Journal of Traditional and Complementary Medicine 10 (2020) 217–229

Contents lists available at ScienceDirect

Journal of Traditional and Complementary Medicine

journal homepage: http://www.elsevier.com/locate/jtcme

Modulation of non-coding RNAs by resveratrol in ovarian cancer cells: *In silico* analysis and literature review of the anti-cancer pathways involved

Letizia Vallino [a, 1], Alessandra Ferraresi [a, 1], Chiara Vidoni [a], Eleonora Secomandi [a], Andrea Esposito [a], Danny N. Dhanasekaran [b], Ciro Isidoro [a, *]

[a] *Laboratory of Molecular Pathology, Department of Health Sciences, Università del Piemonte Orientale "A. Avogadro", Via Solaroli 17, 28100, Novara, Italy*
[b] *Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA*

ARTICLE INFO

Article history:
Received 29 January 2020
Received in revised form
12 February 2020
Accepted 17 February 2020
Available online 4 March 2020

Keywords:
Nutraceutical
Cancer
Epigenetics
Cell metabolism
Warburg effect
Autophagy

ABSTRACT

Background and aim: Non-coding RNAs control cell functioning through affecting gene expression and translation and their dysregulation is associated with altered cell homeostasis and diseases, including cancer. Nutraceuticals with anti-cancer therapeutic potential have been shown to modulate non-coding RNAs expression that could impact on the expression of genes involved in the malignant phenotype.
Experimental procedure: Here, we report on the microarray profiling of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) and on the associated biochemical pathways and functional processes potentially modulated in OVCAR-3 ovarian cancer cells exposed for 24 h to Resveratrol (RV), a nutraceutical that has been shown to inhibit carcinogenesis and cancer progression in a variety of human and animal models, both *in vitro* and *in vivo*. Diana tools and Gene Ontology (GO) pathway analyses along with Pubmed literature search were employed to identify the cellular processes possibly affected by the dysregulated miRNAs and lncRNAs.
Results and conclusion: The present data consistently support the contention that RV could exert anti-neoplastic activity via non-coding RNAs epigenetic modulation of the pathways governing cell homeostasis, cell proliferation, cell death and cell motility.
© 2020 Center for Food and Biomolecules, National Taiwan University. Production and hosting by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Ovarian cancer remains among the deadliest gynecological cancer in women worldwide. Based on a recent statistic, it is predicted that in 2019 in US there will be more than 22,000 new cases of ovary cancer, with about 14,000 deaths that represent 5% of all deaths for cancer.[1] Ovarian cancer is frequently diagnosed in the late stage because it develops asymptomatically in the early stage and manifests its presence after it has spread in the peritoneum and distant organs.[2] In most cases, surgery and chemotherapy elicit an initial good response, which however is followed by relapse of chemoresistant clones that inevitably lead to death the patient.[3,4] The tumor microenvironment, with its unique composition in stromal- and immune cell-derived cytokines and of blood and lymphatic vessels that determine the availability of nutrients, growth factors and oxygen, plays a pivotal role in ovarian cancer cell metabolism and progression.[5–12]

There is an urgent need for understanding the molecular history of ovarian carcinogenesis in order to identify novel pharmacologic targets. Numerous oncogenes and tumor suppressor driver genes are found mutated in chemoresistant ovarian cancers.[13] In addition to these mutations, also the altered epigenetic regulation of oncogenes and tumor suppressor genes contributes to ovarian carcinogenesis.[14,15] Epigenetic regulation of carcinogenic driver genes

Abbreviations: miRNA, microRNA; lncRNA, long non-coding RNA; RV, Resveratrol; GO, Gene Ontology; EMT, Epithelial to Mesenchymal Transition; TCGA, The Cancer Genome Atlas.

* Corresponding author. Dipartimento di Scienze della Salute, Università del Piemonte Orientale "A. Avogadro", Via P. Solaroli 17, 28100, Novara, Italy. Tel.: +39 0321 660 507.
E-mail address: ciro.isidoro@med.uniupo.it (C. Isidoro).

Peer review under responsibility of The Center for Food and Biomolecules, National Taiwan University.

[1] These authors have equally contributed and should be regarded as first co-authors.

https://doi.org/10.1016/j.jtcme.2020.02.006
2225-4110/© 2020 Center for Food and Biomolecules, National Taiwan University. Production and hosting by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

includes abnormal hypermethylation of the tumor suppressor gene promoter, abnormal post-translational modifications of the histones and the production of non-coding RNAs, either microRNAs (miRNA, of approximately 20 nucleotides) and long non-coding RNAs (lncRNA, of 200–250 or more nucleotides). Studies have implicated epigenetic dysregulation in ovarian carcinogenesis.[16–21]

However, our understanding of the involvement of non-coding RNAs in ovarian cancer cell biology remains limited. More importantly, we still need to understand how we can correct these epimutations pharmacologically.

In recent decades there has been a renewed interest for the possible exploitation of natural products in the prevention and cure of cancer. Indeed, a variety of therapeutic phytochemicals found in food stuff (known as nutraceuticals) have shown anti-cancer activity, either *in vitro* and in animal studies, and thus have great potentials for repositioning as complementary drugs for improving the efficacy of chemo- and immune-therapeutics as well as for attenuating the adverse side effects of conventional therapies.[22–25] The anti-cancer effects of such nutraceuticals include induction of cell death, block of cell proliferation, modifications of cancer cell metabolism and of tumor microenvironment.[23,26–28]

Resveratrol [3,4',5-trihydroxy-trans-stilbene (RV)], a nutraceutical found in black and red berries, grape and nuts, is one such epigenetic modulator.[29–31]

In this work, we analyzed the profiling of miRNAs and lncRNAs in ovarian cancer OVCAR-3 cells exposed for 24 h to RV. The cellular processes associated with RV-modulated non-coding RNAs were identified by *in silico* analyses with appropriate software. Based on literature data, our findings support the view that RV elicits its anti-neoplastic activity also via non-coding RNAs epigenetic modulation of the pathways that govern cell homeostasis (particularly protein synthesis, organelle turnover and autophagy), cell metabolism (e.g., glucose uptake and Warburg effect), cell proliferation, cell death and cell motility.

2. Materials and methods

2.1. Cell culture, reagents and treatments

NIH-OVCAR-3 (simply refereed as to OVCAR-3) ovarian cancer cells were maintained in standard conditions (37 °C, 95 v/v% air: 5 v/v% CO2) in RPMI 1640 medium (cod. R8758; Sigma–Aldrich, St. Louis, MO) containing 10% heated-inactivated FBS (cod. ECS0180L; Euroclone, Milano, Italy), supplemented with 1% Glutamine (cod. G7513; Sigma–Aldrich) and 1% Penicillin/Streptomycin (cod. P0781; Sigma–Aldrich). The cells adherent on plastic dishes and at approx. 80% confluency were treated in complete medium for 24 h with 100 μM Resveratrol (RV, cod. R5010; Sigma–Aldrich; stock dissolved in DMSO). At the end, the cell monolayer was washed and processed for RNA extraction.

2.2. One color microarray genome-wide gene expression analysis

Total RNA was isolated from the cells using Absolutely RNA mRNA kit (Agilent Technologies, Palo Alto, CA). mRNA was amplified and labeled by Amino Allyl MessageAmp II aRNA Kit (Ambion, Austin, TX) using NHS ester Cy3 dye (Amersham Biosciences, Arlington Heights, IL). Total RNA quality and labeling was checked by means of RNA 6000 Nanochip assays and run on the Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA). Total RNA amplified and labeled mRNA concentrations were calculated using the NanoDrop ND-1000 Spectrophotometer (NanoDrop Technologies, Wilmington, DE). Equal amounts (0.2 mg) of labeled specimens were fragmented and hybridized to Human Whole Genome Oligo Microarrays 860 K v2 (Agilent Technologies), representing 27958 Entrez Gene RNAs and 7419 lincRNAs. Each step was performed using the *In Situ* Hybridization Kit-Plus (Agilent Technologies) and following the 60-mer oligo microarray processing protocol. Slides were then washed with SSPE and scanned using an Agilent Scanner version C (G2505C, Agilent Technologies). Images were analyzed using the Feature Extraction software v10.7. Raw data elaboration was carried out with Bioconductor (www.bioconductor.org),[32] using R statistical language. Background correction was performed with the normexp method and quantile was used for between-array normalization. The Linear Models for Microarray Analysis (LIMMA) package was then used to identify differentially expressed genes between the different experimental conditions. The empirical Bayes method was used to compute a moderated t-statistics.[33] Transcripts with a log base two-fold change (logFC) greater than +0.20 or lower than −0.20 were considered as differentially expressed.

2.3. One color microarray microRNA expression analysis

One hundred nanograms of total RNA from cells at different experimental conditions were treated following the miRNA microarray protocol (Agilent Technologies, Placerville, CA). Briefly, RNA was dephosphorylated and denatured, followed by a ligation and labeling step. Samples were hybridized to Human miRNA Microarray 8 × 60K glass arrays from the Sanger miRBase database release 16 (2006 human miRNAs represented, Agilent Technologies). After hybridization, slides were washed following the Agilent procedure and scanned with the dual-laser Agilent Scanner version C (G2505C, Agilent Technologies). Images were analyzed using the Feature Extraction software v10.7. Raw data elaboration was carried out with Bioconductor (www.bioconductor.org),[32] using R statistical language. The LIMMA package was then used to identify differentially expressed miRNAs between the different experimental conditions. The empirical Bayes method was used to compute a moderated t-statistics.[33] miRNAs with a log base two-fold change (logFC) greater than +0.58 or lower than −0.58 were considered as differentially expressed.

2.4. Bioinformatic analyses for target processes prediction

TCGA (www.cbioportal.org/) was interrogated for the oncoprint of lncRNAs. This tool allows to obtain the genomic profile of the genes of interest in a cohort of patients by selecting the specific type of cancer. The oncoprint represents the percentage of genetic alterations and permits the comparison of the *status* of several genes in the same patient.

DIANA TOOLS (diana.imis.athena-innovation.gr/) was used to retrieve predicted microRNA targets and Gene Ontology (GO) processes in which it was predicted its involvement.

For these analyses, DIANA-mirPath v3.0 has been applied to obtain miRNA and pathway-related information. mirPath utilizes predicted miRNA targets (in CDS or 3′UTR regions) provided by the DIANA algorithms (TarBase v.7.0, microT-CDS v.5.0 and TargetScan) or even experimentally validated miRNA interactions.

The reverse search tool has been used in order to identify all miRNAs targeting a specific GO pathway. The module takes as input a GO biological process name or an identification code. Based on the algorithm and the specie of interest, a list of the miRNAs targeting the selected pathways and the relative target genes is generated.

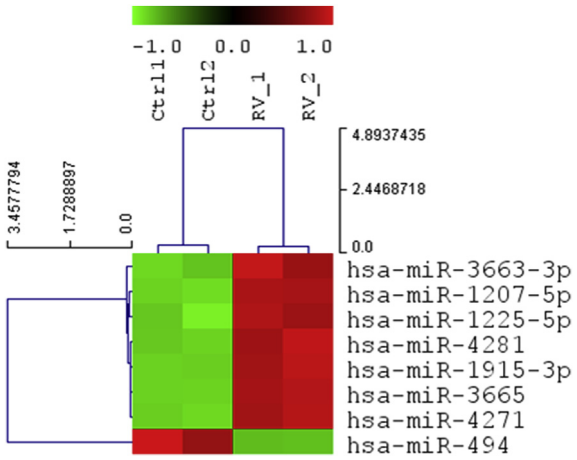

Fig. 1. Heat-map of microRNAs affected by Resveratrol (RV) treatment. Heat-map showing the OVCAR-3 expression profiles of microRNAs differently modulated upon RV treatment (third and fourth column) compared to control condition (first and second column). Green and red bars represent down-regulation and up-regulation, respectively.

3. Results

3.1. MicroRNAs modulated by resveratrol and pathways potentially affected

In a first analysis, where the statistical analysis for differential expression of miRNAs between control and RV-treated cells was based on a log2 fold-change >0.2 (for up-regulated) or < -0.2 (for down-regulated) with adjusted p-value <0.01, a total of forty-four up-regulated miRNAs and fifty-four down-regulated miRNAs were identified (heat-map in Fig. S1). In a more stringent statistical analysis, where the criterion for differentially expressed miRNAs in control and RV-treated cells was a log2 fold-change >0.585 (for up-regulated) and <-0.585 (for down-regulated) with adjusted $p < 0.01$, six miRNAs and one miRNA were found up- and down-regulated, respectively (heat-map in Fig. 1). We used the DIANA software to get a first insight on the predicted pathways in which these miRNAs could be involved. The unsupervised hierarchical clustering analysis of the cellular processes affected by these miRNAs is shown in Fig. 2. The trend of miRNAs up-regulated by RV appears to cluster together, and consistently indicates 'organelle' process as the major process implicated in their regulation. Other processes significantly associated with the modulation of these miRNAs include protein metabolism and function, catabolic processes, phosphatidyl-inositol signaling and gene expression regulation (Fig. 2). The unequivocal *in silico* identification of the miRNA

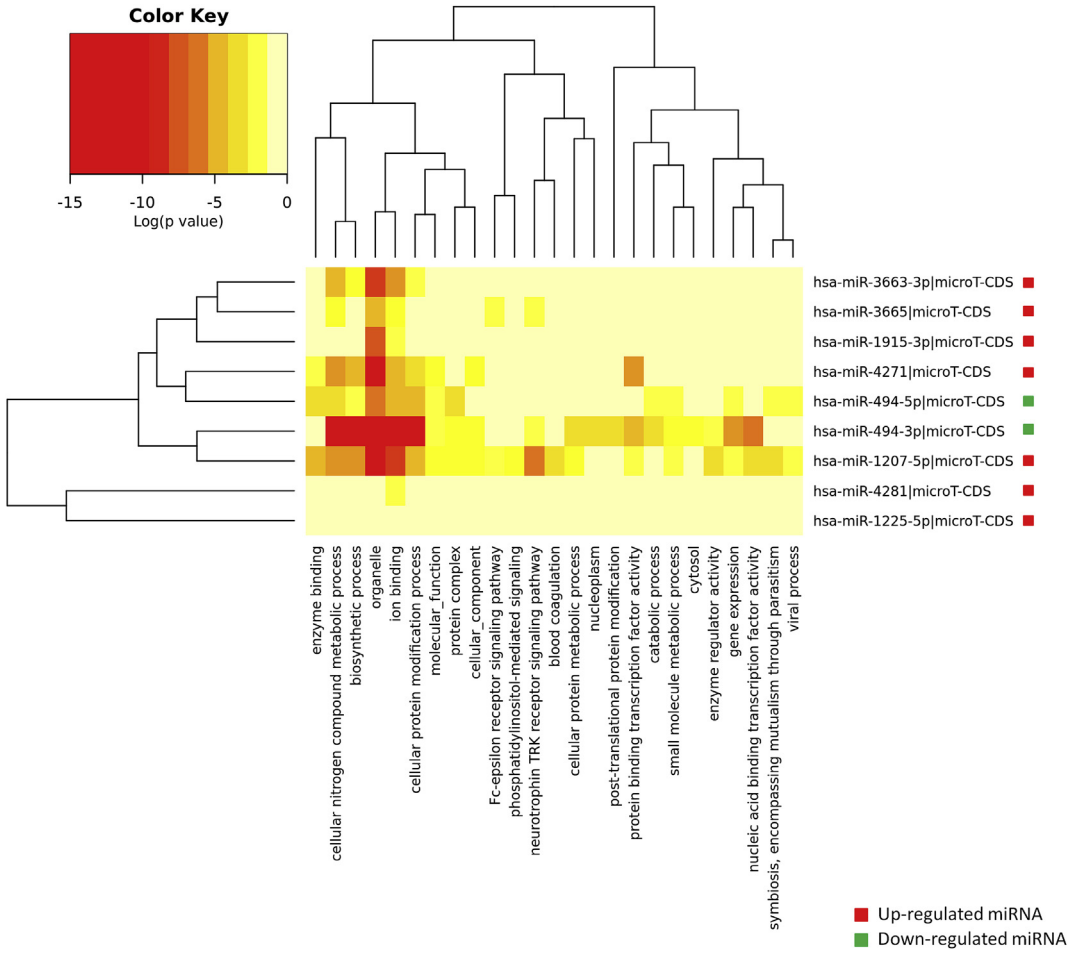

Fig. 2. miRNAs *versus* pathways heat-map. Darker and lighter colors show lower and higher significance values. The dendrogram exhibits hierarchical clustering for miRNAs and pathways, based on similar pathway targeting patterns.

Table 1
Opposite impact on OVCAR-3 miRNome by Resveratrol (RV) treatment and pathways versus target genes. Resveratrol (RV) positively modulates seven miRNAs and negatively affects one miRNA. The table is created as a reverse search, starting with a biological process of interest as input (first column) to catch miRNAs targeting the selected pathway (here we just filtered miRNAs modulated by Resveratrol, showing in the second column). Along each pathway and their relative miRNAs, we identify the corrispective miRNAs target genes (fourth column)

Selection criteria			
logFC > 0.58 for up-regulation logFC < -0.58 for down-regulation			
Pathway	miRNA	logFC	Target
EMT Cell migration	hsa-miR-1207-5p	1.345089789	*HBEGF, SH3KBP1, DGKZ, ODXL*
	hsa-miR-3665	1.330782842	*NOTCH1, GPC6*
	hsa-miR-1225-5p	0.962634046	*LEF1*
	hsa-miR-3663-3p	0.951629515	*TGFB2*
	hsa-miR-1915-3p	0.870670136	*GSK3B*
	hsa-miR-4271	0.696628837	*TGFBR3, FGFR2*
	hsa-miR-494	-0.668439833	*PTEN*
Glucose metabolic process Glycolytic process	hsa-miR-1207-5p	1.345089789	*GAPDH, PFKL, HK1, PGAM1, SLC25A1*
	hsa-miR-4281	1.192915761	*G6PD, PYGB*
	hsa-miR-4271	0.696628837	*PFKFB2, SORD*
Autophagy Lysosome Cellular protein metabolic turnover	hsa-miR-1207-5p	1.345089789	*RPLP1, GOSR2, ALG12, PFDN1, IGF1*
	hsa-miR-3665	1.330782842	*RPL28, RPL5*
	hsa-miR-4281	1.192915761	*TBCD*
	hsa-miR-3663-3p	0.951629515	*ZKSCAN3, TMEM208, LAMTOR1, MGAT5, RPS11*
	hsa-miR-1915-3p	0.870670136	*RPL18A, EIF4G1, SENP5*
	hsa-miR-4271	0.696628837	*IGF1, SYVN1*
	hsa-miR-494	-0.668439833	*EPG5, USP13, ATG4A, ATG4C, RNF152*
Cell death Apoptotic process	hsa-miR-1207-5p	1.345089789	*BIRC6, PIM1, NUAK2, AREL1, DHCR24, EGLN3*
	hsa-miR-3663-3p	0.951629515	*APC*
	hsa-miR-1915-3p	0.870670136	*FAIM2, BCL2*
	hsa-miR-4271	0.696628837	*S100A14, BCL2L1, FGFR, MAPK1*
	hsa-miR-494	-0.668439833	*ROCK1, KLF11, CLPTM1L, SMNDC1, PAWR, RNF152, BBC3, PTEN*
Stem cell maintenance Stem cell proliferation	hsa-miR-1207-5p	1.345089789	*WNT7B*
	hsa-miR-4271	0.696628837	*WNT7B, TRIM71*
Drug metabolic process Drug export	hsa-miR-1207-5p	1.345089789	*CYP2E1*
	hsa-miR-3663-3p	0.951629515	*FMO1*
	hsa-miR-4271	0.696628837	*EPHX2*

Table 2
miRNAs role in cancer. The table shows miRNAs modulated by Resveratrol (Table 2A for up-regulated and Table 2B for down-regulated, respectively); their epigenetic mechanism in cancer is indicated along the bibliographic references. For full references refer to Supplementary file 1 Reference List.

A. Up-regulated miRNAs.

miRNA	Mechanism	Gene Target	Cancer	Reference
miR-1207-5p	Inhibits tumor growth, invasion and metastasis.	*hTERT*	Gastric	[64]
	Inhibits EMT induced by TGF-β and EGF, by indirectly down-regulating PI3K/AKT pathway, STAT3 and some important inflammatory mediators.	*CSF1*	Lung	[65]
	Suppresses invasion and metastasis by targeting genes related to cell migration.	*CD151*	Nasopharyngeal	[66]
	Prevents tumor growth and invasion through the inhibition of AKT/mTOR signaling pathway.	*FASN*	Hepatocellular	[67]
	Increases sensitivity to gemcitabine and reduces cancer growth.	*SRC*	Pancreatic	[68]
miR-1225-5p	Lower expressed in stage III and IV compared to I and II; suppresses cell migration and invasion.	*IRS1*	Glioblastoma	[69]
	Prevents tumor cell proliferation and metastasis by inhibiting the activation of Wnt/β-catenin pathway.	*SIRT3*	Thyroid	[70]
	Acts as tumor suppressor by preventing tumor growth, metastasis and invasion through down-regulation of β-catenin.	*IRS1*	Gastric	[71]
miR-1915-3p	Reduces cell migration and proliferation.	*SETD1A*	Breast	[72]
	Inhibits tumor progression and promotes apoptosis.	*BCL-2*	Gastric	[73]

B. Down-regulated miRNAs.

miRNA	Mechanism	Gene Target	Cancer	Reference
miR-494	Oncogenic miRNA associated with poor prognosis and metastasis, promotes invasion and cell migration.	*PTEN*	Colorectal	[74]
	Associated with short overall survival; its expression is negatively correlated with tumor grade; high expression promotes early invasion and metastasis.	*PTEN*	Lung cancer	[75]
	Promotes proliferation, migration and invasion through the activation of PI3K/AKT pathway. (-3p)	*PTEN*	Endometrial	[76]
	Enhances proliferation, invasion and metastasis. (-3p)	*SOX7*	Nasopharyngeal	[77]
	Inhibits apoptosis and promotes cell growth and invasiveness through PTEN/AKT signaling. (-3p)	*PTEN*	Glioblastoma	[78]
	Stimulates tumor progression and proliferation by activating Wnt/β-catenin pathway.	*APC*	Colorectal	[79]
	Promotes tumorigenesis through the inhibition of apoptosis inducted by cisplatin.	*CASP2*	Lung	[80]
	Associated to poor prognosis and bad clinical outcome, promotes carcinogenesis, tumor growth and proliferation by up-regulating PI3K/AKT pathway.	*PTEN*	Cervical	[81]
	Contributes to cell cycle progression, cell viability, invasion and migration via activation of PI3K/AKT pathway.	*PTEN*	Hepatocellular	[82]

targets and pathways is challenging, because the miRNAs interacting networks have not yet been fully mapped. To get more insights on the relevance of the miRNAs modulated by RV we have pursued a practical direct approach by checking whether these miRNAs were indeed involved in the regulation of malignant features. We chose to focus on the processes that mainly influence the progression and recurrence of ovarian cancers. The following processes were considered: cell metabolism (essentially of glucose), macromolecular cell homeostasis (essentially organelle and protein turnover mediated by autophagy), drug resistance, cell death, stemness, cell migration and Epithelial-to-Mesenchymal Transition (EMT). The miRNAs of interest and their targets involved in these processes were selected and used to build Table 1. All the miRNAs modulated by RV appear involved in the malignant features that characterize cancer. To further substantiate the potential involvement in cancer biology of the miRNAs modulated by RV we made a literature search using as key words the 'miRNA name' of interest and 'cancer'. The data are reported in Table 2. Surprisingly, only a few of these miRNAs have been explored for their involvement in cancer. The most relevant publications were referring only to three of the miRNAs up-regulated (namely, miR-1207-5p, miR-1225-5p and miR-1915-3p) and to the only one down-regulated (miR-494) by RV.

3.2. Long non-coding RNAs modulated by resveratrol and pathways potentially involved

Microarray analysis of lncRNAs differentially expressed in control and RV-treated OVCAR-3 cells selected for differences in the expression of logFC >0.2 or < -0.2 for up- and down-regulation, respectively, revealed changes in a total of fifteen lncRNAs, of which five were up-regulated and ten were down-regulated (heatmap in Fig. 3 and Table 3). The literature search revealed that three

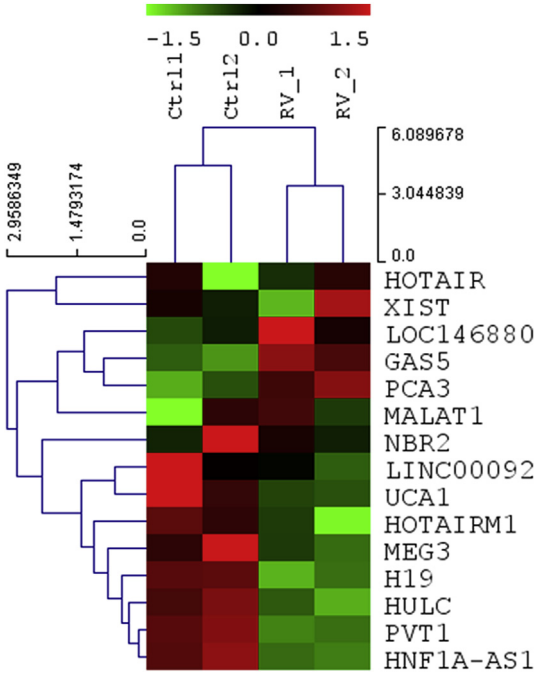

Fig. 3. Heat-map of lncRNAs affected by Resveratrol treatment. Heat-map showing OVCAR-3 expression profiles of lncRNAs differently modulated upon RV treatment (third and fourth column) compared to control condition (first and second column). Green and red bars represent down-regulation and up-regulation, respectively.

Table 3
Opposite impact on OVCAR-3 lncRNAs by Resveratrol treatment. Resveratrol positively modulates five lncRNAs and negatively affects ten lncRNAs.

Selection criteria		
logFC > 0.2 for up-regulation logFC < -0.2 for down-regulation		
RV Modulation	lncRNAs	logFC
Up	GAS5	0.483236212
	LOC146880	0.392972913
	HOTAIR	0.350768196
	PCA3	0.337791511
	NBR2	0.242196768
Down	XIST	-0.203996834
	LINC00092	-0.213428863
	UCA1	-0.226421069
	MALAT1	-0.333386015
	PVT1	-0.421322497
	MEG3	-0.424927463
	H19	-0.504613534
	HULC	-0.59482164
	HOTAIRM1	-0.754784827
	HNF1A-AS1	-1.141108755

of the lncRNAs up-regulated by RV were involved in processes inhibiting cancer progression through facilitating apoptosis, blocking cell proliferation and cell migration, and by inducing autophagy (Table 4A) and, *vice versa*, ten of the lncRNAs down-regulated by RV were acting in oncogenic pathways favoring the progression of several types of cancers (Table 4B). To further understand the clinical relevance of these lncRNAs in ovarian cancer pathogenesis and progression, we interrogated the TCGA database for the presence of altered expression in human samples. The oncoprint relative to the fifteen lncRNAs of interest in one hundred-eighty-two patients is shown in Fig. 4. It appears evident that PVT1 presents alterations in 45% of the cases, UCA1 is altered in 14% of the cases, and HULC is altered in 11% of the cases, XIST is altered in just one case, while HNF1-AS1 and ARHGAP27P1 (also known as LOC146880) show no alterations at all, and all the others present alterations comprised between is 1% and 7%. To be noted, while NBR2 tends to be expressed at very low level all other alterations essentially consist in gene amplification. Approximately 6% of the cases presents both UCA1 and PVT1 or both PVT1 and HULC genes amplification.

3.3. Cancer-related processes regulated by resveratrol-modulated non-coding RNAs

Based on the data above, we have summarized in a visual form the pathways and biological processes in which the non-coding RNAs modulated by RV in ovarian cancer cells are involved and through which they can impinge on the cancer features. The cartoons in Figs. 5 and 6, respectively, illustrate how RV may effectively contrast the malignant behaviour of cancer cells through the up- or down-regulation of miRNAs (Fig. 5) or of lncRNAs (Fig. 6).

4. Discussion

It is now well demonstrated that cancer genesis and progression result not only from gene mutations but also from epimutation in genes that control cell behaviour and cell-to-cell communication. Epimutations consist in the regulation of gene expression through mechanisms that involve the accessibility of the gene, its transcription as well as the stability and translation of the messenger RNA. Non-coding RNAs, which include miRNAs and lncRNAs among others, are part of the third epigenetic mechanism.[34] Non-coding

Table 4
LncRNAs role in cancer. The table shows lncRNAs modulated by Resveratrol (Table 4A for up-regulated and Table 4B for down-regulated lnc-RNAs respectively); their epigenetic mechanism in cancer is indicated along the bibliographic references. For references refer to Supplementary file 1 Reference List.

A. Up-regulated lncRNAs.

LncRNA	Mechanism	Cancer	Reference
GAS5	Stimulates apoptosis, reduces invasion and enhances chemo-sensitivity to cisplatin negatively regulating PI3K/AKT signaling, by sponging miR-21 preserving *PTEN* from degradation.	Cervical	[83]
	Reduces migration, invasion and proliferation acting as miRNA sponge by binding miR-205 to prevent *PTEN* degradation.	Lung	[84]
	Suppresses angiogenesis, tumor development and metastasis by reducing WNT/β-catenin signaling.	Colorectal	[85]
	Suppress tumorigenesis by sponging miR-196a-5p in order to prevent *FOXO1* degradation and attenuate migration and invasion.	Glioma	[86]
	Enhances cell apoptosis by targeting miR-103 to inhibit PTEN protein level reduction.	Endometrial	[87]
	Inhibits invasion, migration and proliferation by reducing Akt/Erk pathway and promoting apoptosis.	Colorectal	[88]
	Prevents tumor growth, invasion and metastasis through a positive *PTEN* regulation by sponging miR-32-5p.	Pancreatic	[89]
	Inhibits cell viability, migration and invasion by preventing miR-203a-mediated *TIMP2* degradation.	Osteosarcoma	[90]
	Acts as a tumor suppressor gene inhibiting tumor growth by preventing the expression of miR-196a and miR-205 in order to preserve *PTEN* and *FOXO1* from degradation.	Cervical	[91]
	Suppresses tumor growth and migration through a positive regulation of miR-137 transcription.	Melanoma	[92]
	Decreases miR-106a-5p expression levels to control cell proliferation, invasion and migration by inactivating the Akt/mTOR pathway.	Gastric	[93]
	Enhances apoptosis and prevents cell proliferation through a negative regulation of miR-182-5p expression in order to inhibit *FOXO3a* degradation.	Colorectal	[94]
	Inhibits cell growth and proliferation by sponging miR-21 and increasing *SPRY2* transcription.	Ovarian	[95]
	Inhibits proliferation and invasion directly binding miR-196a-5p with a negative interaction to prevent downstream FOXO1/PI3K/AKT pathway activation.	Breast	[96]
	Prevents tumor cell proliferation and invasion through PI3K/AKT/mTOR pathway down-regulation.	Esophageal	[97]
	Suppresses tumor progression and cell proliferation by reducing the expression and the secretion of *IL-10* and *VEGF-A* through NF-κB and Erk1/2 pathway regulation.	Colorectal	[98]
	Enhances chemosensitivity and promotes G0/G1 cell cycle arrest and apoptosis by modulating *PARP1* expression through a direct interaction with *E2F4* to its promoter.	Ovarian	[99]
	Decrease tumor growth and proliferation via regulating the AKT/mTOR pathway by sponging miR-103.	Prostate	[100]
	Inhibits tumor growth and increases radiosensitivity down-regulating miR-135b expression levels.	Lung	[101]
HOTAIR	Induces ATG7 up-regulation promoting autophagy as a protective mechanism of radioresistance.	Pancreatic	[102]
	Activates autophagy by increasing ATG3 and ATG7 expression.	Hepatocellular	[103]
NBR2	Under stress conditions interacts with AMPK promoting its activation.	Kidney Breast Prostate	[104]
	Acts as tumor suppressor preventing proliferation, invasion and migration through NOTCH1 regulation.	Osteosarcoma	[105]

B. Down-regulated lncRNAs.

LncRNA	Mechanism	Cancer	Reference
XIST	Promotes proliferation, invasion and migration by regulating positively *EZH2* through down-regulating miR-124.	Laryngeal	[106]
	Promotes tumor growth and proliferation through enhancing *MET* by recruiting miR-34a in order to increase PI3K/AKT signaling.	Thyroid	[107]
	Promotes cell invasion and EMT process by sponging miR-200a to prevent *Fus* degradation.	Cervical	[108]
	Enhances proliferation, migration and invasion by sponging miR-494 in order to up-regulates *CDK6* to control JAK2/STAT3 pathway.	Esophageal	[109]
	Increases migration, invasion and EMT capability by repressing miR-429 to promote *ZEB1* expression.	Pancreatic	[110]
	Leads to proliferation, invasion and metastasis by competing with miR-124-3p in order to modulate *EZH2* expression.	Laryngeal	[111]
	Regulates *RING1* expression directly binding to miR-744 to activate Wnt/β-catenin activation pathway promoting cell growth and migration.	Lung	[112]
	Increases tumor growth through the interaction with miR-132-3p to restore *MAPK1*.	Colorectal	[113]
	Promotes stemness and clone formation by repressing miR-200a.	Bladder	[114]
	Stimulates cell proliferation and cell cycle by keeping active *ORC1* through miR-140-5p inhibition.	Cervical	[115]
	Associated with cell proliferation, migration, invasion and metastasis, sponges miR-101 to increase *EZH2* expression.	Gastric	[116]
	Inhibits apoptosis and promotes proliferation and invasion by repressing tumor suppressive miR-186-5p.	Lung	[117]
	Promotes tumorigenesis by controlling androgen receptor (AR) expression through a direct binding with miR-124.	Bladder	[118]
	Negatively correlated with miR-124, promotes *SGK1* expression to enhances doxorubicin resistance.	Colorectal	[119]
	Inhibits apoptosis and promotes cell cycle progression by sponging miR-139-5p to prevent *PDK1* degradation.	Hepatocellular	[120]
	Promotes migration and invasion preventing *TGF-β2* expression inhibition by sponging miR-141-3p.	Pancreatic	[121]
	Stimulates cancer progression by up-regulating STAT3 through a direct binding with miR-124.	Retinoblastoma	[122]
	Increases cancer progression through EGFR up-regulation by negatively modulating miR-133a.	Pancreatic	[123]
	Promotes tumor growth, migration and invasion by sponging miR-185 to prevent downstream target degradation *TGF-β1*.	Gastric	[124]
	Enhances proliferation, migration and invasion by positively regulating *NOTCH3* via targeting miR-491-5p.	Nasopharyngeal	[125]
	Positively modulated cancer proliferation controlling *MAPK1* expression by sponging miR-194-5p.	Hepatocellular	[126]
	Increases cell proliferation and invasion through targeting miR-195-5p and promoting *YAP* expression.	Osteosarcoma	[127]
	Involved in cancer progression, promotes tumorigenesis by hampering TET1 binding to *p53* promoter.	Bladder	[128]
	Positively affects proliferation, invasion and migration by targeting miR-486-5p promoting *NRP-2*.	Colorectal	[129]
	Facilitates cisplatin chemoresistance via competitive interacting with let7i, preventing *BAG-1* degradation.	Lung	[130]
	Inhibits apoptosis and increases cell cycle progression by up-regulating *MACC1*, functioning as a molecular sponge to miR-497.	Gastric	[131]
	Plays an oncogenic role in tumor progression by sponging miR-101 to regulated *EZH2* expression levels.	Esophageal	[132]
	Promotes cell growth and EMT through a direct interaction with miR-139-5p to prevent Wnt/β-catenin inactivation pathway.	Bladder	[133]
	Drives tumor progression regulating *iASPP* expression by preventing its miR-140-mediated degradation.	Lung	[134]
	Supports chemoresistance up-regulating autophagy by preventing *ATG7* miR-17-induced repression.	Lung	[135]

Table 4 (*continued*)

B. Down-regulated lncRNAs.

LncRNA	Mechanism	Cancer	Reference
	Tumor-promoting gene, acts as sponge by repressing the onco-suppressor miR-34a-5p.	Pancreatic	[136]
	Exerts an oncogenic function promoting cancer proliferation by repressing miR-320b expression and preventing RAP2B down-regulation.	Osteosarcoma	[137]
	Regulates tumor development by inhibiting miR-137 repression mechanism on *EZH2*.	Colorectal	[138]
	Associated with poor survival time and cancer cell proliferation, increases *E2F3* expression levels by sponging miR-34a-5p.	Nasopharyngeal	[139]
LINC00092	Stimulates CAF-induced cancer progression and enhances glycolysis by directly interacting with *PFKFB2*.	Ovarian	[140]
	Promotes glucose metabolism and the Warburg effect by activating mTOR/STAT3 signaling which prevent miR-143 mediated *HK2* degradation.	Bladder	[141]
	Induces aggressive radio-resistance phenotype, cell cycle progression and cell growth by promoting PI3K/AKT signaling.	Prostate	[142]
	Stimulates tumor growth and metastasis through an epigenetic control mediated by EZH2 leading to *E-cadherin* and *p21* expression repression.	Gallbladder	[143]
	Expression induced by TGF-β pathway to promote EMT and stemness in a Slug positively dependent manner, downstream factor of TGF-β signaling.	Glioma	[144]
	Transcription factor C/EBPβ promotes its expression in order to maintain tumor progression and development.	Bladder	[145]
	Promotes carcinoma development preventing *PDL1* repression mediated by miR-26a/b, -193a and -214.	Gastric	[146]
	Increases tumor progression through Wnt/β-catenin activation pathway by up-regulating p-GSK-3β protein levels.	Breast	[147]
	Stimulates cancer cell proliferation and invasion via Wnt/β-catenin by up-regulating *GSK-3β* and *β-catenin*.	Thyroid	[148]
	Hampers apoptosis and cell cycle arrest by sponging miR-143 to exert a positive regulation on *MAPK1*.	Lung	[149]
	Directly interacts with miR-203 by preventing *ZEB2* degradation in order to induce migration, invasion and metastasis.	Gastric	[150]
	Down-regulates miR-182 to promotes cell viability, invasion and proliferation up-regulating *TIMP2*.	Osteosarcoma	[151]
	Stimulates cancer proliferation and cell cycle progression by repressing p21 through methylation promoter sponging miR-495.	Renal	[152]
	Negatively modulates miR-122 promoting cell proliferation, invasion and migration.	Glioma	[153]
	Acts as oncogene to promote cell growth and metastasis by sponging miR-204 and activating *CXCR4*.	Prostate	[154]
	Increases chemoresistance and inhibits apoptosis up-regulating *SF1* through sponging miR-184.	Oral	[155]
	Enhances *CREB1* expression to promotes proliferation and invasion by directly interacting with miR-590-3p.	Gastric	[156]
	Induces cell migration and invasion acting on Wnt/β-catenin pathway promotion.	Oral	[157]
	Facilitates cell proliferation and cell cycle phases transition by directly binding with EZH2 to increase *cyclin D1* expression.	Gastric	[158]
	Leads to cell proliferation, invasion and migration activating Wnt/β-catenin signaling pathway.	Laryngeal	[159]
	Promotes cell viability and enhances cisplatin resistance by increasing Wnt6 expression to stimulates Wnt pathway.	Bladder	[160]
	Increases cancer glycolysis through preventing *PFKFB2* degradation mediated by miR-182.	Glioma	[161]
UCA1	Positively regulates proliferation, invasion and migration and suppresses apoptosis by repressing miR-96 and up-regulating *FOXO3*.	Pancreatic	[162]
	Supports chemoresistance by enhancing glycolysis acting as a molecular sponge on miR-125a preventing *HK2* repression.	Leukemia	[163]
	Promotes cell viability, migratory and invasiveness properties and inhibits apoptosis by negatively affecting miR-182 to prevent TIMP2 degradation.	Gastric	[164]
	Represses miR-28-5p to increase cell proliferation and invasion mediated by HOXB3 activity.	Colon	[165]
	Regulates cell proliferation and inhibits apoptosis through a positive regulation of autophagy pathway.	Colorectal	[166]
	Enhances cell cycle progression and cell viability by directly interacting with EZH2 and facilitating *p21* promoter methylation.	Breast	[167]
	Increases TGFβ1-induced EMT through JAG1 and Notch signaling by negatively affecting miR-124.	Tongue	[168]
	Facilitates apoptosis inhibition, cell viability and EMT process through miR-15a repression and Hippo JNK pathway promotion.	Thyroid	[169]
	Increases cisplatin resistance and inhibits apoptosis by targeting miR-143 and positively modulating *FOSL2*.	Ovarian	[170]
	Activates ERK signaling pathway and promotes FGFR1-mediated cell growth and metastasis through miR-216b repression.	Hepatocellular	[171]
	Positively regulates tumorigenesis by modulating PI3K/AKT/mTOR signaling mediators.	Gastric	[172]
	Correlates with poor clinical outcomes and facilitates cancer growth and development AKT/GSK-3β/CCND1 signaling pathway.	Cholangiocarcinoma	[173]
	Induces cell growth by silencing PTEN/AKT signaling pathway.	Osteosarcoma	[174]
	Targets oncosuppressor miR-129 preventing *SOX4* repression to promotes proliferation, invasion and apoptosis inhibition.	Renal	[175]
	Positively modulates *IGFBP5* expression by sponging miR-204 to enhances proliferation and invasion.	Thyroid	[176]
	Acts as a competing endogenous RNA targeting miR-145 to increase cancer cell invasion and migration.	Nasopharyngeal	[177]
	Increases drug resistance by positively modulating autophagy through *ATG7* expression repressing miR-582-5p.	Bladder	[178]
	Regulates proliferation and metastasis by directly binding miR-144 and preventing *PBX3* degradation.	Lung	[179]
	Positively impacts on drug resistance by repressing miR-129 and promoting *ABCB1* expression.	Ovarian	[180]
	Enhances *HMGB1* expression by repressing anti-tumor miR-193a to sustain cancer cell proliferation and migration.	Lung	[181]
	Stimulates colony formation, proliferation, EMT and radioresistance.	Colorectal	[182]
	Increases cell viability by promoting AKT and mTOR activating phosphorylation to maintain tamoxifen resistance.	Breast	[183]
	Leads to viability and cancer progression through activation of *RBFOX2*, splicing factor linked to EMT.	Ovarian	[184]
	Induces proliferation, invasion, migration and metastasis via activation of autophagic flux.	Pancreatic	[185]
	Inhibits tumor suppressive miR-216b to promotes multi-drug chemo-resistance.	Hepatocellular	[186]
	Contributes to inhibits autophagy in order to increase chemoresistance.	Lymphoma	[187]
	Increases cell viability and metastasis through by repressing miR-22-3p.	Renal	[188]
	Decreases apoptosis by enhancing autophagy through miR-101 repression, promoting LC3-I to LC3-II conversion and reducing *p62* expression.	Colorectal	[189]
MALAT1	Promotes cancer progression and stemness properties by sponging miR-129-5p to increase RET/AKT activation pathway.	Osteosarcoma	[190]
	Negatively modulates miR-204 expression to stimulates cancer development and metastasis by up-regulating *SIRT1*.	Hepatocellular	[191]
	Reduces cisplatin chemosensitivity by inactivating NOTCH1 pathway and up-regulating and down-regulating *BCL-2* and *BAX* expression, respectively.	Ovarian	[192]
	Increases proliferation and inhibits apoptosis through *HDAC4* by acting as a molecular sponge on miR-140-5p.	Osteosarcoma	[193]
	Play an oncogenic control in cancer progression and metastasis by stimulating ERK/MAPK pathway activation.	Gallbladder	[194]
	Promotes invasion and migration by up-regulating *Notch1*, *EZH2* expression and other migratory factors to induces EMT.	Esophageal	[195]

(*continued on next page*)

Table 4 (*continued*)

B. Down-regulated lncRNAs.

LncRNA	Mechanism	Cancer	Reference
	Correlates with migration and invasion and positively modulates EMT through PI3K/AKT pathway activation.	Breast	[196]
	Increases *cyclin D1* expression by sponging miR-34a to support cell viability, invasion and migration.	Osteosarcoma	[197]
	Stimulates proliferation, invasion, migration and angiogenesis by increasing FGF2 protein levels secretion from tumor-associated macrophages.	Thyroid	[198]
	Induces EGFR-mediated cell growth and motility by negatively regulating miR-195.	Hepatocellular	[199]
	Promotes tumor progression and development through preventing *STAT3*-degradation mediated by miR-125b.	Oral	[200]
	Positively regulates cancer progression and development by modulating *CDK9* through miR-206 repression.	Osteosarcoma	[201]
	Enhances Wnt/β-catenin signaling activation to sustain EMT process.	Tongue	[202]
	Promotes invasion and metastasis preventing *SLAIN2* degradation by directly binding to miR-106b-5p.	Colorectal	[203]
	Play an oncogenic role in tumorigenesis acting as a competing endogenous RNA for miR-429.	Renal	[204]
	Promotes cancer initiation and progression through EZH2 and β-catenin up-regulation.	Esophageal	[205]
	Associated with metastasis and low overall survival, increases proliferation and invasion by sponging miR-206 to prevent *ANXA2* and *KRAS* suppression.	Gallbladder	[206]
	Stimulates invasion and migration increasing EMT process through β-catenin and NF-κB signaling pathway activation.	Oral	[207]
	Correlates with migration and invasion and positively modulates EMT through PI3K/AKT pathway activation.	Cholangiocarcinoma	[208]
	Accelerates EMT and cancer progression by negatively affecting miR-124.	Lung	[209]
	Promotes tumor development under hypoxia condition by repressing the onco-suppressor miR-200a.	Hepatocellular	[210]
	Correlates to bad clinical outcome, facilitates tumor development and cell cycle progression by directly interacting with miR-129-5p.	Breast	[211]
PVT1	Increases glycolysis in cancer metabolism by preventing miR-497-mediated *HK2* degradation, acting as miRNA sponge.	Osteosarcoma	[212]
	Up-regulates *SOX2* promoting cancer cell invasion and proliferation.	Ovarian	[213]
	Act as a negative regulator of miR-133a, promoting cell proliferation, cell cycle progression and tumor growth.	Ovarian	[214]
	Stimulates cancer cell proliferation and inhibits apoptosis up-regulating *BCL-2* expression protein levels by sponging miR-497.	Lung	[215]
	Positively regulates apoptosis and autophagy by targeting miR-216b to prevent *Beclin-1* degradation in order to reduce cisplatin sensitivity.	Lung	[216]
	Down-regulates p21 to promote EMT, cell proliferation and migration.	Pancreatic	[217]
	Represses LATS2 transcription by recruiting EZH2 on its promoter and increases cancer cell proliferation.	Lung	[218]
	Induces cell propagation and prevents apoptosis stabilizing EZH2 and MDM2 proteins and repressing p53 expression.	Hepatocellular	[219]
	Stimulates glucose metabolism by sponging miR-143 and enhancing *HK2* expression levels.	Gallbladder	[220]
	Promotes radioresistance by directly interaction with miR-195 acting as a molecular sponge.	Lung	[221]
	Inhibits miR-200b expression by recruiting EZH2 on its promoter and promotes cancer proliferation, cell cycle progression and migration.	Cervical	[222]
	Correlates with poor clinical outcome and increases proliferation and invasion by up-regulating *EZH2*.	Glioma	[223]
	Promotes tumorigenesis, EMT and metastasis by increasing *TWIST1* expression levels through miR-186 sponging.	Prostate	[224]
	Induces proliferation and metastatic capability via *GREM1* by acting as molecular sponge on miR-128-3p.	Glioma	[225]
	Negatively regulates miR-424 to increases cancer cells proliferation, migration and invasion abilities.	Cervical	[226]
	Acts as a competitive endogenous RNA by modulating miR-497 expression to increase cell viability and invasion.	Lung	[227]
	Promotes tumorigenesis and cancer progression by directly interacting with miR-128 to prevent its binding to *VEGFC*.	Bladder	[228]
	Positively affects cancer colony formation, migration and invasion by repressing miR-31 and enhancing *CDK1* expression.	Bladder	[229]
	Increases drug-resistance by inhibiting apoptosis through BCL-2 activation.	Gastric	[230]
	Stimulates tumor growth, invasion and metastasis acting as a competitive endogenous RNA on miR-26b.	Colon	[231]
	Sustains cancer progression and development via p38 phosphorylation.	Prostate	[232]
	Inhibits apoptosis and enhances cancer cell proliferation by positively modulating MCL-1 stability.	Renal	[233]
	Acts as oncogene in cancer proliferation promoting cancer cell development by enhancing chemoresistance, through *HIF-1α* stabilization and acetyltransferase induction.	Nasopharyngeal	[234]
	Promotes cancer cell growth and EMT process by increasing migratory markers expression and activating TGF-β/SMAD pathway.	Pancreatic	[235]
	Stimulates cancer progression by angiogenesis through STAT3 binding and VEGFA activation.	Gastric	[236]
MEG3	Increases cell growth, invasion and metastasis by sponging miR-127 to reduce *ZEB1* down-regulation.	Osteosarcoma	[237]
H19	Enhances chemo-resistance through SIRT1-mediated autophagy acting as miR-194 sponge to prevent SIRT1 miRNA-mediated inhibition.	Colorectal	[238]
	Promotes migratory capability and metastasis by interacting with miR-200a to positively modulate *ZEB1/2*-induced EMT.	Lung	[239]
	Promotes tumor growth and migration and inhibits apoptosis by silencing miR-143 so that its direct target *RUNX2* can activate PI3K/AKT pathway.	Retinoblastoma	[240]
	Reduces chemo-sensitivity inhibiting apoptosis and promoting cell survival by activating AKT pathway.	Breast	[241]
	Induced by oxidative stress acts sponging miR-let-7a/7b to promotes inflammatory role of IL-6 in tumor microenvironment.	Cholangiocarcinoma	[242]
	Positively regulates *STAT3* expression and its downstream targets to enhance cell proliferation, migration and invasion.	Esophageal	[243]
	Enhances tamoxifen chemoresistance through autophagy by reducing methylation in Beclin-1 promoter.	Breast	[244]
	Promotes *FOXM1*-mediated cancer invasion and cell cycle by negative regulating miR-342-3p.	Gallbladder	[245]
	Increases EMT process by preventing miR-194-5p-induced *FOXM1* degradation.	Colorectal	[246]
	Regulates cancer development through β-catenin/GSK-3β activation and EMT markers up-regulation.	Tongue	[247]
	Promotes tumor growth and inhibits apoptosis through *SOX4* up-regulation preventing its degradation mediated by miR-138.	Breast	[248]
	Enhances carcinogenesis by decreasing miR-138-5p expression to increase *SIRT1* activity.	Cervical	[249]
	Facilitates cell viability and EMT process through *STAT3* up-regulation by sponging miR-29b-3p.	Lung	[250]
	Acts as a molecular sponge to miR-152 increasing cell proliferation and invasion through *DNMT1* over-expression.	Breast	[251]
	Plays an oncogenic role promoting cell migration, invasion and EMT process by negatively regulating miR-484 expression, preventing *ROCK2* repression.	Lung	[252]
	Stimulates cancer cell proliferation, migration and invasion induced by *STAT3* by antagonizing miR-93-5p.	Breast	[253]
	Down-regulates *E-cadherin* expression through methylation mechanism and promotes EMT-related factors.	Lung	[254]
	Increases cancer development directly interacting with miR-17 to prevent *STAT3* repression.	Lung	[255]
	Positively affects proliferation, invasion and migration by stimulating NF-κB and PI3K/AKT pathways.	Melanoma	[256]

Table 4 (*continued*)

B. Down-regulated lncRNAs.

LncRNA	Mechanism	Cancer	Reference
HULC	Associated with poor prognosis, stimulates glucose metabolism by sponging miR-106a-5p to up-regulate *E2F3*.	Melanoma	[257]
	Participates to cancer aggressiveness and progression by positively affecting EMT process.	Endometrial	[258]
	Enhances migration and invasion through Ras/MAPK activation pathway.	Colon	[259]
	Promotes cancer cell growth and proliferation, inhibiting apoptosis through enhancing tamoxifen chemoresistance.	Breast	[260]
	Modulates proliferation and invasion by increasing the expression of EMT markers.	Lung	[261]
	Increases tumorigenesis promoting cell proliferation, cell cycle progression and positively regulates metastasis-associated genes.	Esophageal	[262]
	In order to maintain chemo-resistance, stimulates protective autophagy by stabilizing *SIRT1* through USP22 activation preventing SIRT1-ubiquitination.	Hepatocellular	[263]
	Induces tumorigenesis via down-regulation of protein markers of autophagy and through direct binding to *ATG7*.	Ovarian	[264]
	Contributes to tumor maintenance and progression by increasing *HMGA2* expression via miR-186 repression.	Hepatocellular	[265]
	Promotes tumor growth and metastasis enhancing PI3K/AKT, JAK/STAT and NOTCH signaling through silencing of miR-122 that lead to repression of these pathway.	Osteosarcoma	[266]
	Induced by oxidative stress acts sponging miR-372/373 to promotes inflammatory role of CXCR4 in tumor microenvironment.	Cholangiocarcinoma	[242]
	Positively modulates *RTKN* expression to promote cancer cell development by targeting miR-613.	Colon	[267]
	Promotes proliferation, invasion and migration enhancing PI3K/AKT/mTOR signaling pathway by repressing miR-125a-3p.	Ovarian	[268]
	Enhances radioresistance reducing autophagy by binding Beclin-1 and suppressing its phosphorylation through mTOR activation pathway.	Prostate	[269]
	Promotes carcinogenesis inducing PTEN degradation via autophagy-mediated system by inhibiting miR-15a maturation and stimulating LC3 expression.	Liver	[270]
	Associated with bad clinical outcome, modulates EMT process promoting cell growth and metastasis by up-regulating N-cadherin and vimentin and reducing E-cadherin.	Prostate	[271]
	Increases tumorigenesis by positively affecting the expression of protein involved in EMT, proliferation and metastasis.	Oral	[272]
	Plays an oncogenic role promoting apoptosis and inducing cell cycle progression via p53 and p21 down-regulation, respectively.	Nasopharyngeal	[273]
	Promotes cancer development inhibiting apoptosis by increasing chemoresistance to common chemotherapy drugs.	Gastric	[274]
	Stimulates cancer progression by inducing angiogenesis through miR-107 repression to promote the E2F1 binding to SPHK1 promoter.	Liver	[275]
	Enhances angiogenesis by promoting cancer proliferation and invasion through PI3K/AKT/mTOR activation pathway.	Glioma	[276]
	Facilitates cell growth and metastasis by sponging miR-200a-3p to positively regulate *ZEB1*-induced EMT.	Hepatocellular	[277]
HOTAIRM1	Increases proliferation and invasion stimulating HOXA1 oncogene by keeping away histone and DNA methyltransferase from its promoter.	Glioblastoma	[278]
	Promotes cell viability and metastasis modulating *DLGAP1* by sponging miR-148a.	Neck	[279]
HNF1A-AS1	Oncogene inhibiting apoptosis and promoting autophagy by sponging mir-30b-5p preventing *BCL-2* and *ATG5* degradation.	Hepatocellular	[280]
	Enhances cell cycle progression, cell viability and invasion.	Bladder	[281]
	EGR-1-induced transcription increases cell proliferation, migration and metastasis by promoting cell cycle progression.	Gastric	[282]
	STAT3-mediated expression stimulates EMT by positively regulating NOTCH signaling pathway.	Oral	[283]
	Stimulates cancer cells progression and proliferation and inhibits apoptosis by sponging miR-17-5p.	Lung	[284]
	Promotes cancer development increasing *CDK6* expression through miR-149-5p repression.	Lung	[285]
	Induces cell migration and invasion by positively affecting Wnt/β-catenin pathway.	Osteosarcoma	[286]
	Positively correlated with H19, enhances proliferation, migration, invasion and cell cycle progression.	Esophageal	[287]
	Oncogene negatively regulating apoptosis through a direct interaction with miR-30b-5p to prevent *BCL-2* degradation.	Bladder	[288]
	Promotes cell proliferation and cell cycle progression by directly interaction with EZH2 to repressing NKD1 and p21 protein levels.	Hepatocellular	[289]
	Associated with a worse overall survival, increases proliferation, invasion and migration through promoting Wnt/β-catenin pathway activity.	Colorectal	[290]

RNAs arise from gene expression that is influenced by environmental stimuli. Cell-to-cell interactions as well as availability of nutrients, oxygen, cytokines and drugs in the tumour microenvironment have a great epigenetic impact on cancer cell behaviour through modulation of non-coding RNAs.[35]

Herbal- and dietary products-derived phytochemicals with therapeutic potential, also known as nutraceuticals, are attracting the interest of cancer biologists because of their ability to impact on the epigenome of cancer cells, thus opening to novel effective and less toxic therapeutic strategies in the prevention and cure of cancer.[27,36]

Ovarian cancer is among the leading causes of death in the field of gynecological cancers in most developed countries. Epigenetics clearly plays a role in ovarian cancer pathogenesis and progression.[16,17,19–21]

RV is a nutraceutical polyphenol with anti-cancer potential.[22,37,38] RV has been shown effective in causing cancer cell death and cancer cell senescence[39–46] and to inhibit cancer cell invasion and metastasis[30,47–49] in several *in vitro* and *in vivo* models, including ovarian cancer.[30,42,49] It has been shown that autophagy contributes to RV-induced apoptosis in ovarian cancer cells.[50] Further, RV was shown to antagonize EMT and invasion of ovarian cancer cells via activation of the NAD + -dependent deacetylase SIRT1 pathway.[51]

Phytochemicals have been shown to elicit anti-cancer activities via epigenetics.[52–55] In this work we focus on the modulatory activity of non-coding RNAs in ovarian cancer cells exposed to RV. The OVCAR-3 cell line, isolated from the ascites of a malignant and multi-drug resistant ovarian adenocarcinoma, was chosen as representative ovarian cancer cells.

We found that a 24 h incubation of OVCAR-3 cells with 100 μM RV, a dose clinically relevant,[56] results in the modulation of several miRNAs and lncRNAs that potentially target molecular pathways involved in the malignant phenotype. Using a log base 2-fold change (logFC) greater than 0.58 or lower than −0.58 (corresponding to 1.5-fold expression) as a threshold for differentially

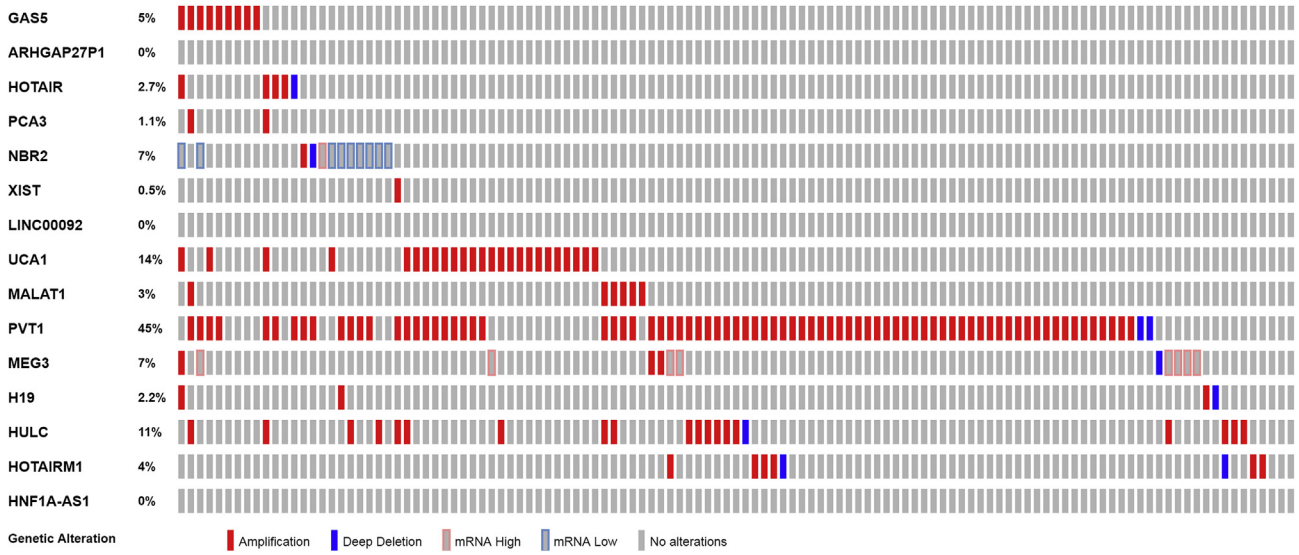

Fig. 4. Oncoprint relative to the lncRNAs affected by Resveratrol treatment. Oncoprint obtained by TCGA data (Ovarian Serous Cystadenocarcinoma - database Provisional; sample = 182 patients) representing the genetic alterations (amplification, deep deletion, no alterations) and mRNA expression (high or low levels) of the lncRNAs considered in the present study.

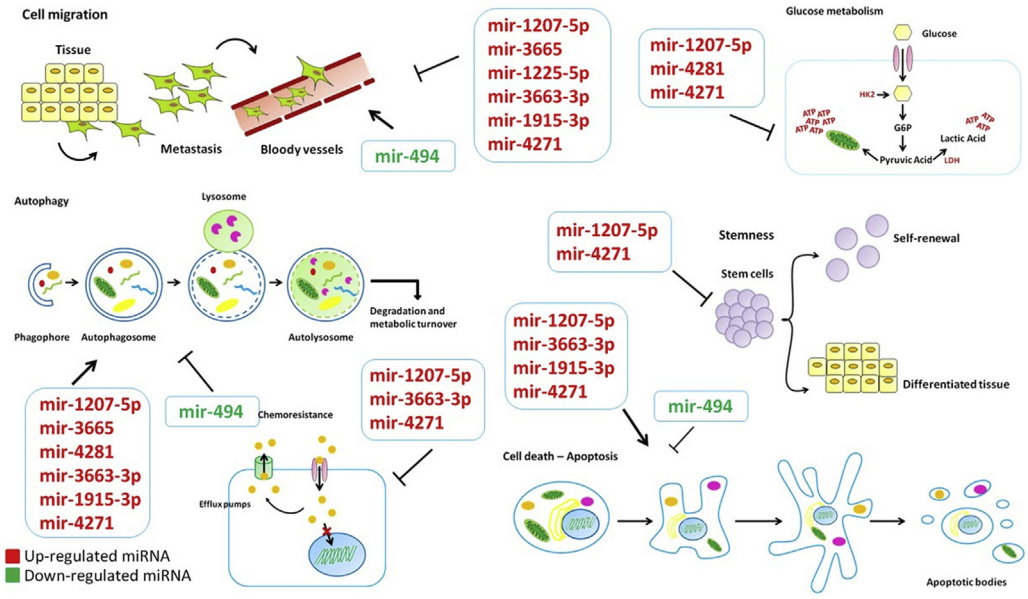

Fig. 5. Cartoon showing miRNAs and related biological processes. Schematic summary of set of miRNAs modulated by Resveratrol treatment and their involvement in main cancer related-processes.

expressed non-coding RNAs, it was found that RV up-regulated seven miRNAs and five lncRNAs and down-regulated two miRNAs and ten lncRNAs.

The miRNAs modulated by RV have been found dysregulated and involved in the malignant aspects of ovarian cancer.[17]

Interestingly, the three miRNAs mostly up-regulated by RV, i.e. miR-1207-5p, miR-3665 and miR-4281, consistently regulate autophagy and glucose metabolism (Table 1), two pathways that are dysregulated in ovarian cancers.[10,11,16,57,58] It is worth noting that two miRNAs up-regulated by RV, namely miR-1207-5p and miR-1225-5p were shown to limit EMT and cancer metastasis in gastric, lung and nasopharyngeal cancers (the former) and to inhibit progression and metastasization of glioblastomas (the latter). For miR-494, contradictory results were found. In some cases, this miRNA acts as an oncomiRNA by targeting the onco-suppressor PTEN (Table 2), while in other cases it seems to act as a tumor-suppressive miRNA since its over expression can inhibit apoptosis and promote cell proliferation of cancer cells. Such apparent contradiction may have at least two possible explanations, both very likely. First, the phenotypic outcome arising from the modulation of a given miRNA is cell-context in that it depends on the genetic background and metabolic status of the cell. Thus, miR-494 may be oncogenic or tumor suppressive in cancer cell lines of different origin and in different environmental conditions. Another possible explanation is that miR-494-3p and miR-494-5p have specificity for different targets thus eliciting different functional effects, and in some studies the 5p or 3p strand was not specified.

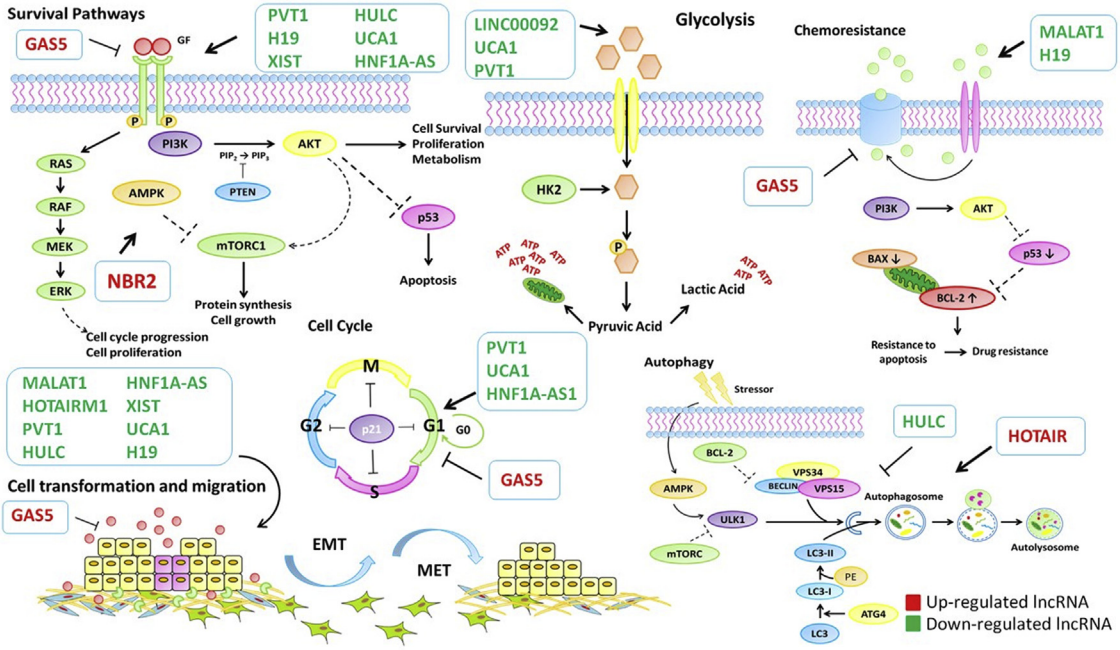

Fig. 6. Cartoon showing lncRNAs and related biological processes. Schematic summary of set of lncRNAs modulated by Resveratrol treatment and their involvement in main cancer related-processes.

Among the fifteen lncRNAs modulated by RV, five were found up-regulated in ovarian cancer TCGA database because of gene amplification (PVT1, UCA1, HULC and GAS5) or of mRNA hyper-expression (MEG3). Interestingly, PVT1, UCA1, HULC and MEG3 have been shown to act as oncogenic lncRNAs in a variety of cancers by promoting cell proliferation, cell migration, metastasis, glycolysis, multi-drug resistance (Table 4), and RV down-regulates their expression in ovarian cancer cells. On the other hand, GAS5 acts as a tumor-suppressive non-coding RNA in a variety of cancer types (Table 4), and RV up-regulated its expression in ovarian cancer (Table 3). To be noted, NBR2 that is found expressed at low level in ten patients (out of 182) in the TCGA database (Fig. 4) and that acts as a tumor suppressor (Table 4) was up-regulated in OVCAR-3 cells exposed to RV. The treatment also down-regulated the expression of XIST, LINC00092, H19, MALAT1 that were shown to act as oncogenic lncRNAs.

Taken together, RV was found to modulate in OVCAR-3 cells non-coding RNAs that consistently opposed oncogenic pathways (summarized in Figs. 5 and 6). One limitation of the present study is that these effects have not been validated in the cells. To this end, experiments are in progress. Further studies shall identify the relevant target molecules of these non-coding RNAs.

Nonetheless, the data here reported substantiate the view that RV has the potential to counteract the progression of ovarian cancer and add to the known anti-cancer mechanisms of this nutraceutical, thus supporting its potential harnessing as an adjuvant therapeutics. In this regard, RV appears well tolerated in both animals and humans and no marked toxicity has been reported in the ongoing clinical trials (recorded on clinicaltrial.gov) testing its anti-cancer effectiveness.[59] RV is an hormetic drug that promotes opposite effects depending on the concentration used.[60] Thus, in the clinical practice the choice of the appropriate dose for obtaining the desired effect depends on some characteristics and habits of the patient in terms of microbiota, hormones, gender, etc.[61] One caveat for the clinical exploitation of RV is its poor bioavailability in the systemic circulation, since it is efficiently absorbed after oral administration and rapidly and extensively metabolized. To overcome such limitations and improve its anti-cancer benefits and pharmacokinetic profile, novel analogs of RV and nano-platforms for its targeted delivery are under development.[62,63]

Section

Special Issue “Nutraceuticals and Diet in Human Health and Disease”.

Declaration of competing interest

No conflict of interest, financial or otherwise, to disclose.

Acknowledgements

AF is recipient of a post-doctoral fellowship “Paolina Troiano” (id. 24094) granted by Associazione Italiana per la Ricerca sul Cancro (AIRC, Milan, Italy). LV and ES are PhD students recipient of a fellowship granted by the Italian Ministry of Education, University and Research (MIUR, Rome, Italy) with the contribution of Associazione per la Ricerca Medica Ippocrate-Rhazi (ARM-IR, Novara, Italy). CV was supported with a fellowship from Associazione per la Ricerca Medica Ippocrate-Rhazi (ARM-IR, Novara, Italy). Authors are grateful to Dr G. Chiorino of Edo & Elvo Tempia Foundation (Biella, Italy) for assistance in performing the microarray.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtcme.2020.02.006.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019 Jan *Ca - Cancer J Clin.* 2019;69(1):7–34. https://doi.org/10.3322/caac.21551. Epub 2019 Jan 8. PubMed PMID: 30620402.
2. Coleman RL, Monk BJ, Sood AK, Herzog TJ. Latest research and treatment of advanced-stage epithelial ovarian cancer. *Nat Rev Clin Oncol.* 2013 Apr;10(4):

211–224. https://doi.org/10.1038/nrclinonc.2013.5. Epub 2013 Feb 5. Review.
3. Vaughan S, Coward JI, Bast Jr RC, Berchuck A, Berek JS, et al. Rethinking ovarian cancer: recommendations for improving outcomes. *Nat Rev Canc*. 2011 Sep 23;11(10):719–725. https://doi.org/10.1038/nrc3144. PubMed PMID: 21941283; PubMed Central PMCID: PMC3380637.
4. Gupta KK, Gupta VK, Naumann RW. Ovarian cancer: screening and future directions. *Int J Gynecol Canc*. 2019 Jan;29(1):195–200. https://doi.org/10.1136/ijgc-2018-000016. Review. PubMed PMID: 30640704.
5. Valente G, Nicotra G, Arrondini M, Castino R, Capparuccia L, et al. Co-expression of plexin-B1 and Met in human breast and ovary tumours enhances the risk of progression. *Cell Oncol*. 2009;31(6):423–436. https://doi.org/10.3233/CLO-2009-0504. PubMed PMID: 19940359; PubMed Central PMCID: PMC4619042.
6. Shuvayeva G, Bobak Y, Igumentseva N, Titone R, Morani F, et al. Single amino acid arginine deprivation triggers prosurvival autophagic response in ovarian carcinoma SKOV3. *BioMed Res Int*. 2014;2014:505041. https://doi.org/10.1155/2014/505041. Epub 2014 Jun 1. PubMed PMID: 24987688; PubMed Central PMCID: PMC4058691.
7. Valente G, Morani F, Nicotra G, Fusco N, Peracchio C, et al. Expression and clinical significance of the autophagy proteins BECLIN 1 and LC3 in ovarian cancer. *BioMed Res Int*. 2014;2014:462658. https://doi.org/10.1155/2014/462658. Epub 2014 Jul 17. PubMed PMID: 25136588; PubMed Central PMCID: PMC4127242.
8. Luo Z, Wang Q, Lau WB, Lau B, Xu L, et al. Tumor microenvironment: the culprit for ovarian cancer metastasis? *Canc Lett*. 2016 Jul 28;377(2):174–182. https://doi.org/10.1016/j.canlet.2016.04.038. Epub 2016 Apr 27. Review. PubMed PMID: 27131957.
9. Curtis M, Mukherjee A, Lengyel E. The tumor microenvironment takes center stage in ovarian cancer metastasis. *Trends Cancer*. 2018 Aug;4(8):517–519. https://doi.org/10.1016/j.trecan.2018.06.002. Epub 2018 Jun 22. PubMed PMID: 30064659.
10. Thuwajit C, Ferraresi A, Titone R, Thuwajit P, Isidoro C. The metabolic cross-talk between epithelial cancer cells and stromal fibroblasts in ovarian cancer progression: autophagy plays a role. *Med Res Rev*. 2018 Jul;38(4):1235–1254. https://doi.org/10.1002/med.21473. Epub 2017 Sep 19. Review. PubMed PMID: 28926101; PubMed Central PMCID: PMC6032948.
11. Ha JH, Radhakrishnan R, Jayaraman M, Yan M, Ward JD, et al. LPA induces metabolic reprogramming in ovarian cancer via a pseudohypoxic response. *Canc Res*. 2018 Apr 15;78(8):1923–1934. https://doi.org/10.1158/0008-5472.CAN-17-1624. Epub 2018 Jan 31. PubMed PMID: 29386184; PubMed Central PMCID: PMC5899640.
12. Radhakrishnan R, Ha JH, Jayaraman M, Liu J, Moxley KM, et al. Ovarian cancer cell-derived lysophosphatidic acid induces glycolytic shift and cancer-associated fibroblast-phenotype in normal and peritumoral fibroblasts. *Canc Lett*. 2019 Feb 1;442:464–474. https://doi.org/10.1016/j.canlet.2018.11.023. Epub 2018 Nov 29. PubMed PMID: 30503552.
13. Patch AM, Christie EL, Etemadmoghadam D, Garsed DW, George J, et al. Whole-genome characterization of chemoresistant ovarian cancer. *Nature*. 2015 May 28;521(7553):489–494. https://doi.org/10.1038/nature14410. Erratum in: Nature. 2015 Nov 19;527(7578):398. PubMed PMID: 26017449.
14. Fang F, Cardenas H, Huang H, Jiang G, Perkins SM, et al. Genomic and epigenomic signatures in ovarian cancer associated with resensitization to platinum drugs. *Canc Res*. 2018 Feb 1;78(3):631–644. https://doi.org/10.1158/0008-5472.CAN-17-1492. Epub 2017 Dec 11. PubMed PMID: 29229600; PubMed Central PMCID: PMC5811373.
15. Papp E, Hallberg D, Konecny GE, Bruhm DC, Adleff V, et al. Integrated genomic, epigenomic, and expression analyses of ovarian cancer cell lines. *Cell Rep*. 2018 Nov 27;25(9):2617–2633. https://doi.org/10.1016/j.celrep.2018.10.096. PubMed PMID: 30485824; PubMed Central PMCID: PMC6481945.
16. Peracchio C, Alabiso O, Valente G, Isidoro C. Involvement of autophagy in ovarian cancer: a working hypothesis. *J Ovarian Res*. 2012 Sep 13;5(1):22. https://doi.org/10.1186/1757-2215-5-22. PubMed PMID: 22974323; PubMed Central PMCID: PMC3506510.
17. Titone R, Morani F, Follo C, Vidoni C, Mezzanzanica D, et al. Epigenetic control of autophagy by microRNAs in ovarian cancer. *BioMed Res Int*. 2014;2014:343542. https://doi.org/10.1155/2014/343542. Epub 2014 Apr 30. PubMed PMID: 24877083; PubMed Central PMCID: PMC4022060.
18. Ferraresi A, Titone R, Follo C, Castiglioni A, Chiorino G, et al. The protein restriction mimetic Resveratrol is an autophagy inducer stronger than amino acid starvation in ovarian cancer cells. *Mol Carcinog*. 2017 Dec;56(12):2681–2691. https://doi.org/10.1002/mc.22711. Epub 2017 Sep 7. PubMed PMID: 28856729.
19. Natanzon Y, Goode EL, Cunningham JM. Epigenetics in ovarian cancer. *Semin Canc Biol*. 2018 Aug;51:160–169. https://doi.org/10.1016/j.semcancer.2017.08.003. Epub 2017 Aug 3. Review. PubMed PMID: 28782606; PubMed Central PMCID: PMC5976557.
20. Yang Q, Yang Y, Zhou N, et al. Epigenetics in ovarian cancer: premise, properties, and perspectives. *Mol Canc*. 2018 Jul 31;17(1):109. https://doi.org/10.1186/s12943-018-0855-4. Review. PubMed PMID: 30064416; PubMed Central PMCID: PMC6069741.
21. Moufarrij S, Dandapani M, Arthofer E, Gomez S, Srivastava A, et al. Epigenetic therapy for ovarian cancer: promise and progress. *Clin Epigenet*. 2019 Jan 15;11(1):7. https://doi.org/10.1186/s13148-018-0602-0. Review. PubMed PMID: 30646939; PubMed Central PMCID: PMC6334391.
22. Valentovic MA. Evaluation of resveratrol in cancer patients and experimental models. *Adv Canc Res*. 2018;137:171–188. https://doi.org/10.1016/bs.acr.2017.11.006. Epub 2017 Dec 15. Review. PubMed PMID: 29405976.
23. Efferth T, Oesch F. Repurposing of plant alkaloids for cancer therapy: pharmacology and toxicology. pii: S1044-579X(19)30408-0 *Semin Canc Biol*. 2019 Dec 26. https://doi.org/10.1016/j.semcancer.2019.12.010 [Epub ahead of print] Review. PubMed PMID: 31883912.
24. Ahmad R, Khan MA, Srivastava AN, Gupta A, Srivastava A, et al. Anticancer potential of dietary natural products: a comprehensive review. *Anticancer Agents Med Chem*. 2019 Oct 14. https://doi.org/10.2174/1871520619666191015103712 [Epub ahead of print] PubMed PMID: 31749433.
25. Dutta S, Mahalanobish S, Saha S, Ghosh S, Sil PC. Natural products: an upcoming therapeutic approach to cancer. *Food Chem Toxicol*. 2019 Jun;128:240–255. https://doi.org/10.1016/j.fct.2019.04.012. Epub 2019 Apr 13. Review. PubMed PMID: 30991130.
26. Liskova A, Kubatka P, Samec M, Zubor P, Mlyncek M, et al. Dietary phytochemicals targeting cancer stem cells. pii: E899 *Molecules*. 2019 Mar 4;24(5). https://doi.org/10.3390/molecules24050899. Review. PubMed PMID: 30836718; PubMed Central PMCID: PMC6429493.
27. Vidoni C, Ferraresi A, Secomandi E, Vallino L, Dhanasekaran DN, et al. Epigenetic targeting of autophagy for cancer prevention and treatment by natural compounds. pii: S1044-579X(19)30010-0 *Semin Canc Biol*. 2019 May 2. https://doi.org/10.1016/j.semcancer.2019.04.006 [Epub ahead of print] Review. PubMed PMID: 31054926.
28. Ranjan A, Ramachandran S, Gupta N, Kaushik I, Wright S, et al. Role of phytochemicals in cancer prevention. pii: E4981 *Int J Mol Sci*. 2019 Oct 9;(20):20. https://doi.org/10.3390/ijms20204981. Review. PubMed PMID: 31600949; PubMed Central PMCID: PMC6834187.
29. Fernandes GFS, Silva GDB, Pavan AR, Chiba DE, Chin CM, et al. Epigenetic regulatory mechanisms induced by resveratrol. pii: E1201 *Nutrients*. 2017 Nov 1;9(11). https://doi.org/10.3390/nu9111201. Review. PubMed PMID: 29104258; PubMed Central PMCID: PMC5707673.
30. Ferraresi A, Phadngam S, Morani F, Galetto A, Alabiso O, et al. Resveratrol inhibits IL-6-induced ovarian cancer cell migration through epigenetic up-regulation of autophagy. *Mol Carcinog*. 2017 Mar;56(3):1164–1181. https://doi.org/10.1002/mc.22582. Epub 2016 Nov 3. PubMed PMID: 27787915.
31. Lee PS, Chiou YS, Ho CT, Pan MH. Chemoprevention by resveratrol and pterostilbene: targeting on epigenetic regulation. *Biofactors*. 2018 Jan;44(1):26–35. https://doi.org/10.1002/biof.1401. Epub 2017 Dec 8. Review. PubMed PMID: 29220106.
32. Gentleman RC, Carey VJ, Bates DM, Bolstad B, Dettling M, et al. Bioconductor: open software development for computational biology and bioinformatics. *Genome Biol*. 2004;5(10):R80. Epub 2004 Sep 15. PubMed PMID: 15461798; PubMed Central PMCID: PMC545600.
33. Smyth GK. Linear models and empirical bayes methods for assessing differential expression in microarray experiments. *Stat Appl Genet Mol Biol*. 2004;3. Article3. Epub 2004 Feb 12. PubMed PMID: 16646809.
34. Wei JW, Huang K, Yang C, Kang CS. Non-coding RNAs as regulators in epigenetics (Review). *Oncol Rep*. 2017 Jan;37(1):3–9. https://doi.org/10.3892/or.2016.5236. Epub 2016 Nov 8. Review. PubMed PMID: 27841002.
35. Li CH, Chen Y. Insight into the role of long noncoding RNA in cancer development and progression. *Int Rev Cell Mol Biol*. 2016;326:33–65. https://doi.org/10.1016/bs.ircmb.2016.04.001. Epub 2016 May 17.
36. Shankar E, Kanwal R, Candamo M, Gupta S. Dietary phytochemicals as epigenetic modifiers in cancer: promise and challenges. *Semin Canc Biol*. 2016 Oct;40–41:82–99. https://doi.org/10.1016/j.semcancer.2016.04.002. Epub 2016 Apr 23.
37. Rauf A, Imran M, Butt MS, Nadeem M, Peters DG, Mubarak MS. Resveratrol as an anti-cancer agent: a review. *Crit Rev Food Sci Nutr*. 2018 Jun 13;58(9):1428–1447. https://doi.org/10.1080/10408398.2016.1263597.
38. Carter LG, D'Orazio JA, Pearson KJ. Resveratrol and cancer: focus on in vivo evidence. *Endocr Relat Canc*. 2014 May 6;21(3):R209–R225. https://doi.org/10.1530/ERC-13-0171. Print 2014 Jun. Review. PubMed PMID: 24500760; PubMed Central PMCID: PMC4013237.
39. Castino R, Pucer A, Veneroni R, Morani F, Peracchio C, et al. Resveratrol reduces the invasive growth and promotes the acquisition of a long-lasting differentiated phenotype in human glioblastoma cells. *J Agric Food Chem*. 2011 Apr 27;59(8):4264–4272. https://doi.org/10.1021/jf104917q. Epub 2011 Mar 11. PubMed PMID: 21395220.
40. Trincheri NF, Nicotra G, Follo C, Castino R, Isidoro C. Resveratrol induces cell death in colorectal cancer cells by a novel pathway involving lysosomal cathepsin D. *Carcinogenesis*. 2007 May;28(5):922–931. Epub 2006 Nov 20. PubMed PMID: 17116725.
41. Trincheri NF, Follo C, Nicotra G, Peracchio C, Castino R, et al. Resveratrol-induced apoptosis depends on the lipid kinase activity of Vps34 and on the formation of autophagolysosomes. *Carcinogenesis*. 2008 Feb;29(2):381–389. Epub 2007 Nov 28. PubMed PMID: 18048384.
42. Zhong LX, Zhang Y, Wu ML, Liu YN, Zhang P, et al. Resveratrol and STAT inhibitor enhance autophagy in ovarian cancer cells. *Cell Death Dis*. 2016 Jan 25;2:15071. https://doi.org/10.1038/cddiscovery.2015.71. eCollection 2016. PubMed PMID: 27551495; PubMed Central PMCID: PMC4979504.
43. Park D, Jeong H, Lee MN, Koh A, Kwon O, et al. Resveratrol induces autophagy by directly inhibiting mTOR through ATP competition. *Sci Rep*. 2016 Feb 23;6:21772. https://doi.org/10.1038/srep21772. PubMed PMID: 26902888; PubMed Central PMCID: PMC4763238.
44. Venkatadri R, Muni T, Iyer AK, Yakisich JS, Azad N. Role of apoptosis-related miRNAs in resveratrol-induced breast cancer cell death. *Cell Death Dis*. 2016

Feb 18;7, e2104. https://doi.org/10.1038/cddis.2016.6. PubMed PMID: 26890143; PubMed Central PMCID: PMC5399194.
45. Selvaraj S, Sun Y, Sukumaran P, Singh BB. Resveratrol activates autophagic cell death in prostate cancer cells via downregulation of STIM1 and the mTOR pathway. *Mol Carcinog*. 2016 May;55(5):818–831. https://doi.org/10.1002/mc.22324. Epub 2015 Apr 27. PubMed PMID: 25917875; PubMed Central PMCID: PMC4624064.
46. Zhang P, Li H, Yang B, et al. Biological significance and therapeutic implication of resveratrol-inhibited Wnt, Notch and STAT3 signaling in cervical cancer cells. *Genes Cancer*. 2014 May;5(5-6):154–164. PubMed PMID: 25061499; PubMed Central PMCID: PMC4104760.
47. Thongchot S, Ferraresi A, Vidoni C, Loilome W, Yongvanit P, et al. Resveratrol interrupts the pro-invasive communication between cancer associated fibroblasts and cholangiocarcinoma cells. *Canc Lett*. 2018 Aug 28;430:160–171. https://doi.org/10.1016/j.canlet.2018.05.031. Epub 2018 May 23. Erratum in: Cancer Lett. 2018 Oct 10;434:206-207. PubMed PMID: 29802929.
48. Sun Y, Zhou QM, Lu YY, Zhang H, Chen QL, et al. Resveratrol inhibits the migration and metastasis of MDA-MB-231 human breast cancer by reversing TGF-β1-induced epithelial-mesenchymal transition. pii: E1131 *Molecules*. 2019 Mar 21;(6):24. https://doi.org/10.3390/molecules24061131. PubMed PMID: 30901941; PubMed Central PMCID: PMC6471699.
49. Baribeau S, Chaudhry P, Parent S, Asselin É. Resveratrol inhibits cisplatin-induced epithelial-to-mesenchymal transition in ovarian cancer cell lines. *PloS One*. 2014 Jan 22;9(1), e86987. https://doi.org/10.1371/journal.pone.0086987. eCollection 2014. PubMed PMID: 24466305; PubMed Central PMCID: PMC3899376.
50. Lang F, Qin Z, Li F, Zhang H, Fang Z, Hao E. Apoptotic cell death induced by resveratrol is partially mediated by the autophagy pathway in human ovarian cancer cells. *PloS One*. 2015 Jun 11;10(6), e0129196. https://doi.org/10.1371/journal.pone.0129196. eCollection 2015. PubMed PMID: 26067645; PubMed Central PMCID: PMC4466135.
51. Ray U, Roy SS, Chowdhury SR. Lysophosphatidic acid promotes epithelial to mesenchymal transition in ovarian cancer cells by repressing SIRT1. *Cell Physiol Biochem*. 2017;41(2):795–805. https://doi.org/10.1159/000458744. Epub 2017 Feb 14. PubMed PMID: 28214851.
52. Arora I, Sharma M, Tollefsbol TO. Combinatorial epigenetics impact of polyphenols and phytochemicals in cancer prevention and therapy. pii: E4567 *Int J Mol Sci*. 2019 Sep 14;20(18). https://doi.org/10.3390/ijms20184567. Review. PubMed PMID: 31540128; PubMed Central PMCID: PMC6769666.
53. Shukla S, Penta D, Mondal P, Meeran SM. Epigenetics of breast cancer: clinical status of epi-drugs and phytochemicals. *Adv Exp Med Biol*. 2019;1152:293–310. https://doi.org/10.1007/978-3-030-20301-6_16. Review. PubMed PMID: 31456191.
54. Carlos-Reyes Á, López-González JS, Meneses-Flores M, Gallardo-Rincón D, Ruíz-García E, et al. Dietary compounds as epigenetic modulating agents in cancer. *Front Genet*. 2019 Mar 1;10:79. https://doi.org/10.3389/fgene.2019.00079. eCollection 2019. Review. PubMed PMID: 30881375; PubMed Central PMCID: PMC6406035.
55. Mishra S, Verma SS, Rai V, Awasthee N, Chava S, et al. Long non-coding RNAs are emerging targets of phytochemicals for cancer and other chronic diseases. *Cell Mol Life Sci*. 2019 May;76(10):1947–1966. https://doi.org/10.1007/s00018-019-03053-0. Epub 2019 Mar 16. Review. PubMed PMID: 30879091.
56. Howells LM, Berry DP, Elliott PJ, Jacobson EW, Hoffmann E, et al. Phase I randomized, double-blind pilot study of micronized resveratrol (SRT501) in patients with hepatic metastases-safety, pharmacokinetics, and pharmacodynamics. *Canc Prev Res*. 2011 Sep;4(9):1419–1425. https://doi.org/10.1158/1940-6207.CAPR-11-0148. Epub 2011 Jun 16. PubMed PMID: 21680702; PubMed Central PMCID: PMC3173869.
57. Ornelas A, McCullough CR, Lu Z, et al. Induction of autophagy by ARHI (DIRAS3) alters fundamental metabolic pathways in ovarian cancer models. *BMC Canc*. 2016 Oct 26;16(1):824. PubMed PMID: 27784287; PubMed Central PMCID: PMC5080741.
58. Zhang XY, Zhang M, Cong Q, Zhang MX, Zhang MY, et al. Hexokinase 2 confers resistance to cisplatin in ovarian cancer cells by enhancing cisplatin-induced autophagy. *Int J Biochem Cell Biol*. 2018 Feb;95:9–16. https://doi.org/10.1016/j.biocel.2017.12.010. Epub 2017 Dec 13. PubMed PMID: 29247711.
59. Cottart CH, Nivet-Antoine V, Laguillier-Morizot C, Beaudeux JL. Resveratrol bioavailability and toxicity in humans. *Mol Nutr Food Res*. 2010 Jan;54(1):7–16. https://doi.org/10.1002/mnfr.200900437. Review. PubMed PMID: 20013887.
60. Mukherjee S, Dudley JI, Das DK. Dose-dependency of resveratrol in providing health benefits. *Dose Response*. 2010 Mar 18;8(4):478–500. https://doi.org/10.2203/dose-response.09-015.
61. Ramírez-Garza SL, Laveriano-Santos EP, Marhuenda-Muñoz M, et al. Health effects of resveratrol: results from human intervention trials. pii: E1892 *Nutrients*. 2018 Dec 3;10(12). https://doi.org/10.3390/nu10121892. Review. PubMed PMID: 30513922; PubMed Central PMCID: PMC6317057.
62. Honari M, Shafabakhsh R, Reiter RJ, Mirzaei H, Asemi Z. Resveratrol is a promising agent for colorectal cancer prevention and treatment: focus on molecular mechanisms. *Canc Cell Int*. 2019 Jul 15;19:180. https://doi.org/10.1186/s12935-019-0906-y. eCollection 2019. Review. PubMed PMID: 31341423; PubMed Central PMCID: PMC6631492.
63. Ko JH, Sethi G, Um JY, et al. The role of resveratrol in cancer therapy. pii: E2589 *Int J Mol Sci*. 2017 Dec 1;18(12). https://doi.org/10.3390/ijms18122589. Review. PubMed PMID: 29194365; PubMed Central PMCID: PMC5751192.