Function and regulation of interleukin-10 in breast cancer

Samed Ahmed Al-Ezzi Al-Ameri ^{a, b}; Hui Zhao ^{a, b}; Li Yali ^{a, b}; Dong Nana ^{a, b}; Abakundana Nsenga Ariston Gabriel ^{a, b}; Umwali Yvette ^{b, c}; Mao Haiting* ^{a, b}.

^a School of Medicine, Shandong University, 44 Wenhua, West Road, Jinan 250012, Shandong, People's Republic of China.

^b Department of Clinical Laboratory, The Second Hospital, Cheeloo College of Medicine, Shandong University, 250033, Jinan, Shandong Province, People's Republic of China.

^c Department of Clinical Laboratory, Qilu Hospital, Cheeloo College of Medicine, Shandong University, 250012, Jinan, Shandong Province, People's Republic of China.

Abstract

Breast Cancer (BC) is the most common cancer in women and the second cause of death in females due to cancers. Most genetic studies point to a significant relationship between Interleukin 10 (IL-10) and BC. IL-10 is strongly expressed in tissues of BC and negatively correlated with the prognosis of several tumors, including breast cancer. In breast cancer cells, the down-regulation of miRNA-141 inhibits IL-10 and contributes to an up-regulation of COX-2, PGE-2, and TNF- α expression. Long non-coding RNR SNHG1 has been increased in CD4 + TIL cells in patients with breast cancer, whereas siRNA-SNHG1 can decrease the expression of Foxp3 and IL-10. Overexpression of IL-10 failed to manage immunogenic cancer. And the inhibition of IL-10R α improved the therapeutic benefit of chemotherapy in the breast cancer model. The mechanisms of IL-10 in breast cancer are controversial. Interleukin-10 is documented to demonstrate both anti- and pro-tumor acts. IL-10 is strongly expressed in tissues of BC, which has a negative correlation with breast cancer prognosis and tumor marker. Besides, IL10 levels in serum are elevated for patients with BC than normal controls people, which also correlates with poorer outcomes. IL-10 stimulated cancer cell replication and metastasis. IL10 is currently under study as a potential therapeutic targeting inflammatory disease as well as cancer. In conclusion, IL-10 seems to be the future diagnostic biomarker and therapy target of breast cancer. Though lncRNA seems to be a significant research spot, very little research in lncRNA and IL-10 is found. Consequently, in future IL-10 research topics, new studies related to lncRNA could occur.

Keywords

Breast Cancer, Interleukin-10, miRNA, lncRNA

*Corresponding author: Mao Haiting

Department of Clinical Laboratory, The Second Hospital,
Cheeloo College of Medicine, Shandong University, 250033,
Jinan, Shandong Province, People's Republic of China.
Email: maohaiting@sdu.edu.cn

Open Access: This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by-sa/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.

Please cite this article as: Al-Ameri SAA, Zhao H, Yali L, Nana D, Gabriel ANA, Yvette U, Haiting M. Function and regulation of interleukin-10 in breast cancer. *Annals Res* 2020; 3:162-183.

List of Abbreviations**BC**= Breast cancer**IL-10**= Interleukin-10**TGF- β** = Transforming growth factor-beta**NK**= Natural killer cells**DC**= Dendritic cells**HR**= Hormone receptor**HER**= Human epidermal growth factor receptor**ER**= Estrogen receptor**PR**= Progesterone receptor**CSIF**= Cytokine synthesis inhibitory factor**JAK1**= Janus kinase-1**TYK2**= Tyrosine kinase-2**STAT-3**= Signal transmitter and enhancer of transcription-3**SOCS3**= Suppressor of Cytokine Signaling 3**NDRG2**= N-Myc downstream-regulated Gene 2 Protein**N-Myc**= Proto-oncogene protein**TAMs**= Tumor-associated macrophages**BCL-2**= Apoptosis Regulator gene**mRNA**= Messenger Ribonucleic acid**VEGF**= Vascular Endothelial Growth Factor**MMP-9**= Matrix metalloproteinase 9**CLA**= Conjugated linoleic acid**GPER**= G-protein coupled estrogen receptor.

of death among women with cancers [1]. The BC is heterogeneous, more than twenty different histopathological subtypes are identified [2]. The etiology of breast cancer has yet to be identified, but this multifactorial disease has frequently correlated with lifestyle, genetic and environmental factors [3]. BC can be divided into five major molecular groups based on estrogen (ER+), progesterone (PR+), and human epidermal growth factor receptor 2 (HER 2) status. Moreover, five subtypes of molecular BC defined by profiling of gene expression and immunohistochemistry (IHC) include: (1) Luminal A expressing ER+/PR+, of a low-grade and low-Ki67 index (a proliferative marker); (2) Luminal B, ER+/PR+ of higher grade and proliferative index; (3) HER2+ with or without ER; (4) HER2 being HER2+ by IHC and either ER+ve or ER-ve; and (5) “basal-like” or triple-negative, not expressing either of the three receptors [4]. These are characteristic features of cancer development. It is important to identify the dialog between cancer and the host immune system to deliver new therapeutic options.

Cancer cells develop immune tolerance by turning immunity toward T helper cells 2 (TH2) phenotype and suppressing the innate and adaptive immune system by encouraging the expansion and function of the phenotype suppressor. On a systemic scale, neoplastic cells resist immune recognition through decreasing antigen presentation and secreting immunosuppressive cytokines [5]. Cancer cells that have effectively eluded the immune system continue to grow, ultimately resulting in clonal expansion of resistant variants [6]. These are characteristic features of cancer development. It is important to identify the dialog between cancer and the host immune system to deliver new therapeutic options. Accumulating studies have suggested that the disorders of the immune response are involved in BC initiation and development [7]. Some cytokines like TNF- α , IL-10, IL-2, IL-8, and IL-6 are essential components of biological situations associated with breast carcinogenesis [8, 9].

INTRODUCTION

Breast cancer (BC) is the most common cancer diagnosed in women and the second leading cause

The interleukin-10 (IL-10) family of cytokines consists of nine members, IL-10; IL-20 subfamily members IL-19, IL-20, IL-22, IL-24, and IL-26; and distantly related cytokines IL-28A, IL-28B, and IL-29, which are more generally classified as Type III interferons (IFNs) [10]. Interleukin 10 (IL-10) was reported in 1989 by Mosmann and colleagues as an activity produced by murine type 2 helper T cells (TH2) that inhibited the production of cytokines by type 1 helper T cells and was first described as cytokine synthesis inhibitory factor (CSIF) [11]. Mature IL-10 consists of 160 amino acids, which form a monomeric structure with around 18kDa molecular weight [7]. As an anti-inflammatory cytokine, IL-10 is primarily secreted from monocytes, T lymphocytes, B lymphocytes (basically Breg cells), macrophages, natural killer cells, and dendritic cells [12], and even by tumor tissues [13]. IL-10 suppresses the expression of several genes, including pro-inflammatory cytokines, chemokines, and chemokine receptors [12]. Concerning its suppressive activities on T lymphocytes, IL-10 helps stimulate the survival, differentiation, and

proliferation of B lymphocytes. It promotes the synthesis of IgG4 by plasma cells [14–16]. Some study has reported that the upregulation of IL-10 is related to tumorigenesis, autoimmunity, and resistance of transplantation [17]. Interleukin-10, which plays a significant coordinated role in breast carcinogenesis, is an anti-inflammatory cytokine that regulates the immune system response [18] and inhibits the pro-inflammatory actions of antigen-presenting cells (APCs) by expression of antagonizing costimulatory molecules [19]. Nevertheless, the mechanisms of IL-10 in breast cancer are controversial, and the objective biological function of IL-10 included in the pathophysiology of BC is not yet well understood [20]. Here we review the role of IL-10 in BC and epigenetic of IL10 and correlation with miRNA and lncRNA in the different diseases.

The IL-10 Genes and its epigenetic regulation

The genes of Human IL-10 (hIL-10) and Mouse IL-10 (mIL-10) are carried on chromosomes one by five exons [21, 22], Table 1 shows the properties of Gene, mRNA, and protein of human

Table. 1: Gene, mRNA, and protein properties of human IL-10 [129]:

Chromosomal localization	1q32
Genomic NCBI annotation	NT_167186.1
Gene length	4892
Number of exons	5
Number of protein-coding exons	5
mRNA NCBI annotation	NM_000572.2
mRNA product length (b)	1629
mRNA open reading length (b)	537
Protein NCBI annotation	NP_000563.1
Protein product length (aa)	178
Predicted signal peptide length (aa)	18
Predicted mature protein length (aa)	160
Tertiary structure	Dimer

Diagram 1. Epigenetic modifications that influence IL-10 expression in multiple cells. In human peripheral blood mononuclear cells, the IL-10 promoter has transcription and hypomethylation activity and is silenced in epithelia due to hypermethylation in the epithelial cells. B cells treated with a histone deacetylase inhibitor could raise the expression of IL-10. In T cells, enhanced STAT3 activation will lead to increased recruitment of regulatory regions and competitive replacement of STAT5, promoting IL-10 expression. Overexpression of miRNA-146a in bloodstream mononuclear cells enhances the expression of IL-10. Up-regulation of miRNA-19a in B cells decreases IL-10 expression, and the similar up-regulation of miRNA-98 can also inhibit IL-10 expression, and inadequate expression of miRNA-21-5p is one of the causes for reduced IL-10 expression in B cells.

IL-10. IL-10 can be expressed by different cells in response to an activation stimulus. The expression of IL-10 is controlled explicitly by other cell types, such as T lymphocytes, macrophages, and monocytes [22]. Most genetic studies point to a significant relationship between IL-10 and BC [7]. The transcription of IL-10 can be regulated by either the Sp1 and Sp3 transcription agents [1], expressed in several different cell types [23]. Epigenetic mechanisms regulate the transcription of the IL-10 gene by affecting the status of chromatin [24]. Epigenetic regulation of IL-10 is performed by different mechanisms. The first mechanism is Chromatin remodeling in IL-10 locus by ATP-dependent chromatin remodeling complexes. The ATP-

dependent chromatin remodelers regulate how tightly DNA is stocked around nucleosomes and how the transcription machinery is accessible to the gene. Second is the regulation of IL-10 by histone modifications (Histone acetylation enhances chromatin accessibility and stimulates transcription and Histone methylation). The third one is the regulation of IL-10 by DNA methylation, mediates gene inaccessibility, and suppress transcription; the last mechanism is regulation of IL-10 by 3D chromatin loops [24]. [Diagram 1](#) shows summary of the epigenetic of IL10.

Figure 1: Interleukin-10 receptor structure consisting of two IL-10R1 and two IL-10R2. Binding IL-10 to IL-10R1 results in the phosphorylation of JAK1 (Janus kinase 1) and TyK2 (Tyrosine kinase 2) which enhance STAT-3 (Signal transducer and activator of transcription 3) phosphorylation and translocate to the nucleus and stimulate the transcription of anti-apoptotic and cell cycle differentiation genes.

Signaling pathways of IL-10

Interleukin-10 signals via a tetrameric transmembrane receptor structure consisting of

two IL-10R1 (also defined as IL-10RA) and two IL-10R2 (also called IL-10RB) proteins [18]. These receptors are classified as class II receptors family, each containing one intracellular, transmembrane, and extracellular domain [18]. Both receptor complexes are formed consecutively; IL-10RA has a stronger affinity to the IL-10 than IL-10RB. Binding IL-10 to the extracellular domain of IL-10R1 results in the phosphorylation of JAK1 (Janus kinase-1) and TYK2 (tyrosine kinase-2), while Signal transmitter and enhancer of transcription-3 (STAT-3) is phosphorylated by JAK1 [25]. Once phosphorylated, STAT-3 is translocated to the nucleus and stimulates the transcription of genes related to anti-apoptosis and cell cycle-progression genes (SMAD1, SMAD5, SMAD9, NFkB1, SOCS3, MAFB, and MAPK1) [26] see Figure 1. [18]. Besides, the expression of IL-10 is

controlled by the stability of STAT-3 and the suppression of SOCS3 (suppressor of cytokine signaling-3); the silencing of STAT-3 reduces the expression of IL-10 [7]. New studies have shown that N-Myc downstream-regulated Gene 2 Protein (NDRG2) inhibits STAT-3 via induction of SOCS3 and inhibits IL-10 production [27]. A relatively large volume of IL-10 is produced by tumor-associated macrophages (TAMs), which is shown to be responsible for the resistance of drugs in BC [19]. The mechanism of TAMs-modulated drug resistance may be related to increased expression of BCL-2 and up-regulation of STAT3 signaling in cancer cells; however, the suppression of TAMs-induced IL-10 by neutralizing antibody leads to reduced expression of BCL-2 and activation of STAT3, and subsequently increased sensitivity of breast cancer cells to drug therapy [14]. TAMs may induce drug resistance through the IL-10/STAT3/bcl-2 signaling pathway [37].

Expression and role of IL-10 in breast cancer:

Previous studies have already shown that IL-10 is strongly expressed in tissues of BC and negatively correlated with the prognosis of several tumors, including breast cancer [29–31]. High plasma levels of IL-10 and elevated expression of IL-10 in BC indicates a poor prognosis. However, the level of IL-10 is not associated with the grade of cancer [30, 32]. Moreover, there are no noticeable differences in the level of IL-10 in the serum of patients with BC and suspected breast mass with negative breast biopsy [33]. Normal breast tissue does not express IL-10 protein, but IL-10 is significantly increased in breast cancer tissue, especially in those from negative PR and ER cancer patients [34]. The mRNA levels of IL-10 in BC increased significantly compared with normal breast tissue [30, 35].

IL-10 expression in animal models and human tumors is associated with immune responses to cancer [19]. The role of IL-10 in BC is still not fully understood. IL-10 is documented to have both anti-and pro-tumor activities in different studies. On the one hand, studies demonstrate a strong association between the serum IL-10 level and BC [36], and IL-10 is a bad breast cancer prognosticator [29]. IL-10 is also proved to promote tumor development by influencing both tumor cells and immune cells. IL-10 stimulates replication and metastasis of the cancer cells [22]. It inhibits the proliferation and function of T lymphocytes [29], thus decreases the immune response to the tumors [37,38]. Another immunosuppression mechanism is mediated by cancer-derived factors that may cause DC dysfunction and inhibit immune responses [7]. Simultaneously, IL-10 has an inhibitory effect on DC function in cancer and is an effective suppressor of DCs, which may be associated with the decrease of anti-tumor immunity [37]. On the other hand, IL-10 expression was related to disease-free survival [39], and lower expression of IL-10 leads to worse survival outcomes [39] [40]. Some studies have mentioned that the anti-cancer function of IL-10 is likely related to stimulating the activity of a natural killer cell [40].

In contrast, others have shown that the anti-cancer effect of IL-10 is based on the function of CD4+ or CD8+ T lymphocytes [41]. Alternatively, IL-10 promotes pro-inflammatory effects by increasing the secretion of IP-10 and IFN- γ [42].

Interleukin-10 as apoptosis regulator

Cytokines are small proteins or glycoproteins that play a significant role in cell-to-cell communication via paracrine or autocrine signaling, with 160 amino acids with less than 18 kDa molecular weight [7]. Cytokines are secreted by white blood cells that monitor and control the responses of the immune system by enhancing or suppressing cell activities like proliferation, differentiating, and apoptosis [7], inflammatory regulation, and hematopoiesis [43]. The IL-10 expression indicates a relationship with apoptosis-related cancer markers, i.e., negative correlation to p53 and positive correlation to the Bcl-2 protein family [29]. Another study demonstrates no correlation between IL-10 and apoptotic markers in BC. However, it displayed that the presence of IL-10 and the increasing concentration of Bcl-2 in tumors may indicate breast cancer aggressiveness [29]. The same study also revealed that IL-10 level was highly positively correlated with Bax expression, even though Bax was a part of the Bcl-2 family, a pro-apoptotic influence [29, 44]. Besides, the effect of IL-10 on cell survivability also increased IL-6 level, which promoted cell proliferation through up-regulating Bcl-2 expression, thereby affecting the balance of apoptosis/proliferation towards neoplastic cell division [45]. Moreover, higher expression of IL-6 and its receptors might promote cell proliferation in breast cancers[45].

Factors that regulate IL-10

IgA can stimulate IL-10 expression in monocytes [46, 47]. TGF- β and IL-6 enhance IL-10 and IL-17 in physiological state, and IL -10 also helps to control the actions of IL-17 [48]. IL-27 and TGF- β stimulate both IL-10 production and producing cells of IL-10[49, 50]. TNF- α and IL-1 α are reported to activate IL-10 expression [46] weakly.

Many immunomodulators have been confirmed to block IL-10. The immunosuppressive agent cyclosporin inhibits the synthesis of IL-10 [51]. The immunomodulator ammonium trichloro (dioxoethylene-o,o') tellurite AS101, suppresses IL-10 signaling [52]. 14-prostaglandin J2 (15d-PGJ2), 15-Deoxy-Delta12 suppress IL-10 mediated activation of STAT3 [53]. Up to now, factors other than immunomodulators have been recognized to suppress the production of IL-10. For example, Rituximab suppresses IL-10 and promotes apoptosis of lymphoma cells [54]. CLA (conjugated linoleic acid) has been shown to stimulate IL-10, which has, in effect, an immunostimulatory influence on PBMCs through the up-regulation production of TNF- α . However, IL-10 induces downregulation of TNF- α synthesis and maintains an anti-inflammatory act on LPS-induced PBMCs [55]. A further study also finds that G-1, GPER (G-protein coupled estrogen receptor) agonist, and thalidomide may induce the expression IL-10, which acts specifically on Th17 or hybrid T lymphocytes [56]. Transcription factors like cMaf maintain IL-10 expression and T-effector maturation as well [57].

Role of miRNAs in IL-10 signaling regulated breast cancer

In breast cancer cells, the down-regulation of miRNA-141 inhibits IL-10 and contributes to an up-regulation of COX-2, PGE-2, and TNF- α expression [58]. The miRNAs are a group of non-coding RNA molecules with a length of 18 to 24 nucleotides [59]. In breast cancer, miR-10 families have been shown to participate in both development and metastasis through miR-10a and miR-10b [60]. In metastatic breast cancer cells, miR-10b is highly over-expressed and induces cell migration and invasion by targeting the HOXD10 gene in the murine xenograft model of breast cancer [61]. miR-21 is one of the major miRNAs associated with breast cancer cell migration and invasion and thus leads to tumor progression and metastasis [62, 63]. The miR-21

expression is negatively associated with breast cancer expression of PTEN and is also associated with advanced stage and metastasis, and poor survival [64, 65]. In breast cancer, transforming growth factor- β (TGF- β) was observed to upregulate miR-21 expression. Expression of elevated miR-21 is associated with the severity of disease status, including high tumor grade, negative receptor hormone status, and ductal carcinoma. miR-17~92 cluster, including miR-18b, miR-19b, miR-20a, miR-92, miR-93 and miR-106. However, in invasive MDA-MB-231 breast cancer cells, miR-17-5p was shown to be highly expressed but not in non-invasive MCF-7 breast cancer cells. Ectopic expression in MCF-7 cells of this miRNA will lead to more invasive and migratory phenotypes by targeting the pathway of HBP1/ β -catenin. Likewise, in vitro migration and invasion of MDA-MB-231 cells is suppressed by downregulation of miR-17-5p [66]. MiR-205 can also target Her3 and interact with the survival pathway of PI3K/Akt in addition to enhancing responsiveness to tyrosine kinase inhibitor drugs such as gefitinib and lapatinib [66]. p53-induced miR-205 can act as a tumor suppressor in triple-negative breast cancer, and re-expression can significantly decrease cell proliferation, cell cycle progression, and clonogenic potential in vitro and inhibit tumor growth in vivo. Like miR-205, miR-145 is substantially underexpressed in breast cancer compared to normal breast tissue. Due to the early manifestation of altered miR-145 expression in breast cancer, this miRNA may have clinical diagnostic potential as a novel biomarker for early detection of cancer [66].

IL-10 expression is inversely associated with miRNA-98-5p in peripheral blood mononuclear cells [67]. In peripheral blood mononuclear cells, overexpression of miRNA-146a enhanced IL-10 expression [68]. Elevated IL-10 release following a hip fracture can lead to significant systemic inflammatory response and acute lung injury (ALI) following hip fracture, and increased IL-10 release is significantly correlated with the up-

regulation of miR-146a and the down-regulation of miRNA-150 [69]. Besides, miRNA-10a is positively associated with serum IL-10 levels and plays a significant role in atherosclerotic inflammation [70]. It has been demonstrated that miRNA-155 plays a role in immune activation and inflammatory responses and is suppressed by IL-10 [71, 72]. Likewise, IL-10 was found to inhibit TLR4-induced miRNA-155 expression [73]. Antagonism between IL-10 and miRNA-155 is required to balance host defense and immune activation in vivo, and this balance is especially important in inhibiting Lyme myocarditis [74]. Besides, TNF- α , IFN- γ , and IL-4 suppress IL-10 expression in B cells by up-regulating miRNA-19a expression [75, 76]. Some studies have shown that the levels of miRNA-19a in B-cells of sensitized mice were higher for inducing intestinal allergy-related inflammation, which was inhibiting the expression of IL-10 in B-cells [77]. Further research has shown that the IL-10 expression was positively associated with the miRNA-21-5p expression in B cells of allergic purpura (HSP) patients [78]. In the placenta in patients with preeclampsia (PE), the expression of miRNA-210 was substantially increased, whereas the IL-10 levels were considerably lower than those of normal pregnant women [79]. The relative expression of rno-miRNA-211 was up-regulated in BALF derived macrophages from ARDS rats, followed by a decrease in secretory IL-10 [80]. Increased expression of miRNA-223 in T cells in patients with RA contributes to a decrease in insulin-like growth factor-1 induced synthesis of IL-10, leading to an imbalance between pro-inflammatory cytokines and anti-inflammatory cytokines [81]. The rno-miRNA-30b-5p is down-regulated in the spleen, lymph nodes, and eye tissues of experimental autoimmune uveitis rats, whereas down-regulation of rno-miRNA-30b-5p may be regulated by IL-10 and TLR4 may affect the proportion of positive IL-10 cells in the cell population, thus inhibiting the formation of uveitis. The expression of IL-10 and TLR4 genes and proteins can be decreased by rno-miRNA-

30b-5p mimics, therefore influencing the pathogenesis of uveitis. Thus, rno-miRNA-30b-5p may be a new therapeutic target for uveitis [82]. Researches have also shown that miRNA-410 is a major regulator of SLE pathogenesis by targeting STAT3 to control IL-10 expression [83]. The down-regulation of miRNA-98 was followed by the up-regulation of IL-10 in tumor-associated macrophages of hepatocellular carcinoma (HCC), indicating that IL-10 is a direct target for miRNA-98 [84]. The administration of miRNA-98 liposomes could significantly decrease the number of B10 cells in tumor-bearing mice and suppress the growth of experimental tumors, showing that IL-10-producing B cells play a significant role in the effect of tumor tolerance, while miRNA-98 upregulation can inhibit IL-10 expression in B cells, leading to suppress the body's lung cancer tolerance [85]. At the same time, miRNA-98 also plays a significant role in myocarditis by suppressing IL-10 expression in cardiac B cells [86]. In peripheral B cells of airway-allergy patients, miRNA-98 is associated with the transcriptional regulation of interleukin-10 [87]. Besides, miRNA-98 inhibition reverses the IL-10 expression capability in B cells [88]. Furthermore, post-transcriptional regulation of the immunosuppressive cytokines IL-10 and TGF- β can include miR-27b-3p and miR-330-3p [89]. miRNA-21 prevents the IL-10 + Breg cell differentiation and induces autoimmunity by targeting the 3' untranslated IL-10 mRNA region [90]. Other research have shown that histone acetyltransferase p300 is included in the IL-4 / miRNA-98 / IL-10 axis in peripheral blood B cells in patients with airway hypersensitivity. Thus, p300 inhibitors have a therapeutic potential in the treatment of allergic diseases [87]. The IL-10 negatively regulates miRNA-7025-5p, which regulates osteoblast differentiation. In vivo studies have shown that pre-injection of IL-10 results in increased bone strength while injecting of miRNA-7025-5p slows healing of fractures. For this reason, IL-10 is a hopeful therapeutic strategy to enhance fracture healing [91]. In nasal polyps (NPs), miRNA-4492 was down-regulated,

Table. 2. Functions of lncRNAs in Breast Cancer.

lncRNA	Functions	Reference
Oncogene		
ARNILA	Invasion and metastasis	[130]
Lnc015192	Migration, invasion, and EMT	[131]
EPIC1	Cell cycle progression	[132]
GACAT3	Proliferation	[133]
ITGB2-AS1	Migration and Invasion	[134]
MIR100HG	Proliferation	[135]
CHET1	Proliferation, invasion, and migration	[136]
NNT-AS1	Progression	[137]
P10247	Metastasis	[138]
EZR-AS1	Tumor growth and metastasis	[139]
TUG1	Apoptosis, proliferation, and metastasis	[140, 141]
PRLB	Proliferation and metastasis	[142]
PVT1	Proliferation	[143]
LNC00511	Proliferation and invasion	[144]
ATB	Epithelial–mesenchymal transition (EMT)	[145]
NEAT1	Metastasis	[146]
AC026904.1	Metastasis	[147]
UCA1	Metastasis	[147]
Suppressor		
ANCR	Invasion and metastasis	[148]
MEG3	Proliferation and EMT	[149]
PTENP1	Proliferation and migration	[150]
MAGI2-AS3	Cell growth	[151]
XIST	Brain metastasis and cell growth	[152, 153]
PDCD4-AS1	Progression	[154]
NKILA	EMT	[155]

whereas IL-10 in NPs was up-regulated, and the two were inversely related. This indicates that a primary mechanism for chronic sinusitis with NPs could be miRNA-4492 / IL-10 axis participation in the Jak / STAT signaling pathway [92]. In patients with advanced liver cancer, combined treatment with curcumin, piperine, and taurine for 3 consecutive months could minimize serum IL-10 and miRNA-21 levels, and the overall survival rate was worse in patients with elevated baseline IL-10 and miRNA-21 levels. Therefore, variations in serum IL-10 and miRNA-21 expressions may be prognostic biomarkers in the treatment of HCC [93]. At last, miRNA-27a stimulates the antibacterial activity of macrophages and suppresses the expression of

IL-10, further regulating the innate immune response [94].

Roles of lncRNA in IL-10 signaling-regulated breast cancer

Cellular signaling plays an important role in different cellular processes, including breast cancer metastasis, and some lncRNAs are mainly associated with certain signaling pathways that are also essential to a complex cascade of breast cancer metastasis and metastasis-related gene expression. Emerging research indicates that signaling lncRNAs can serve as regulators for different pathways, such as TGF- β , NF- κ b, STAT3, Hippo, EGF, Wnt, PI3K/AKT, p53. TGF- β signaling pathway, it was found that lncRNA ANCR involved in the TGF- β signal pathway by inhibition of RUNX2 expression,

further inhibition of breast cancer cell invasion and metastasis [95]. NF- κ B signaling pathway Several lncRNAs play key regulatory functions in the NF- κ B pathway. LncRNA NKILA was first discovered to be upregulated in breast cancer by inflammatory cytokines TNF- α via the NF- κ B pathway [96]. STAT3 signaling pathway, Research has demonstrated that the STAT3 pathway plays a significant role in the metastasis of breast cancer, and many lncRNAs are involved in this process (e.g., HOTAIR and lnc-BM). In breast cancer cells, lnc-BM increased STAT3-dependent ICAM1 and CCL2 expression, which influenced vascular co-option and brain macrophage recruitment, respectively [97]. The function of lncRNA in breast cancer is summarized in Table 2.

LncRNA SNHG1 has been increased in CD4 + TIL cells in patients with breast cancer, whereas siRNA-SNHG1 can decrease the expression of Foxp3 and IL-10 [98]. LncRNA is described as a long RNA transcript of more than 200 nucleotides that cannot be encoded into a protein [99]. Recently, increasing numbers of studies have demonstrated that lncRNA plays a significant role in cancer. In non-small cell lung cancer (NSCLC), lncRNA actin filament-associated protein 1 antisense RNA 1 (AFAP1-AS1) was strongly expressed, followed by elevated IL-10 and interferon (IFN)- γ expression levels [100]. LncRNA cox-2 siRNA can raise the expression concentrations of IL-10, Arg-1, and Fizz-1 in M2 macrophages [101]. The suppression of lnc-LINC00473 can decrease the expression of IL-10 in the B-cell [102]. Besides, the overexpression of lnc-MALAT1 can raise IL-10 expression, thereby suppressing neuronal apoptosis and enhancing axon development [103]. High expression of lncRNA-MALAT1 can reduce IL-10 expression, thus up-regulating neuronal apoptosis and aggravating brain injury in rats with cerebral infarction [104]. LncRNA production capture specific transcript 5 (GAS5) was down-regulated in colorectal cancer (CRC) and corresponding functional experiments revealed that knockout of GAS5 stimulated CRC cell proliferation and

colony production, while knockdown of GAS5 increased IL-10 expression and suppressed CRC cell proliferation and colony development [105]. Though lncRNA seems to be a significant research spot, very little research in lncRNA and IL-10 is found. Consequently, in future IL-10 research topics, new studies related to lncRNA could occur.

Diseases associated with IL-10 correlated with miRNA expression: See Table 3.

IL-10 used as a treatment and immunotherapy for cancer

Recombinant human IL-10 (Tenovil) has been found to have a potential role in preventing inflammation [106]. Furthermore, two kinds of diseases are related to the largest number of data on the practical use of IL-10 therapy: Crohn's disease and psoriasis [107]. IL-10 is also studied in patients with rheumatoid arthritis, hepatitis C, HIV infection, and inhibition of cytokine releases in organ transplantation [108–110]. Pretreatment with IL-10 altogether prevents arthritis and markedly reduces intestinal inflammation of the peptidoglycan-polysaccharide granulomatous enterocolitis model [111, 112]. Tenovil has been given subcutaneously for 12 weeks following Crohn's disease (CD) ilecolectomy is safe and well-tolerated [106]. Moreover, there is no evidence of renal or hepatotoxicity, no thrombocytopenia observed, and no clinical concern of anemia during treatment Crohn's disease patient with Tenovil [106]. IL-10 almost completely prevents chronic arthritis, usually by lower regulation of IL-1, IL-6, or TNF- α , as shown in the liver [111]. Another IL-10-related therapeutic agent F8-IL-10 (Dekavil), is a complete human immunocytokine consisting of an antibody fragment F8, particularly to the extra domain A of fibronectin (EDA-FN), fused to the anti-inflammatory cytokine IL-10 [113]. Dekavil is currently under study as a potential therapeutic approach targeting inflamed rheumatoid arthritis (RA) tissues [113].

Table. 3: The table shows diseases associated with IL-10 and correlation with miRNA

Disease	miRNA	miRNA expression	IL-10 level	References
Breast cancer	miRNA-141	DOWN	DOWN	[58]
Elderly hip fracture	MiRNA-146a/150	UP/DOWN	UP	[69]
coronary artery disease (CAD)	MiRNA-10a	DOWN	DOWN	[70]
Lyme carditis	miRNA-155	UP	DOWN	[74]
Allergen-related inflammation	miRNA-19a	UP	DOWN	[77]
Preeclampsia	miRNA-210	UP	DOWN	[79]
Henoch-Schonlein purpura (HSP)	miRNA-21-5p	DOWN	DOWN	[78]
acute respiratory distress syndrome (ARDS)	rno-miRNA-211	UP	DOWN	[80]
rheumatoid arthritis (RA)	miRNA-223	UP	DOWN	[81]
Uveitis	rno-miRNA-30b-5p	DOWN	UP	[82]
Systemic lupus erythematosus (SLE)	miRNA-98	DOWN	UP	[83]
hepatocellular carcinoma (HCC)	miRNA-98	DOWN	UP	[84]
Lung cancer	miRNA-98	UP	DOWN	[85]
Myocarditis	miRNA-98	UP	DOWN	[86]
Allergic diseases	miRNA-98	UP	DOWN	[87]
Atherosclerosis	miRNA-98	UP	DOWN	[88]

The immunosuppressive effect of IL-10 led to the general view that its presence through cancer would promote the immune escape of cancer [114]. This hypothesis is confirmed in several animal models. Overexpression of IL-10 failed to manage immunogenic cancer [115], And the inhibition of IL-10R α improved the therapeutic benefit of chemotherapy in the breast cancer model [116], And for other transplantable cancers in the context of CpG immunostimulatory oligonucleotide by reversal of tumor-induced DC dysfunction [117]. IL-10 deficiency also confers resistance to UV-induced skin carcinogenesis [118]. The presence of IL-10 in the tumor microenvironment of the different cancer was identified in patients and was overall associated with poor prognosis [119]. However, early

evidence indicates an unexpected protective role for IL-10 in tumors. Both IL-10 overexpression and IL-10 regulation have been reported to be associated with cancer shrinkage and rejection [120–122]. More recently, pegylated IL-10 application to mouse models of breast cancer or squamous cell carcinoma has provided clear preclinical indications of the effectiveness of IL-10 as cancer immunotherapy [123]. Mechanically, IL-10 enhanced CD8 T cell infiltration in tissue, stimulated IFN- γ production, and favored effective T cell memory responses [123, 124]. As a result of these researches, a pegylated human IL-10 was developed [125] and has been shown to induce CD8 T cell immunity in patients with solid cancers [126]. Therefore, in some kinds of cancer, IL-10 may be useful as immunotherapy

by enhancing the activity of CD8 T antitumor cells [10, 127]. However, a recent study has demonstrated that tumor-infiltration of regulatory T cells by their expressions IL-10 and IL-35 can lead to the exhaustion of intratumor CD8 T cells through the up-regulation of the transcription factor Blimp-1 [128]. The discrepancies between these different studies can be explained by several factors, including IL-10 targeted cells in different tumors (for example, myeloid versus T cells) or variations in the response of T cells to IL-10 at different effector phases. Therefore, to better target cancer therapy, it is important to evaluate the context in which IL-10 can provide a protective or harmful role in tumor treatment.

CONCLUSION

As an anti-inflammatory interleukin, the actions of IL-10 in breast cancer are not fully understood and are controversial. IL-10 is a highly potent cytokine formed by a wide range of cells. It controls cell growth and differentiation, involves inflammatory and immune reactions, and is currently identified as an inflammation and immunosuppressive factor. It is also an effective means of treating associated diseases as well. IL-10 is demonstrated to have both anti- and pro-tumor activities, and no more studies are conducted to clarify the correlation between IL-10 and breast cancer. Here we give a review and suggest more studies to discover the mysterious puzzle between IL-10 and BC. Also, the relationship of IL-10 with various types of BC and other biomarkers of BC. Together, IL-10 seems to be the future diagnostic biomarker and therapy target of breast cancer.

Declarations

Funding: Not Applicable.

Conflicts of interest: The authors declare that they have no conflict of interest.

Ethical Approval: Not applicable

Availability of data and material: Not Applicable.

Code availability: Not Applicable.

Authors' contributions: SAAA designed and drafted the manuscript. HZ, LY, DN, ANAG, UY, and MH discussed and revised the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. ACS. American Cancer Society. Breast Cancer Facts & Figures 2019-2020. [Internet]. 2019 [cited 2020 Nov 19]. Available from: <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf>
2. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH van de VM. WHO Classification of Tumors of the Breast. [Internet]. IARC Press. 2012 [cited 2020 Oct 23]. p. 13–59. Available from: <https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-The-Breast-2012>
3. Dignam JJ, Mamounas EP. Obesity and breast cancer prognosis: An expanding body of evidence. *Ann Oncol*. 2004;15(6):850–1.
4. Brisken C, Hess K, Jeitziner R. Progesterone and overlooked endocrine pathways in breast cancer pathogenesis. *Endocrinology*. 2015;156(10):3442–50.
5. Vinay DS, Ryan EP, Pawelec G, Talib WH, Stagg J, Elkord E, et al. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Semin Cancer Biol* [Internet]. 2015;35:S185–98. Available from: <http://dx.doi.org/10.1016/j.semcancer.2015.03.004>
6. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: From immunosurveillance to tumor escape. *Nat Immunol*. 2002;3(11):991–8.

7. Hamidullah, Changkija B, Konwar R. Role of interleukin-10 in breast cancer. *Breast Cancer Res Treat.* 2012;133(1):11–21.
8. Rao VSR, Dyer CE, Jameel JKA, Drew PJ, Greenman J. Potential prognostic and therapeutic roles for cytokines in breast cancer (review). *Oncol Rep.* 2006;15(1):179–85.
9. Carpi A, Nicolini A, Antonelli A, Ferrari P, Rossi G. Cytokines in the management of high risk or advanced breast cancer: an update and expectation. *Curr Cancer Drug Targets* [Internet]. 2009 Dec [cited 2019 Nov 6];9(8):888–903. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20025599>
10. Ouyang W, O'Garra A. IL-10 Family Cytokines IL-10 and IL-22: from Basic Science to Clinical Translation. *Immunity* [Internet]. 2019;50(4):871–91. Available from: <https://doi.org/10.1016/j.immuni.2019.03.020>
11. Fiorentino DF, Bond MW, Mosmann TR. Two types of mouse t helper cell: IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. *J Exp Med.* 1989;170(6):2081–95.
12. Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Cramer R, et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β , and TNF- α : Receptors, functions, and roles in diseases. *J Allergy Clin Immunol.* 2016;138(4):984–1010.
13. Chen Q, Daniel V, Maher DW, Hersey P. Production of IL-10 by melanoma cells: Examination of its role in immunosuppression mediated by melanoma. *Int J Cancer.* 1994;56(5):755–60.
14. Akdis CA, Akdis M. Mechanisms of immune tolerance to allergens: Role of IL-10 and Tregs. *J Clin Invest.* 2014;124(11):4678–80.
15. Van De Veen W, Stanic B, Yaman G, Wawrzyniak M, Söllner S, Akdis DG, et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. *J Allergy Clin Immunol.* 2013;131(4):1204–12.
16. Stanic B, Van De Veen W, Wirz OF, Rückert B, Morita H, Söllner S, et al. IL-10-overexpressing B cells regulate innate and adaptive immune responses. *J Allergy Clin Immunol.* 2015;135(3):771–780.e8.
17. Katsikis PD, Chu CQ, Brennan FM, Maini RN, Feldmann M. Immunoregulatory role of interleukin 10 in rheumatoid arthritis. *J Exp Med.* 1994;179(5):1517–27.
18. Acuner-Ozbabacan ES, Engin BH, Guven-Maiorov E, Kuzu G, Muratcioglu S, Baspinar A, et al. The structural network of Interleukin-10 and its implications in inflammation and cancer. *BMC Genomics.* 2014;15(4):1–17.
19. Sheikhpour E, Noorbakhsh P, Foroughi E, Farahnak S, Nasiri R, Neamatzadeh H. A survey on the role of interleukin-10 in breast cancer: A narrative. *Reports Biochem Mol Biol.* 2017;7(1):30–7.
20. Smyth MJ, Cretney E, Kershaw MH, Hayakawa Y. Cytokines in cancer immunity and immunotherapy. *Immunol Rev* [Internet]. 2004 Dec [cited 2019 Nov 7];202:275–93. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15546400>
21. Kim JM, Brannan CI, Copeland NG, Jenkin NA, Tariq A. Structure of the mouse IL-10 gene and chromosomal localization of the mouse and human genes. J M Kim, C I Brannan, N G Copeland, N A Jenkins, T A Khan and K W Moore Why The JI? Submit online. • No Triage! Every submission reviewed by practicing sc. 2019;
22. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin -10 and the Interleukin -10 Receptor. *Annu Rev Immunol.* 2001;19(1):683–765.
23. Tone M, Powell MJ, Tone Y, Thompson SAJ, Waldmann H. IL-10 Gene Expression Is

Controlled by the Transcription Factors Sp1 and Sp3. *J Immunol.* 2000;165(1):286–91.

24. Zhang H, Kuchroo V. Epigenetic and transcriptional mechanisms for the regulation of IL-10. *Semin Immunol* [Internet]. 2019;44(July):101324. Available from: <https://doi.org/10.1016/j.smim.2019.101324>

25. 1471-2164-15-S4-S2 @ www.biomedcentral.com [Internet]. Available from: <http://www.biomedcentral.com/1471-2164/15/S4/S2>

26. Verma R, Balakrishnan L, Sharma K, Khan AA, Advani J, Gowda H, et al. A network map of Interleukin-10 signaling pathway. *J Cell Commun Signal* [Internet]. 2016;10(1):61–7. Available from: <http://dx.doi.org/10.1007/s12079-015-0302-x>

27. Lee EB, Kim A, Kang K, Kim H, Lim J-S. NDRG2-mediated Modulation of SOCS3 and STAT3 Activity Inhibits IL-10 Production. *Immune Netw.* 2010;10(6):219.

28. Yang C, He L, He P, Liu Y, Wang W, He Y, et al. Increased drug resistance in breast cancer by tumor-associated macrophages through IL-10/STAT3/bcl-2 signaling pathway. *Med Oncol.* 2015;32(2).

29. Llanes-Fernández L, Álvarez-Goyanes RI, Arango-Prado M del C, Alcocer-González JM, Mojarrieta JC, Pérez XE, et al. Relationship between IL-10 and tumor markers in breast cancer patients. *Breast.* 2006;15(4):482–9.

30. Liu C, Wang Q, Sun B, Meng X, Li L, Yang L, et al. Low BMI is correlated with increased TGF- β and IL-10 mRNA levels in the peripheral blood of breast cancer patients. *IUBMB Life.* 2018;70(3):237–45.

31. Korobeinikova E, Myrzaliyeva D, Ugenskiene R, Raulinaityte D, Gedminaite J, Smigelskas K, et al. The prognostic value of IL10 and TNF alpha functional polymorphisms in premenopausal early-stage breast cancer patients. *BMC Genet* [Internet]. 2015;16(1):1–

11. Available from: <http://dx.doi.org/10.1186/s12863-015-0234-8>

32. Kozłowski L, Zakrzewska I, Tokajuk P, Wojtukiewicz MZ. Concentration of interleukin-6 (IL-6), interleukin-8 (IL-8) and interleukin-10 (IL-10) in blood serum of breast cancer patients. *Rocz Akad Med w Białymstoku.* 2003;48:82–4.

33. Lyon DE, McCain NL, Walter J, Schubert C. Cytokine comparisons between women with breast cancer and women with a negative breast biopsy. *Nurs Res.* 2008;57(1):51–8.

34. Chavey C, Bibeau F, Gourgou-Bourgade S, Burlincho S, Boissière F, Laune D, et al. Oestrogen receptor negative breast cancers exhibit high cytokine content. *Breast Cancer Res.* 2007;9(1):1–11.

35. Venetsanakos E, Beckman I, Bradley J, Skinner JM. High incidence of interleukin 10 mRNA but not interleukin 2 mRNA detected in human breast tumours. *Br J Cancer.* 1997;75(12):1826–30.

36. Kozłowski L, Zakrzewska I, Tokajuk P, Wojtukiewicz MZ. Concentration of interleukin-6 (IL-6), interleukin-8 (IL-8) and interleukin-10 (IL-10) in blood serum of breast cancer patients. *Rocz Akad Med w Białymstoku.* 2003;48(ii):82–4.

37. Pinzon-Charry A, Maxwell T, López JA. Dendritic cell dysfunction in cancer: A mechanism for immunosuppression. *Immunol Cell Biol.* 2005;83(5):451–61.

38. Joimel U, Gest C, Soria J, Pritchard LL, Alexandre J, Laurent M, et al. Stimulation of angiogenesis resulting from cooperation between macrophages and MDA-MB-231 breast cancer cells: Proposed molecular mechanism and effect of tetrathiomolybdate. *BMC Cancer.* 2010;10:1–13.

39. Li Y, Gao P, Yang J, Yu H, Zhu Y, Si W. Relationship between IL-10 expression and

- prognosis in patients with primary breast cancer. *Tumor Biol.* 2014;35(11):11533–40.
40. Kundu N, Beaty TL, Jackson MJ, Fulton AM. Antimetastatic and antitumor activities of interleukin 10 in a murine model of breast cancer. *J Natl Cancer Inst.* 1996;88(8):536–41.
 41. Mocellin S, Marincola FM, Young HA. Interleukin-10 and the immune response against cancer: a counterpoint. *J Leukoc Biol.* 2005;78(5):1043–51.
 42. Mocellin S, Panelli MC, Wang E, Nagorsen D, Marincola FM. The dual role of IL-10. *Trends Immunol.* 2003;24(1):36–43.
 43. Deverman BE, Patterson PH. Cytokines and CNS Development. *Neuron* [Internet]. 2009;64(1):61–78. Available from: <http://dx.doi.org/10.1016/j.neuron.2009.09.002>
 44. Amirghofran Z, Monabati A, Khezri A, Malek-Hosseini Z. Apoptosis in transitional cell carcinoma of bladder and its relation to proliferation and expression of P53 and Bcl-2. *Pathol Oncol Res.* 2004;10(3):154–8.
 45. Garcia-Tuñón I, Ricote M, Ruiz A, Fraile B, Paniagua R, Royuela M. IL-6, its receptors and its relationship with bcl-2 and bax proteins in infiltrating and in situ human breast carcinoma. *Histopathology.* 2005;47(1):82–9.
 46. Geissmann F, Launay P, Pasquier B, Lepelletier Y, Leborgne M, Lehuen A, et al. A Subset of Human Dendritic Cells Expresses IgA Fc Receptor (CD89), Which Mediates Internalization and Activation Upon Cross-Linking by IgA Complexes. *J Immunol.* 2001;166(1):346–52.
 47. Pilette C, Nouri-Aria KT, Jacobson MR, Wilcock LK, Detry B, Walker SM, et al. Grass Pollen Immunotherapy Induces an Allergen-Specific IgA2 Antibody Response Associated with Mucosal TGF- β Expression. *J Immunol.* 2007;178(7):4658–66.
 48. McGeachy MJ, Bak-Jensen KS, Chen Y, Tato CM, Blumenschein W, McClanahan T, et al. TGF- β and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain TH-17 cell-mediated pathology. *Nat Immunol.* 2007;8(12):1390–7.
 49. Fitzgerald DC, Zhang GX, El-Behi M, Fonseca-Kelly Z, Li H, Yu S, et al. Suppression of autoimmune inflammation of the central nervous system by interleukin 10 secreted by interleukin 27-stimulated T cells. *Nat Immunol.* 2007;8(12):1372–9.
 50. Awasthi A, Carrier Y, Peron JPS, Bettelli E, Kamanaka M, Flavell RA, et al. A dominant function for interleukin 27 in generating interleukin 10-producing anti-inflammatory T cells. *Nat Immunol.* 2007;8(12):1380–9.
 51. Durez BP, Abramowicz D, Grard C, Mechelen M Van, Amraoui Z, Dubois C, et al. From the *Laboratoire Pluridisciplinaire de Recherche Expérimentale Biomédicale; the CDépartement of Medical Genetics and IRIBHN, Hôpital Erasme, and the SDépartement of. 1993;177(February).
 52. Kalechman Y, Gafter U, Weinstein T, Chagnac A, Freidkin I, Tobar A, et al. Inhibition of interleukin-10 by the immunomodulator AS101 reduces mesangial cell proliferation in experimental mesangioproliferative glomerulonephritis. Association with dephosphorylation of STAT3. *J Biol Chem.* 2004;279(23):24724–32.
 53. Ji JD, Kim HJ, Rho YH, Choi SJ, Lee YH, Cheon HJ, et al. Inhibition of IL-10-induced STAT3 activation by 15-deoxy- $\Delta^{12,14}$ -prostaglandin J2. *Rheumatology.* 2005;44(8):983–8.
 54. Alas S, Emmanouilides C, Bonavida B. Inhibition of interleukin 10 by Rituximab results in down-regulation of Bcl-2 and sensitization of B-cell non-Hodgkin's lymphoma to apoptosis. *Clin Cancer Res.* 2001;7(3):709–23.
 55. Kim K, Kim D, Kim S, Jung E, Kang J, Jeung E, et al. Cytokine production by lipopolysaccharide-stimulated porcine peripheral

blood mononuclear cells through induction of interleukin-10. *Cytokine* [Internet]. 2011;56(2):224–30. Available from: <http://dx.doi.org/10.1016/j.cyto.2011.06.019>

56. Brunsing RL, Prossnitz ER. Induction of interleukin-10 in the T helper type 17 effector population by the G protein coupled estrogen receptor (GPER) agonist G-1. *Immunology*. 2011;134(1):93–106.

57. Xu J, Yang Y, Qiu G, Lal G, Wu Z, Levy DE, et al. c-Maf Regulates IL-10 Expression during Th17 Polarization. *J Immunol*. 2009;182(10):6226–36.

58. Zhang Q, Xin H, Fen T. Function of microRNA-141 in human breast cancer through cytotoxic CD4+ T cells regulated by MAP4K4 expression. *Mol Med Rep*. 2018;17(6):7893–901.

59. Kim VN, Han J, Siomi MC. Biogenesis of small RNAs in animals. *Nat Rev Mol Cell Biol*. 2009;10(2):126–39.

60. Zhang L, Huang J, Yang N, Greshock J, Megraw MS, Giannakakis A, et al. <microRNAs exhibit high frequency genomic.pdf>. *Proc Natl Acad Sci*. 2006;103(24).

61. Ma L, Teruya-Feldstein J, Weinberg RA. Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. *Nature*. 2007;449(7163):682–8.

62. Han M, Liu M, Wang Y, Chen X, Xu J, Sun Y, et al. Antagonism of miR-21 reverses epithelial-mesenchymal transition and cancer stem cell phenotype through AKT/ERK1/2 inactivation by targeting PTEN. *PLoS One*. 2012;7(6):1–11.

63. Han M, Liu M, Wang Y, Mo Z, Bi X, Liu Z, et al. Re-expression of miR-21 contributes to migration and invasion by inducing epithelial-mesenchymal transition consistent with cancer stem cell characteristics in MCF-7 cells. *Mol Cell Biochem*. 2012;363(1–2):427–36.

64. Yan LX, Huang XF, Shao Q, Huang MY, Deng L, Wu QL, et al. MicroRNA miR-21 overexpression in human breast cancer is associated with advanced clinical stage, lymph node metastasis and patient poor prognosis. *Rna*. 2008;14(11):2348–60.

65. Lai PEIC, Chiu TEDH, Huang YENTA. Overexpression of BDNF and TrkB in human. *Anticancer Res*. 2010;31(12):1265–70.

66. Li H, Bian C, Liao L, Li J, Zhao RC. miR-17-5p promotes human breast cancer cell migration and invasion through suppression of HBP1. *Breast Cancer Res Treat*. 2011;126(3):565–75.

67. Takuse Y, Watanabe M, Inoue N, Ozaki R, Ohtsu H, Saeki M, et al. Association of IL-10-Regulating MicroRNAs in Peripheral Blood Mononuclear Cells with the Pathogenesis of Autoimmune Thyroid Disease. *Immunol Invest* [Internet]. 2017;46(6):590–602. Available from: <https://doi.org/10.1080/08820139.2017.1322975>

68. Khorrami S, Hosseini AZ, Mowla SJ, Soleimani M, Rakhshani N, Malekzadeh R. MicroRNA-146a induces immune suppression and drug-resistant colorectal cancer cells. *Tumor Biol*. 2017;39(5).

69. Gan L, Sun T, Li B, Tian J, Zhang J, Chen X, et al. Serum miR-146a and miR-150 as Potential New Biomarkers for Hip Fracture-Induced Acute Lung Injury. *Mediators Inflamm*. 2018;2018.

70. Moradi N, Fadaei R, Ahmadi R, Kazemian E, Fallah S. Lower Expression of miR-10a in Coronary Artery Disease and its Association with Pro/Anti-Inflammatory Cytokines. *Clin Lab* [Internet]. 2018 May 1 [cited 2020 Oct 29];64(05/2018):847–54. Available from: <http://www.clin-lab-publications.com/article/2725>

71. Lochhead RB, Ma Y, Zachary JF, Baltimore D, Zhao JL, Weis JH, et al. MicroRNA-146a Provides Feedback Regulation of Lyme Arthritis but Not Carditis during

- Infection with *Borrelia burgdorferi*. *PLoS Pathog.* 2014;10(6):17–21.
72. Kurowska-Stolarska M, Alivernini S, Ballantine LE, Asquith DL, Millar NL, Gilchrist DS, et al. MicroRNA-155 as a proinflammatory regulator in clinical and experimental arthritis. *Proc Natl Acad Sci U S A.* 2011;108(27):11193–8.
 73. Fairfax KA, Gantier MP, Mackay F, Williams BRG, McCoy CE. IL-10 regulates Aicda expression through miR-155. *J Leukoc Biol.* 2015;97(1):71–8.
 74. Lochhead RB, Zachary JF, Rosa LD, Ma Y, Weis JH, O'Connell RM, et al. Antagonistic Interplay between MicroRNA-155 and IL-10 during Lyme Carditis and Arthritis. *PLoS One.* 2015;10(8):1–21.
 75. Ren ZQ, Liu N, Zhao K. Micro RNA-19a suppresses IL-10 in peripheral B cells from patients with atherosclerosis. *Cytokine [Internet].* 2016;86:86–91. Available from: <http://dx.doi.org/10.1016/j.cyto.2016.07.019>
 76. Geng XR, Qiu SQ, Yang LT, Liu ZQ, Yang G, Liu JQ, et al. Allergen-specific immune response suppresses interleukin 10 expression in B cells via increasing micro-RNA-17-92 cluster. *Cell Biochem Funct.* 2016;34(6):449–54.
 77. Liu ZQ, Yang G, Geng XR, Liu JQ, Mo LH, Liu ZG, et al. Micro RNA-17-92 cluster mediates interleukin-4-suppressed IL-10 expression in B cells. *Am J Transl Res.* 2016;8(5):2317–24.
 78. Luo Y, Huang YY, Jin Y, Li CR, Yang J. [Effect of miR-21 on the expression of interleukin-10 in B cell of patients with Henoch-Schonlein purpura]. *Zhonghua er ke za zhi = Chinese J Pediatr [Internet].* 2018 Dec 1 [cited 2020 Oct 28];56(12):939–44. Available from: <https://europepmc.org/article/med/30518009>
 79. Chen J, Zhao L, Wang D, Xu Y, Gao H, Tan W, et al. Contribution of regulatory T cells to immune tolerance and association of microRNA-210 and Foxp3 in preeclampsia. *Mol Med Rep.* 2019;19(2):1150–8.
 80. Wang S, Li Z, Chen Q, Wang L, Zheng J, Lin Z, et al. NF- κ B-Induced MicroRNA-211 Inhibits Interleukin-10 in Macrophages of Rats with Lipopolysaccharide-Induced Acute Respiratory Distress Syndrome. *Cell Physiol Biochem.* 2018;45(1):332–42.
 81. Lu MC, Yu CL, Chen HC, Yu HC, Huang HB, Lai NS. Increased miR-223 expression in T cells from patients with rheumatoid arthritis leads to decreased insulin-like growth factor-1-mediated interleukin-10 production. *Clin Exp Immunol.* 2014;177(3):641–51.
 82. Sun Y, Guo D, Liu B, Yin X, Wei H, Tang K, et al. Regulatory Role of rno-miR-30b-5p in IL-10 and Toll-like Receptor 4 Expressions of T Lymphocytes in Experimental Autoimmune Uveitis In Vitro. *Mediators Inflamm.* 2018;2018.
 83. Liu D, Zhang N, Zhang X, Qin M, Dong Y, Jin L. MiR-410 Down-Regulates the Expression of Interleukin-10 by Targeting STAT3 in the Pathogenesis of Systemic Lupus Erythematosus. *Cell Physiol Biochem.* 2016;39(1):303–15.
 84. Li L, Sun P, Zhang C, Li Z, Zhou W. MiR-98 suppresses the effects of tumor-associated macrophages on promoting migration and invasion of hepatocellular carcinoma cells by regulating IL-10. *Biochimie [Internet].* 2018;150:23–30. Available from: <https://doi.org/10.1016/j.biochi.2018.04.016>
 85. Li Y, Rong J, Qin J, He JY, Chen HG, Huang SH. Micro RNA-98 interferes with expression interleukin-10 in peripheral B cells of patients with lung cancer. *Sci Rep [Internet].* 2016;6(August):8–13. Available from: <http://dx.doi.org/10.1038/srep32754>
 86. Li J, Chen C, Bi X, Zhou C, Huang T, Ni C, et al. DNA methylation of CMTM3, SSTR2, and MDFI genes in colorectal cancer. *Gene*

[Internet]. 2017;630:1–7. Available from: <http://dx.doi.org/10.1016/j.gene.2017.07.082>

87. Luo XQ, Yang SB, Qiu SQ, Xie R Di, Yang LT, Ke YX, et al. Post-transcriptional regulation of interleukin-10 in peripheral B cells of airway allergy patients. *Am J Transl Res*. 2016;8(12):5766–72.

88. Huo Y, Chu Y, Guo L, Liu L, Xia X, Wang T. Cortisol is associated with low frequency of interleukin 10-producing B cells in patients with atherosclerosis. *Cell Biochem Funct*. 2017;35(3):178–83.

89. Rouas R, Merimi M, Najar M, El Zein N, Fayyad-Kazan M, Berehab M, et al. Human CD8 + CD25 + CD127 low regulatory T cells: microRNA signature and impact on TGF- β and IL-10 expression. *J Cell Physiol* [Internet]. 2019 Oct 25 [cited 2020 Oct 28];234(10):17459–72. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/jcp.28367>

90. Wang H, Xu W, Shao Q, Ding Q. miR-21 silencing ameliorates experimental autoimmune encephalomyelitis by promoting the differentiation of IL-10- producing B cells. *Oncotarget*. 2017;8(55):94069–79.

91. Xiong Y, Yan C, Chen L, Endo Y, Sun Y, Zhou W, et al. IL-10 induces MC3T3-E1 cells differentiation towards osteoblastic fate in murine model. *J Cell Mol Med*. 2020;24(1):1076–86.

92. Li L, Feng J, Zhang D, Yong J, Wang Y, Yao J, et al. Differential expression of miR-4492 and IL-10 is involved in chronic rhinosinusitis with nasal polyps. *Exp Ther Med*. 2019;3968–76.

93. Hatab HM, Abdel Hamid FF, Soliman AF, Al-Shafie TA, Ismail YM, El-Houseini ME. A combined treatment of curcumin, piperine, and taurine alters the circulating levels of IL-10 and miR-21 in hepatocellular carcinoma patients: A pilot study. *J Gastrointest Oncol*. 2019;10(4):766–76.

94. Hussain T, Zhao D, Shah SZA, Wang J, Yue R, Liao Y, et al. MicroRNA 27a-3p regulates antimicrobial responses of murine macrophages infected by *Mycobacterium avium* subspecies paratuberculosis by targeting interleukin-10 and TGF- β -activated protein kinase 1 binding protein 2. *Front Immunol*. 2018;8(JAN):1–18.

95. Li Z, Dong M, Fan D, Hou P, Li H, Liu L, et al. LncRNA ANCR down-regulation promotes TGF- β -induced EMT and metastasis in breast cancer. *Oncotarget*. 2017;8(40):67329–43.

96. Liu L, Zhang Y, Lu J. The roles of long noncoding RNAs in breast cancer metastasis. *Cell Death Dis* [Internet]. 2020;11(9). Available from: <http://dx.doi.org/10.1038/s41419-020-02954-4>

97. Wang S, Liang K, Hu Q, Li P, Song J, Yang Y, et al. JAK2-binding long noncoding RNA promotes breast cancer brain metastasis. *J Clin Invest*. 2017;127(12):4498–515.

98. Pei X, Wang X, Li H. LncRNA SNHG1 regulates the differentiation of Treg cells and affects the immune escape of breast cancer via regulating miR-448/IDO. *Int J Biol Macromol* [Internet]. 2018;118(2017):24–30. Available from: <https://doi.org/10.1016/j.ijbiomac.2018.06.033>

99. Guo X, Gao L, Wang Y, Chiu DKY, Wang T, Deng Y. Advances in long noncoding RNAs: Identification, structure prediction and function annotation. *Brief Funct Genomics*. 2016;15(1):38–46.

100. Tang X Di, Zhang DD, Jia L, Ji W, Zhao YS. LncRNA AFAP1-AS1 Promotes Migration and Invasion of Non-Small Cell Lung Cancer via Up-Regulating IRF7 and the RIG-I-Like Receptor Signaling Pathway. *Cell Physiol Biochem*. 2018;50(1):196–213.

101. Ye Y, Xu Y, Lai Y, He W, Li Y, Wang R, et al. Long non-coding RNA cox-2 prevents immune evasion and metastasis of hepatocellular carcinoma by altering M1/M2 macrophage

polarization. Vol. 119, Journal of Cellular Biochemistry. 2018. 2951–2963 p.

102. Zhou WY, Zhang MM, Liu C, Kang Y, Wang JO, Yang XH. Long noncoding RNA LINC00473 drives the progression of pancreatic cancer via upregulating programmed death-ligand 1 by sponging microRNA-195-5p. *J Cell Physiol.* 2019;234(12):23176–89.

103. Ma P, Li Y, Zhang W, Fang F, Sun J, Liu M, et al. Long Non-coding RNA MALAT1 Inhibits Neuron Apoptosis and Neuroinflammation While Stimulates Neurite Outgrowth and Its Correlation With MiR-125b Mediates PTGS2, CDK5 and FOXQ1 in Alzheimer's Disease. *Curr Alzheimer Res.* 2019;16(7):596–612.

104. Zhao JH, Wang B, Wang XH, Wang JR, Xu CW. Influence of lncRNA ANRIL on neuronal apoptosis in rats with cerebral infarction by regulating the NF- κ B signaling pathway. *Eur Rev Med Pharmacol Sci.* 2019;23(22):10092–100.

105. Li Y, Li Y, Huang S, He K, Zhao M, Lin H, et al. Long non-coding RNA growth arrest specific transcript 5 acts as a tumour suppressor in colorectal cancer by inhibiting interleukin-10 and vascular endothelial growth factor expression. *Oncotarget.* 2017;8(8):13690–702.

106. Colombel JF, Rutgeerts P, Malchow H, Jacyna M, Nielsen OH, Rask-Madsen J, et al. Interleukin 10 (Tenovil) in the prevention of postoperative recurrence of Crohn's disease. *Gut.* 2001;49(1):42–6.

107. Fioranelli M, Roccia MG. Twenty-five years of studies and trials for the therapeutic application of IL-10 immunomodulating properties. From high doses administration to low dose medicine new paradigm. *J Integr Cardiol.* 2014;1(1):2–6.

108. Pott GB, Sailer CA, Porat R, Peskind RL, Fuchs AC, Angel JB, et al. Effect of a four-week course of interleukin-10 on cytokine production in a placebo-controlled study of HIV-1-infected

subjects. *Eur Cytokine Netw.* 2007 Jun;18(2):49–58.

109. Asadullah K, Sterry W, Volk HD. Interleukin-10 therapy - Review of a new approach. *Pharmacol Rev.* 2003;55(2):241–69.

110. Martin Wissing K, Morelon E, Legendre C, De Pauw L, Lebeaut A, Grint P, et al. A pilot trial of recombinant human interleukin-10 in kidney transplant recipients receiving OKT3 induction therapy. *Transplantation.* 1997 Oct 15;64(7):999–1006.

111. Herfarth HH, Mohanty SP, Rath HC, Tonkonogy S, Sartor RB. Interleukin 10 suppresses experimental chronic, granulomatous inflammation induced by bacterial cell wall polymers. *Gut.* 1996;39(6):836–45.

112. Herfarth HH, Bocker U, Janardhanam R, Sartor RB. Subtherapeutic corticosteroids potentiate the ability of interleukin 10 to prevent chronic inflammation in rats. *Gastroenterology.* 1998;115(4):856–65.

113. Galeazzi M, Sebastiani GD, Bazzichi L, Garcia Gonzalez E, Ravenni N, Giovannoni L, et al. SAT0196 Dekavil (F8-IL10), A Novel Therapeutic Approach for Rheumatoid Arthritis: Ongoing Phase IB Clinical Trial Results. *Ann Rheum Dis.* 2015 Jun 1;74(Suppl 2):726.2-727.

114. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity.* 2004;21(2):137–48.

115. Hagenbaugh A, Sharma S, Dubinett SM, Wei SHY, Aranda R, Cheroutre H, et al. Altered immune responses in interleukin 10 transgenic mice. *J Exp Med.* 1997;185(12):2101–10.

116. Ruffell B, Chang-Strachan D, Chan V, Rosenbusch A, Ho CMT, Pryer N, et al. Macrophage IL-10 Blocks CD8⁺ T Cell-Dependent Responses to Chemotherapy by Suppressing IL-12 Expression in Intratumoral Dendritic Cells. *Cancer Cell [Internet].*

- 2014;26(5):623–37. Available from: <http://dx.doi.org/10.1016/j.ccell.2014.09.006>
117. Vicari AP, Chiodoni C, Vaure C, Ait-Yahia S, Dercamp C, Matsos F, et al. Reversal of tumor-induced dendritic cell paralysis by CpG immunostimulatory oligonucleotide and anti-interleukin 10 receptor antibody. *J Exp Med*. 2002;196(4):541–9.
 118. Loser K, Apelt J, Voskort M, Mohaupt M, Balkow S, Schwarz T, et al. IL-10 Controls Ultraviolet-Induced Carcinogenesis in Mice. *J Immunol*. 2007;179(1):365–71.
 119. Nemunaitis J, Fong T, Shabe P, Martineau D, Ando D. Comparison of serum interleukin-10 (il-10) levels between normal volunteers and patients with advanced melanoma. *Cancer Invest*. 2001;19(3):239–47.
 120. Berman RM, Suzuki T, Tahara H, Robbins PD, Narula SK, Lotze MT. Systemic administration of cellular IL-10 induces an effective, specific, and long-lived immune response against established tumors in mice. *J Immunol* [Internet]. 1996;157(1):231–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8683120>
 121. Zheng BLM, Ojcius DM, Garaud E, Roth C, Maxwell E, Li Z, et al. Interleukin-10 Inhibits Tumor Metastasis Through an NK Cell-dependent Mechanism By L.M. Zheng,* D.M. Ojcius,~ E Garaud, C. Roth,~ E. Maxwell,* Z. Li,* H. Kong,* J. Chen,* X.Y. Wang,* J.J. Catino,* and I. King*. *J Exp Med*. 1996;184(August):579–584.
 122. Groux H, Cottrez F, Rouleau M, Mauze S, Antonenko S, Hurst S, et al. A transgenic model to analyze the immunoregulatory role of IL-10 secreted by antigen-presenting cells. *J Immunol* [Internet]. 1999;162(3):1723–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9973435>
 123. Mumm JB, Emmerich J, Zhang X, Chan I, Wu L, Mauze S, et al. IL-10 Elicits IFN γ -Dependent tumor immune surveillance. *Cancer Cell* [Internet]. 2011;20(6):781–96. Available from: <http://dx.doi.org/10.1016/j.ccr.2011.11.003>
 124. Emmerich J, Mumm JB, Chan IH, LaFace D, Truong H, McClanahan T, et al. IL-10 directly activates and expands tumor-resident CD8+ T cells without De Novo infiltration from secondary lymphoid organs. *Cancer Res*. 2012;72(14):3570–81.
 125. Naing A, Papadopoulos KP, Autio KA, Ott PA, Patel MR, Wong DJ, et al. Safety, antitumor activity, and immune activation of pegylated recombinant human interleukin-10 (AM0010) in patients with advanced solid tumors. *J Clin Oncol*. 2016;34(29):3562–9.
 126. Naing A, Infante JR, Papadopoulos KP, Chan IH, Shen C, Ratti NP, et al. PEGylated IL-10 (Pegilodecakin) Induces Systemic Immune Activation, CD8+ T Cell Invigoration and Polyclonal T Cell Expansion in Cancer Patients. *Cancer Cell* [Internet]. 2018;34(5):775-791.e3. Available from: <https://doi.org/10.1016/j.ccell.2018.10.007>
 127. Autio K, Oft M. Pegylated Interleukin-10: Clinical Development of an Immunoregulatory Cytokine for Use in Cancer Therapeutics. *Curr Oncol Rep*. 2019;21(2).
 128. Sawant D V., Yano H, Chikina M, Zhang Q, Liao M, Liu C, et al. Adaptive plasticity of IL-10+ and IL-35+ Treg cells cooperatively promotes tumor T cell exhaustion. *Nat Immunol* [Internet]. 2019;20(6):724–35. Available from: <http://dx.doi.org/10.1038/s41590-019-0346-9>
 129. Sabat R. IL-10 family of cytokines. *Cytokine Growth Factor Rev* [Internet]. 2010;21(5):315–24. Available from: <http://dx.doi.org/10.1016/j.cytogfr.2010.11.001>
 130. Yang F, Shen Y, Zhang W, Jin J, Huang D, Fang H, et al. An androgen receptor negatively induced long non-coding RNA ARNILA binding to miR-204 promotes the invasion and metastasis of triple-negative breast cancer. *Cell Death Differ* [Internet].

2018;25(12):2209–20. Available from:

<http://dx.doi.org/10.1038/s41418-018-0123-6>

131. Huang X, Xie X, Liu P, Yang L, Chen B, Song C, et al. Adam12 and lnc015192 act as ceRNAs in breast cancer by regulating miR-34a. *Oncogene* [Internet]. 2018;37(49):6316–26. Available from:

<http://dx.doi.org/10.1038/s41388-018-0410-1>

132. Wang Z, Yang B, Zhang M, Guo W, Wu Z, Wang Y, et al. LncRNA epigenetic landscape analysis identifies EPIC1 as an oncogenic lncRNA that interacts with MYC and promotes cell cycle progression in cancer. *Cancer Cell*. 2019;33(4):706–20.

133. Zhong H, Yang J, Zhang B, Wang X, Pei L, Zhang L, et al. LncRNA GACAT3 predicts poor prognosis and promotes cell proliferation in breast cancer through regulation of miR-497/CCND2. *Cancer Biomark*. 2018;22(4):787–97.

134. Liu M, Gou L, Xia J, Wan Q, Jiang Y, Sun S, et al. LncRNA ITGB2-AS1 could promote the migration and invasion of breast cancer cells through up-regulating ITGB2. *Int J Mol Sci*. 2018;19(7):1–13.

135. Wang S, Ke H, Zhang H, Ma Y, Ao L, Zou L, et al. LncRNA MIR100HG promotes cell proliferation in triple-negative breast cancer through triplex formation with p27 loci. *Cell Death Dis* [Internet]. 2018;9(8). Available from: <http://dx.doi.org/10.1038/s41419-018-0869-2>

136. Song R, Zhang J, Huang J, Hai T. Long non-coding RNA GHET1 promotes human breast cancer cell proliferation, invasion and migration via affecting epithelial mesenchymal transition. *Cancer Biomarkers*. 2018;22(3):565–73.

137. Li Y, Lv M, Song Z, Lou Z, Wang R, Zhuang M. Long non-coding RNA NNT-AS1 affects progression of breast cancer through miR-142-3p/ZEB1 axis. *Biomed Pharmacother* [Internet]. 2018;103(April):939–46. Available

from:

<https://doi.org/10.1016/j.biopha.2018.04.087>

138. Yang YX, Wei L, Zhang YJ, Hayano T, Piñeiro Pereda M del P, Nakaoka H, et al. Long non-coding RNA p10247, high expressed in breast cancer (lncRNA-BCHE), is correlated with metastasis. *Clin Exp Metastasis* [Internet]. 2018;35(3):109–21. Available from: <http://dx.doi.org/10.1007/s10585-018-9901-2>

139. Bai Y, Zhou X, Huang L, Wan Y, Li X, Wang Y. Long noncoding RNA EZR-AS1 promotes tumor growth and metastasis by modulating Wnt/ β -catenin pathway in breast cancer. *Exp Ther Med*. 2018;16(3):2235–42.

140. Fan S, Yang Z, Ke Z, Huang K, Liu N, Fang X, et al. Downregulation of the long non-coding RNA TUG1 is associated with cell proliferation, migration, and invasion in breast cancer. *Biomed Pharmacother* [Internet]. 2017;95(May):1636–43. Available from: <http://dx.doi.org/10.1016/j.biopha.2017.09.076>

141. Li T, Liu Y, Xiao H, Xu G. Long non-coding RNA TUG1 promotes cell proliferation and metastasis in human breast cancer. *Breast Cancer*. 2017;24(4):535–43.

142. Liang Y, Song X, Li Y, Sang Y, Zhang N, Zhang H, et al. A novel long non-coding RNA-PRLB acts as a tumor promoter through regulating miR-4766-5p/SIRT1 axis in breast cancer. *Cell Death Dis* [Internet]. 2018;9(5):1–16. Available from: <http://dx.doi.org/10.1038/s41419-018-0582-1>

143. Tang J, Li Y, Sang Y, Yu B, Lv D, Zhang W, et al. LncRNA PVT1 regulates triple-negative breast cancer through KLF5/ β -catenin signaling. *Oncogene*. 2018;37(34):4723–34.

144. Lu G, Li Y, Ma Y, Lu J, Chen Y, Jiang Q, et al. Long noncoding RNA LINC00511 contributes to breast cancer tumourigenesis and stemness by inducing the miR-185-3p/E2F1/Nanog axis. *J Exp Clin Cancer Res*. 2018;37(1):1–11.

145. Li RH, Chen M, Liu J, Shao CC, Guo CP, Wei XL, et al. Long noncoding RNA ATB promotes the epithelial–mesenchymal transition by upregulating the miR-200c/Twist1 axis and predicts poor prognosis in breast cancer. *Cell Death Dis* [Internet]. 2018;9(12). Available from: <http://dx.doi.org/10.1038/s41419-018-1210-9>
146. Li W, Zhang Z, Liu X, Cheng X, Zhang Y, Han X, et al. The FOXN3-NEAT1-SIN3A repressor complex promotes progression of hormonally responsive breast cancer. *J Clin Invest*. 2017;127(9):3421–40.
147. Li GY, Wang W, Sun JY, Xin B, Zhang X, Wang T, et al. Long non-coding RNAs AC026904.1 and UCA1: A “one-two punch” for TGF- β -induced SNAIL2 activation and epithelial-mesenchymal transition in breast cancer. *Theranostics*. 2018;8(10):2846–61.
148. Li Z, Hou P, Fan D, Dong M, Ma M, Li H, et al. The degradation of EZH2 mediated by lncRNA ANCR attenuated the invasion and metastasis of breast cancer. *Cell Death Differ* [Internet]. 2017;24(1):59–71. Available from: <http://dx.doi.org/10.1038/cdd.2016.95>
149. Zhang W, Shi S, Jiang J, Li X, Lu H, Ren F. LncRNA MEG3 inhibits cell epithelial-mesenchymal transition by sponging miR-421 targeting E-cadherin in breast cancer. *Biomed Pharmacother* [Internet]. 2017;91:312–9. Available from: <http://dx.doi.org/10.1016/j.biopha.2017.04.085>
150. Zhang D, Shi G, Qiu J, Shi C, Liang Y, Yuan L, et al. Overexpression of long noncoding RNA ENST433110 inhibits cell proliferation and migration and enhances cell apoptosis of thyroid cancer cells. *All Life*. 2020;13(1):259–67.
151. Yang Y, Yang H, Xu M, Zhang H, Sun M, Mu P, et al. Long non-coding RNA (lncRNA) MAGI2-AS3 inhibits breast cancer cell growth by targeting the Fas/FasL signalling pathway. *Hum Cell* [Internet]. 2018;31(3):232–
41. Available from: <https://doi.org/10.1007/s13577-018-0206-1>
152. Sanders S, Jin G, Singh R, Vidi P, Metheny-Barlow LJ, Jr RBDA, et al. Loss of XIST in breast cancer activates MSN-c-Met and reprograms microglia via exosomal microRNA to promote brain metastasis. *Cancer Res*. 2019;78(15):4316–30.
153. Zheng R, Lin S, Guan L, Yuan H, Liu K, Liu C, et al. Long non-coding RNA XIST inhibited breast cancer cell growth, migration, and invasion via miR-155/CDX1 axis. *Biochem Biophys Res Commun* [Internet]. 2018;498(4):1002–8. Available from: <https://doi.org/10.1016/j.bbrc.2018.03.104>
154. Jadaliha M, Gholamalamdari O, Tang W, Zhang Y, Petracovici A, Hao Q, et al. A natural antisense lncRNA controls breast cancer progression by promoting tumor suppressor gene mRNA stability. *PLoS Genet*. 2018;14(11):1–24.
155. Wu W, Chen F, Cui X, Yang L, Chen J, Zhao J, et al. LncRNA NKILA suppresses TGF- β -induced epithelial–mesenchymal transition by blocking NF- κ B signaling in breast cancer. *Int J Cancer*. 2018;143(9):2213–24.