic approaches have spurred the identification of diverse mechanisms of drug resistance, tumor heterogeneity, metastasis and emerging preclinical targets. Recent breakthroughs in oncogenic cell signaling pathways have forged new links and multi-disciplinary researchers have unraveled different facets of signaling landscapes. Natural product research has witnessed breakneck developments mainly in the context of the ever-expanding list of bioactive components having significantly pharmacological properties. Genistein has gradually gained appreciation because of its multifaceted roles in the prevention and inhibition of carcinogenesis and metastasis. More importantly, the entry of genistein into various phases of clinical trials substantiates the medicinal and pharmacological significance of genistein in cancer chemoprevention. In this review, we have attempted to summarize how genistein regulated different oncogenic pathways in carcinogenesis and metastasis. Furthermore, genistein-mediated regulation of non-coding RNAs is also an interesting feature that has been included in this review to realistically analyze how genistein-mediated control of miRNAs, lncRNAs and circRNAs influence carcinogenesis. In the later sections, we have provided a summary of clinical trials related to genistein for cancer prevention/inhibition. However, apart from the optimistic approaches to further investigate genistein-mediated cancer-inhibitory effects, certain hints have emerged which underscore the pro-metastatic role of genistein. Therefore, the pro-metastatic role of genistein in different cancers should be rationally tested in a broader context because these properties in the future may reduce the enthusiasm in the quest to pursue genistein as a potent cancer chemopreventive agent.

## Introduction

Spatiotemporal regulation of signal transmission in cells has vital importance because deregulation of signaling cascades plays a central role in carcinogenesis. Scientific insights gleaned from recent years have set the stage for 'next-generation' clinical initiatives in prevention and precision oncology (1-5). Natural product research has ushered in a resurgence of interest in the critical evaluation of pharmacological properties of different natural products (6-13). Genistein started to gain the attention of researchers in the 1980s and a series of interesting research works provided evidence about the medicinal significance of genistein (14-16). In this review, we have provided a summary of the regulatory role of genistein in the inhibition of carcinogenesis and metastasis. We have systematically sub-divided this mini-review into various sections and mechanistically analyzed how genistein regulated PI3K/AKT/mTOR, TRAIL, SHH/GLI and NOTCH pathways in different cancers. Moreover, regulation of non-coding RNAs has also been discussed and seminal research works have been critically analyzed.

## Regulation of PI3K/AKT/mTOR pathway

A complex equilibrium of biological signals exists within the human body for the control of normal cellular functions. Classically viewed as a "master regulator", mTOR (mechanistic Target of Rapamycin) regulates an intricate transduction cascade that controls a wide variety of cellular mechanisms. The PI3K-AKT-mTOR pathway is frequently deregulated in cancer and different types of compounds that target key proteins of this signaling network have been tested in preclinical and clinical studies (17-20). However, unfortunately, the clinical development of many of these agents has not moved to later-phase randomized trials.

DEPTOR expression has been reported to be downregulated in genistein-resistant cells (21). Whereas, upregulation of DEPTOR improved sensitivity of PANC-1 and PaCa cancer cells to genistein. Everolimus, an mTOR-specific antagonist enhanced genistein sensitivity. ELK1 transcriptionally downregulated DEPTOR and enhanced resistance against genistein. Intraperitoneally injected genistein and intragastrically administered everolimus led to shrinkage of the tumor mass in NOD/SCID mice implanted with genistein-resistant PaCa and Panc-1 cells (21).

Genistein suppressed the levels of NFκB, p-AKT, p-mTOR, p-p70S6K1, p-4E-BP1 and enhanced the anti-tumor effects of cisplatin in HeLa cells (22).

Gefitinib and genistein were found to be effective against mutant EGFR non-small cell lung cancer cells. Gefitinib and genistein efficiently suppressed the activation of EGFR, AKT and m-TOR in H1975 cells. Genistein and gefitinib induced regression of the tumors in mice xenografted with H1975 cancer cells (23).

Collectively, PI3K/AKT/mTOR signaling axis is highly important in carcinogenesis and metastasis. Therefore, genistein-mediated targeting of this signaling axis is indeed exciting and warrants further research.

### Regulation of TRAIL-mediated Signaling

TRAIL-mediated apoptotic death has gained extraordinary appreciation and limelight because of its characteristically unique features to kill cancer cells while leaving normal cells unharmed. These earlier findings were highly intriguing and compelled researchers to mechanistically analyze TRAIL-mediated apoptotic pathways in a detailed manner (24-35). In this section, we have enlisted how genistein regulated pro-apoptotic and anti-apoptotic proteins to enhance TRAIL-mediated apoptotic death in resistant cancer cells.

Genistein in combination with TRAIL synergistically and rapidly induced apoptotic death in TRAIL-resistant glioma cells (36). Genistein induced proteasomal degradation of short isoforms of c-FLIP. Significantly, overexpression of short isoforms of c-FLIP severely abrogated genistein driven-TRAIL-induced apoptotic death (36).

Genistein worked efficiently with TRAIL and upregulated the expression of Bax and simultaneously suppressed anti-apoptotic Bcl-XL in TRAIL-resistant AGS cancer cells (37). Combinatorial treatments with genistein and TRAIL significantly upregulated DR5. Genistein sensitized AGS cancer cells to TRAIL-mediated apoptosis by activation of caspase-3 (37).

Genistein and TRAIL combinatorially induced tumor shrinkage in the mice orthotopically implanted with AsPC-1 cells into the splenic lobe of the pancreas (38). However, there was evidence of a larger amount of extra-pancreatic tissues invaded by cancerous cells. But still, there is a need to further analyze the growth-inhibitory effects of genistein and TRAIL in tumor-bearing mice.

Indole-3-carbinol, genistein has previously been reported to work efficiently with TRAIL against endometrial cancer. Levels of DR4, DR5 and cleaved caspase-8 were found to be enhanced whereas, levels of FLIP were suppressed in Ishikawa cells (39).

It has been convincingly revealed in a series of research works that transportation of truncated BID (tBID) to the mitochondrion is instrumental to trigger intrinsic apoptosis. Accordingly, genistein and TRAIL have also been shown to enhance the entry of tBID into the mitochondria to trigger apoptosis (40).

Seemingly, we have gathered initial basic works related to TRAIL-sensitizing activity of genistein but there is a need to address these questions more rationally in rodent models.

In the next section, we will discuss how SHH/GLI signaling is pharmacologically targeted by genistein in different cancers.

## Regulation of SHH/GLI Pathway

Hedgehog ligands bind to patched, leading to internalization and degradation, thereby releasing smoothened, where it promotes dissociation of a SUFU (Suppressor-of-fused)–glioma-associated oncogene homolog (GLI) complex. Therefore, smoothened mediated disassembly of SUFU and GLI promoted the activation and nuclear translocation of GLI1 and GLI2 transcriptional factors (41,42).

Genistein exerted inhibitory effects on renal CSCs by inactivation of the SHH pathway. Levels of SHH, SMO, GLI1 and GLI2 were noted to be suppressed by genistein in ACHN and 786-O sphere-forming cells (43). Likewise, genistein significantly suppressed the levels of SHH, SMO, and GLI1 in CNE2 and HONE1 cells (44).

GLI1-knockdown cells exhibited similar features to genistein-treated cells because genistein inhibited migratory abilities of CD44$^+$ stem cell-like gastric cancer cells (45).

Genistein led to significant inhibition of the tumor-sphere-forming ability of tumorsphere cells of 22RV1 and DU145 cells (46). SHH-treated cells generated larger tumorspheres and the capacity to form tumorspheres were found to be increased significantly by SHH. Contrastingly, GANT61 (GLI inhibitor) reduced tumorsphere size. Furthermore, the size of tumorsphere was found to be reduced by genistein. Intriguingly, genistein and docetaxel inhibited tumor growth in mice xenografted with either DU145-tumorsphere cells or 22RV1 tumorsphere cells. Genistein significantly reduced GLI1 protein expression in tumor tissues derived from prostate cancer tumorsphere cells (46).

Importantly, for detailed functions of the SHH pathway in carcinogenesis and metastasis, dissection of the intermeshed gene networks that are involved and identification of the commonalities between the networks in different cell types will enable researchers to gain valuable insights.

## Regulation of NOTCH Pathway

Genistein reversed the epithelial-to-mesenchymal transition of colon cancer cells by downregulation of N-cadherin and simultaneous upregulation of E-cadherin. Additionally, genistein suppressed of EMT-associated proteins, such as SNAIL/SLUG, TWIST1, ZEB1 and ZEB2. Genistein reduced the levels of NOTCH-1 in HT-29 cells (47).

NOTCH-1 inhibition blocked nuclear accumulation of NF-κB in MDA-MB-231 cancer cells. Genistein dose-dependently inhibited the activation of NF-κB in MDA-MB-231 cancer cells. Moreover, genistein also suppressed the levels of NOTCH-1 in MDA-MB-231 cancer cells (48).

In another interesting study, it was shown that genistein suppressed NOTCH-1 by increasing the expression of miRNA-34a in pancreatic cancer cells (49).

Although medicinal chemists have identified small molecules having characteristically unique ability to pharmacologically manipulate a versatile biological pathway responsible for cell fate decisions in cancer cells, tumor microenvironment and metastasis, unfortunately, safe and effective 'drugging' of this pathway is not straightforward. Importantly, phenotypic screening of individual tumors, using patient-derived organotypic spheroids can yield relevant findings for the design and development of next-generation of NOTCH pathway-targeting molecules. More importantly, patient-derived 3D models that can be challenged with experimental agents might be viewed as another valuable addition to the screening toolbox as researchers sketch the landscape of the next generation of NOTCH pathway-targeting molecules.

## Regulation of non-coding RNAs:

The mysterious world of RNAs inside cells has been expanding consistently for decades. Each discovery adds a new and often surprising layer of intricacy to biological regulations and functions.

More recently, various other types of ncRNAs such as lncRNAs (long non-coding RNAs) (50-53) and circular RNAs (54-55) have also gained the limelight and are reported to play dynamic roles in the regulation of gene networks and involved in carcinogenesis and metastasis.

## MicroRNAs

MicroRNAs (miRNAs) are small, ribonucleic acid (RNA) molecules involved in the regulation of gene expression by binding to specific mRNAs (56-59).

## Oncogenic miRNAs

Genistein-mediated downregulation of miR-155 played a central role in the induction of apoptosis in breast cancer cells (60). Genistein downregulated oncogenic miR-223 in gemcitabine-resistant pancreatic cancer cells (61).

## Tumor Suppressor miRNAs

RTCB is a GTP-dependent 3′-phosphate/5′-OH RNA ligase (Hsieh). Genistein induced upregulation of miR-34a in tumor-initiating cells of head and neck cancer. miR-34a directly targeted RTCB and considerably suppressed self-renewal abilities, invasion properties and colony-forming features. Moreover, tumors derived from HNC-TICs were smaller in size treated with genistein. Tumor tissues developed from HNC-TICs demonstrated higher expression of miR-34a and lower expression of RTCB (62). Genistein stimulated p53-mediated upregulation of miRNA-1469. Moreover, miRNA-1469 directly targeted MCL1 and enhanced apoptotic death in laryngeal cancer cells (63). Genistein induced upregulation of miR-27a in A549 cancer cells. miR-27a negatively regulated MET and suppressed the proliferation of A549 cancer cells (64). A combination of various tumor suppressor microRNA mimics in "cocktails", together with genistein might prove to be an exciting strategy for inhibition of cancer in xenografted mice.

## Long non-coding RNAs

The activity of PRC2 is mediated by one of the two catalytic subunits, EZH1/EZH2 (enhancer of Zeste homologues, as well as two other core components, SUZ12 (Suppressor of Zeste 12) and EED (embryonic ectoderm development). Genistein effectively inhibited the interaction of HOTAIR with PRC2, thus resulting in tumor suppression. Genistein reduced EED levels in PRC2 which consequently impaired the interaction between HOTAIR and PRC2 (65). Whereas, overexpression of EED in the presence of genistein led to an increase in the interaction of HOTAIR with PRC2. HOTAIR and PRC2 worked synchronously and transcriptionally downregulated zona occludens 1 (ZO-1) (Figure 1). Contrarily, genistein blocked the interaction between HOTAIR and PRC2 and stimulated the expression of ZO-1. HOTAIR interacted with ARID1A and SMARCB1,

subunits of the SWI/SNF chromatin remodeling complexes but genistein significantly abolished these interactions. Genistein interfered with the interaction between SMARCB1 and HOTAIR and inhibited the expression of SNAIL (Figure 1) (65).

Calycosin and genistein considerably inhibited the activation of AKT and also reduced the expression of oncogenic HOTAIR in MCF-7 cancer cells (66).

Tumor growth rates were noted to be markedly reduced in mice xenografted with HOTAIR-silenced DU145 cancer cells. Genistein induced downregulation of HOTAIR and simultaneously upregulated miR-34a (67).

Ago2 is the major protein involved in the cleavage of target transcripts of miRNAs in mammalian cells (68). Ago2 knockdown drastically reduced HOTAIR silencing by miRNA-141. Incubation of in-vitro transcribed HOTAIR with Ago2 immunocomplex led to degradation of HOTAIR into smaller segments. Genistein led to suppression of HOTAIR and a concurrent increase in the expression of miR-141 (68).

## Circular RNAs

Circ_0031250 has been shown to play an oncogenic role by enhancing the expression of FOXM1 in non-small-cell lung cancer cells (**69**). miR-873-5p is a tumor suppressor and directly targets FOXM1 for the inhibition of carcinogenesis. Importantly, circ_0031250 acted as a sponge, sequestered away miRNA-873-5p and blocked miR-873-5p-mediated targeting of FOXM1. Genistein induced a significant regression rate of the tumor mass in mice xenografted with circ_0031250-silenced A549 cancer cells (**69**).
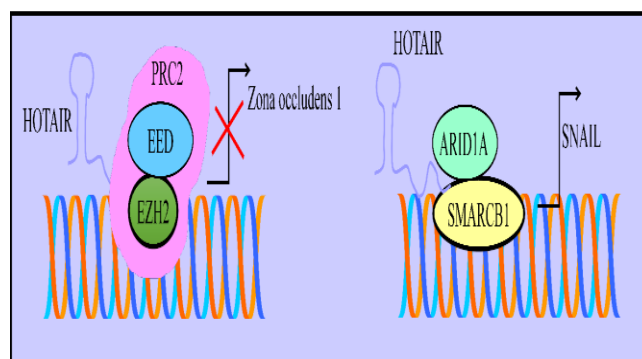


**Figure 1.** HOTAIR is a long non-coding RNA and regulates the expression of different target genes. HOTAIR formed a complex with PRC2 through EED and transcriptionally inactivated ZO-1. HOTAIR worked synchronously with SMARCB1 and ARID1A and stimulated the expression of SNAIL.

## Tumor growth inhibition by Genistein in Xenografted Mice

Pioneering studies had shown that the co-culture of macrophages with ovarian cancer stem-like cells (OCSLCs) triggered the stemness of SKOV3 cancer cells via activation of the interleukin-8/STAT3 pathway (70). Genistein-mediated inhibition of M2 polarization suppressed the secretion of interleukin-8 and inactivated STAT3 in THP-1 macrophages co-cultured with ovarian cancer stem-like cells. Depletion of interleukin-8 and genistein treatment together reduced the levels of p-STAT3 and CD163 in THP-1 macrophages. Notably, depletion of interleukin-8 and genistein treatment combinatorially reduced the levels of CD133 and CD44 in SKOV3 cancer cells. Furthermore, co-injections of SKOV3-derived OCSLCs and THP-1 macrophages led to the formation of subcutaneous tumors in experimental models. Interactions between THP-1 macrophages and SKOV3-derived OCSLCs promoted the growth of tumors in experimental mice. Genistein and Ad-STAT3 shRNA caused a reduction in the weights and size of tumor xenografts in experimental models co-injected with SKOV3-derived OCSLCs and THP-1 macrophages (70). Collectively, these findings highlighted that genistein inhibited tumor growth in mice co-inoculated with THP-1 macrophages and SKOV3-derived OCSLCs through blockade of the IL-8/STAT3 pathway.

Genistein blocked JAK/STAT3 and AKT/MDM2/p53 signaling cascades (71). Genistein inhibited phosphorylation of JAK1, JAK2 and STAT3. Moreover, inhibition of AKT and MDM2 by genistein inhibited the proliferation of cancer cells. Genistein with GLPG0634 (JAK1 pathway inhibitor) and/or MK-2206 (AKT pathway inhibitor) synergistically induced regression of the tumors in xenografted mice (71).

ZDHHC17-MAP2K4-JNK/p38 signaling module contributed to Glioblastoma Multiforme development and metastasis by promoting tumorigenicity and self-renewal of glioma stem cells (72). ANK domain of ZDHHC17 was found to be responsible for interactions with MAP2K4. Genistein specifically inhibited the MAP2K4 and ZDHHC17 interactions. ZDHHC17-expressing, as well as ZDHHC17-deficient GSCs derived from U118MG cells, were implanted into the brains of immunocompromised NOD/SCID mice. ZDHHC17-expressing GSCs competently developed and formed intracranial tumors, whereas depletion of ZDHHC17 led to suppression of tumor growth. Knockdown of MAP2K4 and/or genistein injections inhibited tumor growth and prolonged the survival rates of mice implanted with ZDHHC17-expressing cells (72).

DNA-PK (DNA-dependent protein kinase) has been shown to phosphorylate 473rd serine of client proteins (73). DNA-PKcs is required for activation of AKT. X-ray irradiation led to activation of DNA-PKcs. Phosphorylated-DNA-PKcs (Serine-2056) were remarkably higher in the irradiation alone group in U87 and M059K cells. Importantly, genistein blocked the activity of DNA-PKcs. Genistein suppressed phosphorylation of AKT at serine-473 in U87 and M059K cells. X-rays induced tumor cell invasion into adjacently located normal tissue areas in mice intracranially injected with U87 cells. Radiation independently induced an increase in the levels of DNA-PKcs, AKT2, and RAC1. Contrarily, this increase was suppressed considerably by genistein. Moreover, genistein reduced the levels of matrix metalloproteinase-2 and vimentin but simultaneously increased the levels of E-cadherin in irradiated tumor-bearing mice (73).

## Metastasis-inhibitory role of Genistein

6,8-diprenylgenistein inhibited lymphangiogenesis and lymph node metastasis in VEGF-A-mediated OCSLN animal models. The volume of the sentinel lymph nodes in the SCCVII/mVEGF-A injected group was increased but 6,8-diprenylgenistein reduced the volume increase of sentinel lymph nodes by VEGF-A (74).

Co-administration of genistein with doxorubicin-loaded polypeptide nanoparticles potently inhibited tumor growth in RM-1 tumor-bearing mice (75). Importantly, metastatic lesions were found to be reduced in mice co-administered with genistein and doxorubicin-loaded polypeptide nanoparticles. Metastatic areas of liver tissues demonstrated a significant reduction in genistein and doxorubicin-treated group, which suggested that tumor cell metastasis was reduced because of an increase in the oxidative damage in the genistein and doxorubicin-treated group (75).

Genistein remarkably inhibited metastasis nodes and micro-metastatic foci on the lungs of nude mice. Moreover, the number of intrahepatic metastases was found to be reduced in genistein (76).

Genistein dose-dependently inhibited pulmonary and hepatic metastasis in mice orthotopically implanted with HCT116 cancer cells. Genistein reduced the levels of MMP2 and VEGFR3 in the tumor tissues of orthotopically implanted mice (77).

Genistein markedly reduced pulmonary metastasis in mice orthotopically implanted with PC3-M prostate cancer cells (78).

Genistein reduced the volume and number of osteolytic bone metastasis and the number of osteoclasts. Besides, genistein significantly enhanced trabecular area, trabecular thickness as well as trabecular number (79).

## The darker side of Genistein: Pro-metastatic role

Surprisingly, apart from the metastasis-inhibitory role of genistein, the pro-metastatic role of genistein has also been documented in different scientific studies. The pro-metastatic role of another soy isoflavone equol has also been reported (80).

Bone is a common site for metastasis during breast cancer progression (81). Micro-metastasis in bone marrow is detected in breast cancer patients and is associated with a poor prognosis. However, surprisingly, it was shown that dietary soy isoflavones triggered an increase in pulmonary metastasis in an experimental model of breast cancer with bone micro-metastasis (81). These findings are highly important and need to be tested in detail. Another study provided evidence about the pro-metastatic role of genistein. Genistein stimulates tumor growth development and metastasis in a prostate cancer model (82).

## Clinical Trials

The study was designed to analyze the combinatorial effects of genistein and gemcitabine hydrochloride in the treatment of stage IV breast cancer patients (NCT00244933). However, the decision was made to close the study after 17 patients because of lack of efficacy.

Another study was terminated in which clinicians analyzed the effects of genistein in the treatment of patients with localized prostate cancer planning to undergo radical prostatectomy (NCT00058266).

In another study, maximum tolerated doses, efficacy and safety of the Decitabine-genistein drug combinations were sought to be determined in advanced solid tumors and non-small cell lung cancer (NCT01628471).

An intervention consisting of mixed soy isoflavones did not reduce breast epithelial proliferation in healthy, high-risk adult western females. Clinical researchers did not find evidence about the efficiency of mixed soy isoflavones for the prevention of breast cancer (83).

Genistein was clinically evaluated for the treatment of patients with stage II, stage III, or stage IV prostate cancer patients (NCT00005827). Moreover, genistein-mediated effects were also analyzed for the treatment of pancreatic cancer patients (NCT00882765). However, the results have not been shared or posted for a clear conclusion.

## Concluding remarks

Recent breakthroughs in our knowledge about the molecular basis of cellular processes, identification of pharmacologically relevant therapeutic targets and refinements within the regulatory landscapes have generated exciting, unprecedented and invaluable opportunities in the field of oncology drug development. However, higher costs, longer development timelines and steeper rates of attrition continue to create roadblocks in the tortuous pathway of drug development. Interestingly, the cancer chemopreventive roles of genistein have attracted the attention of interdisciplinary researchers. Yet, apart from the optimistic approaches to further investigate genistein-mediated cancer-inhibitory effects, certain clues have emerged that highlight the pro-metastatic role of genistein. Therefore, the pro-metastatic role of genistein in different cancers should be rationally tested in a broader context by critical analysis of tumor-microenvironment and how genistein promotes the invasion, colonization and outgrowth of cancer cells in the distant organs.

## Interest conflict
None.

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