Review

Epithelial-to-Mesenchymal Transition and MicroRNAs in Lung Cancer

Antoine Legras 1,2, Nicolas Pécuchet 1,3, Sandrine Imbeaud 4, Karine Pallier 1, Audrey Didelot 1, Hélène Roussel 5,6, Laure Gibault 5, Elizabeth Fabre 1,3, Françoise Le Pimpec-Barthes 2,4, Pierre Laurent-Puig 1,7 and Hélène Blons 1,7,*

1 INSERM UMR-S1147, CNRS SNC 5014, Saints-Pères Research Center, 45 rue des Saints-Pères
Paris-Descartes University, Sorbonne Paris Cité University, 75006 Paris, France; antlegras@gmail.com (A.L.); nicolas.pecuchet@me.com (N.P.); pallier.karine@gmail.com (K.P.); audrey.didelot@parisdescartes.fr (A.D.); elizabeth.fabre@aphp.fr (E.F.); pierre.laurent-puig@parisdescartes.fr (P.L.-P.)

2 Thoracic Surgery and Lung Transplantation Department, Georges Pompidou European Hospital, 20 rue Leblanc, Assistance Publique-Hôpitaux de Paris, 75015 Paris, France; francoise.lepimpec-barthes@aphp.fr

3 Medical Thoracic Oncology Department, Georges Pompidou European Hospital, 20 rue Leblanc, Assistance Publique-Hôpitaux de Paris, 75015 Paris, France

4 INSERM UMR-S1162, 27 rue Juliette Dodu, 75010 Paris, France; sandrine.imbeaud@inserm.fr

5 Pathology Department, Georges Pompidou European Hospital, 20 rue Leblanc, Assistance Publique-Hôpitaux de Paris, 75015 Paris, France; helene.roussel@aphp.fr (H.R.); laure.gibault@aphp.fr (L.G.)

6 INSERM UMR-S970, Paris Centre de Recherche Cardiovasculaire, Georges Pompidou European Hospital, 20 rue Leblanc, 75015 Paris, France

7 Molecular Biology Department, Georges Pompidou European Hospital, 20 rue Leblanc, Assistance Publique-Hôpitaux de Paris, 75015 Paris, France

* Correspondence: helene.blons@parisdescartes.fr; Tel.: +33-1-42-86-40-67; Fax: +33-1-42-86-20-72

Academic Editor: Joëlle Roche
Received: 24 June 2017; Accepted: 26 July 2017; Published: 3 August 2017

Abstract: Despite major advances, non-small cell lung cancer (NSCLC) remains the major cause of cancer-related death in developed countries. Metastasis and drug resistance are the main factors contributing to relapse and death. Epithelial-to-mesenchymal transition (EMT) is a complex molecular and cellular process involved in tissue remodelling that was extensively studied as an actor of tumour progression, metastasis and drug resistance in many cancer types and in lung cancers. Here we described with an emphasis on NSCLC how the changes in signalling pathways, transcription factors expression or microRNAs that occur in cancer promote EMT. Understanding the biology of EMT will help to define reversing process and treatment strategies. We will see that this complex mechanism is related to inflammation, cell mobility and stem cell features and that it is a dynamic process. The existence of intermediate phenotypes and tumour heterogeneity may be debated in the literature concerning EMT markers, EMT signatures and clinical consequences in NSCLC. However, given the role of EMT in metastasis and in drug resistance the development of EMT inhibitors is an interesting approach to counteract tumour progression and drug resistance. This review describes EMT involvement in cancer with an emphasis on NSCLC and microRNA regulation.

Keywords: epithelial-mesenchymal transition; microRNAs; lung neoplasms; biomarkers; tumour

1. Introduction

Epithelial-to-mesenchymal transition (EMT) is an evolutionarily conserved but complex molecular and cellular program in which cells undergo conversion from epithelial to mesenchymal state [1]. Epithelial differentiated characteristics are lost, including cell-cell adhesion, planar and apical-basal polarity and lack of mobility. On the contrary, mesenchymal features are briefly acquired, such as
cell mobility, invasiveness, gain of stem cell properties and a reinforced resistance to apoptosis. EMT was initially described as a cell culture phenomenon before being recognized in vivo and studied in embryonic development. This process is obviously reversible and is highly conserved from diploblasts (medusa) 800 million years ago to nowadays [2]. It aims at dissociating epithelium and degrading basement membranes so that cells acquire a fibroblastic or glial-cell phenotype and finally migrate. This state was defined as “mesenchyme” (from Greek, μέσο, μέσο, middle and ἐνκυώμα in fusion) to describe a poorly organized state between two tissues. After migration, such cells are able to reverse their phenotype with the mesenchymal to epithelial transition (MET). EMT and MET are included under the term epithelial-mesenchymal plasticity [3]. Both play an important play in organogenesis (i.e., in renal epithelium or cardiac organogenesis formation) [4] but also in cancer [5,6].

1.1. Cellular Pathways and EMT

Many signalling pathways control EMT according to the different cellular contexts [5,7]. Transforming Growth Factor β (TGFβ) [8] and Epidermal Growth Factor (EGF) [9] pathways have been extensively studied but others are also known to drive EMT in specific situations (tumour cells including NSCLC): the Fibroblast Growth Factor (FGF) [10,11], Hepatocyte Growth Factor (HGF) [12], Platelet-derived Growth Factor (PDGF), Insulin-like Growth Factor (IGF) [13], Vascular Endothelial Growth Factor (VEGF), Oestrogens, Hypoxia [14,15], Autocrine Motility Growth Factor (AMF), bile acids, nicotine, ultraviolet light, integrins, Wnt, Notch [16], Interleukin-related Protein (ILER), Interleukin-6 (IL-6), Sonic hedgehog (Shh), Bone Morphogenetic Protein (BMP), Stem Cell Factor (SCF), cyclooxygenase-2/prostaglandin E2 (COX-2/PGE2) [17] and also extracellular matrix changes, as shown for collagen I and hyaluronan [18,19]. Depending on the experimental model and the stimulation nearly all signalling pathways may eventually promote a mesenchymal transition.

1.2. Transcriptional Regulation of EMT

Several transcription factors act as molecular switches for the EMT program [20]. The loss of E-cadherin is a hallmark of EMT. This cadherin is responsible for cell cell adhesion and cytoskeleton organisation. Its loss leads to the conversion from epithelial cells to motile and invasive mesenchymal cells [21] which is orchestrated by transcriptional repressors [5]. Direct transcriptional repression of E-cadherin is coordinated by several transcription factors interacting together. SNAIL superfamily members (such as zinc finger proteins SNAI1/SNAIL and SNAI2/SLUG) interact with several corepressors and epigenetic remodelling complexes to repress E-cadherin through N-terminal SNAG domain binding to the E-box promoter sequence [22]. Other direct repressors are ZEB family members ZEB1 (Zinc finger E-box-binding homeobox 1, previously known as TCF8 and δEF1) and ZEB2/SIP1, E47 and the Krüpple-like factor 8 (KLF8) [23,24]. Furthermore, TWIST family members (basic helix-loop-helix transcription factors TWIST1 and TWIST2), Goosecoid, E2.2/TCF4 and FOXC2 indirectly repress E-cadherin transcription [6]. TWIST is a transcription factor fully implicated in EMT [25]. Its proteins belong to the family of basic helix-loop-helix transcription factors which are able to modulate expression of different target genes through E-box responsive elements [26]. TWIST1 and TWIST2, highly conserved, share the Twist-box protein interaction surface in their C-terminal half [27]. TWIST forms functional homo- and heterodimers with TCF3/E2A and Hand2, the balance between homo- and heterodimers regulating limb development and cranial suture fusion. In adulthood, TWIST1 expression was reported in mesoderm-derived tissues including heart, skeletal muscles, placenta [27] and also brown fat with a specific thermoregulation function [28]. TWIST proteins physically interact with NF-κB and specifically prevent its ability to activate pro-inflammatory cytokine-encoding genes [29]. Furthermore, TWIST proteins reduce TNFα induction response to T-cell receptor activation [30].

EMT network is highly controlled. The high-mobility group protein HMGA2 and the homeodomain-containing protein SIX1 act as a coordinator of EMT inducers [31,32]. In development and in carcinogenesis, SNAIL1 appears at the onset of EMT then SNAIL2, ZEB, E47 and TWIST are...
induced to maintain the migratory mesenchymal state [33] suggesting an orchestration in time of the process. Moreover EMT transcription factors may undergo post-translational regulation. For example SNAIL1 nuclear stabilization is promoted by NF-κB [34] and the zinc transporter LIV1 [35].

1.3. Junctions, Cytoskeleton and Matrix

The cadherin switch through the loss of E-cadherin represents a universal marker of EMT. E-cadherin is the major constituent of epithelial adherens junctions which mediate intercellular adhesion with tight junctions, forming the zonula adherens. Epithelial cells lose cell-cell adhesion and cell polarity. Following E-cadherin loss, the expression of mesenchymal markers such as vimentin, fibronectin, N-cadherin, alpha-smooth muscle actin (αSMA), and the activity of matrix metalloproteinases (MMP-2, MMP-3, MMP-9) increase. SNAIL1 represses the expression of tight junction components such as claudin-3, -4 and -7 [36]. Furthermore, EMT inducers directly repress the protein complexes involved in apico-basal polarity of epithelial cells (Par, Crumbs and Scribble) [37] and enhance expression of metalloproteinases that degrade the basement membrane, thereby favouring cell migration and invasion. Interestingly, MMP3 can trigger EMT through a positive regulatory feedback loop [38]. Finally, EMT transcription factors induce the expression of mesenchymal proteins such as fibronectin and N-cadherin [39] and are involved in the remodelling of the actin cytoskeleton [21]. The complexity of interactive downstream effector pathways and the fact that EMT is not a simple matter of changes in cell adhesive capabilities or in cytoskeletal organization leads to a wide range of different profiles of expression of the markers described [21]. The choice of the markers and the changes in their expression levels will depend upon the diversity of signals inducing EMT.

2. EMT in Cancer

2.1. Carcinogenesis

Recent evidences show that transcription factors linked to EMT may directly be involved in carcinogenesis. TWIST and ZEB proteins can prevent cells from undergoing oncogene-induced senescence and apoptosis by inhibiting both TP53 and RB-dependent pathways, leading to a deregulation of MYC, RAS, ERBB2 and cell cycle inhibitors P14, P16 and P21 expression [40,41]. This may explain how TWIST1 and TWIST2 can cooperate with an activated version of RAS to transform mouse embryonic fibroblasts [41]. Furthermore, TWIST proteins also downregulate PP2A phosphatase activity and efficiently cooperate with an oncogenic version of H-RAS in malignant transformation of human mammary epithelial cells, leading to claudin-low tumours, which are believed to be the most primitive breast malignancies [42]. Thus, by downregulating crucial tumour suppressor functions, EMT inducers make cells particularly prone to malignant conversion. Beside this effect, EMT was linked to progression and metastasis through its effects on matrix, motility and gain of stem cell properties.

Both TWIST genes were reported overexpressed in many types of cancers: prostate, breast, cervical, endometrial, ovarian, head and neck cancer, oesophageal squamous cell carcinoma, gastric, hepatocellular carcinoma, pancreas, colon, kidney, glioma, melanoma, neuroblastoma, parathyroid, pheochromocytoma, sarcoma [41,43] and also NSCLC [44].

TWIST proteins are reported to induce EMT and to be one of its main actor: TWIST induces loss of E-cadherin-mediated cell-cell adhesion and an EMT in epithelial cells [45,46]. In NSCLC, the overexpression rate of TWIST proteins was 38% in tissues samples and results correlated with mRNA high level and N-cadherin expression [47]. Such a pattern was associated with worst prognosis. In cell lines, TWIST down expression inhibited cell invasion and increased apoptosis [47]. In Epidermal Growth Factor Receptor (EGFR)-mutated lung adenocarcinoma, we previously reported on surgical samples that TWIST1 expression was linked to EGFR mutations, low E-cadherin expression and low disease-free survival [44]. In cell lines, we demonstrated that EMT and the associated cell mobility were dependent upon TWIST1 expression in cells with EGFR mutation. Moreover a decrease of EGFR
pathway stimulation through EGF retrieval or an inhibition of TWIST1 expression by small RNA technology reversed the phenomenon [44]. Such results are consistent with with EGF promoting E-cadherin endocytosis to induce EMT [48] but also induction of both SNAIL and TWIST [9,49].

EMT is common in NSCLC [50] and could in some patients be related to tobacco exposure. Indeed, cigarette smoke was proved to induce EMT [51,52]. In lung adenocarcinoma cell lines (H358), cigarette smoke extracts was able to induce EMT with activation of SRC kinase and the SRC kinase inhibitor PP2 inhibited cigarette smoke-stimulated EMT changes, suggesting that SRC is critical in cigarette smoke-stimulated EMT induction [53].

2.2. Lymph Node Metastases

To the best of our knowledge, presence of EMT-MET phenomenon remains poorly studied in the metastatic lymph nodes. In gastric cancer, the expression of N-cadherin in metastatic lymph nodes was associated to a bad prognosis [54]. An other study related the heterogeneity between primary tumours and metastatic lymph nodes in oesophageal cancer, with distinct EMT phenotypes and thus, a novel independent prognostic indicator [55]. Similar results were found in head and neck cancer [56] and breast cancer [57]. Concerning NSCLC, only one study investigated EMT markers in metastatic lymph nodes [58]. Expression of Brachyury in 115 surgically resected primary NSCLC and the corresponding metastatic lymph node samples were evaluated by immunohistochemical staining. Brachyury is a highly conserved cellular protein that belongs to the T-box transcription factor family and was reported to be essential for mesoderm formation in the early embryo [59]. In recent studies Brachyury was also linked to the EMT process during cancer progression [60]. Gene expression was associated with IL-8 expression and inversely associated with E-cadherin expression in NSCLC [14]. In metastatic lymph nodes Brachyury expression was significantly higher than in the primary tumour and lymph node level of expression was inversely associated with survival [58]. In models of NSCLC, lymphangiogenesis leads to proliferation, invasiveness and nodal metastasis [61]. Vascular endothelial growth factors (VEGF) -C and -D and their corresponding receptor (VEGFR3/Flt4) are the main actors in the development of tumour-associated lymphatic vessels [62]. They recruit endothelial cells and others stromal cells to develop and maintain an unrefined lymphatic network within the tumour microenvironment [62,63]. Furthermore, they might be involved in pre-metastatic lymph nodes by preparing the lymphatic vasculature to host the cancer cells [64]. These markers were correlated in NSCLC to nodal metastasis and, thus, patient survival, with heterogeneous results [65]. A meta-analysis found a correlation between VEGF-C, Lymphatic Vessel Density and lymph node metastasis in NSCLC [65]. Links between lymphangiogenesis and EMT remain to be elucidated but EMT markers were already associated with lymphatic vessel density in surgical specimen of NSCLC [66].

2.3. Distant Metastases

Development of metastasis involves distinct steps with specific underlying molecular mechanisms, which are: detachment of tumour cells from the primary tumour, invasion into surrounding tissues, intravasation into blood or lymphatic vessels, dissemination in the blood stream or the lymphatic system and finally, extravasation and outgrowth at a secondary site [21]. Despite solid evidence showing EMT implication in distant metastases [67], the metastatic process remains unclear for many points. Reversion of EMT (MET) seems to play a role in the metastatic process, MET could at some points explain the histologic similarity between metastases and primary tumours. First, different observations reported association of MET with metastatic tumour formation: (i) epithelial phenotype seems to be of importance in the formation of secondary tumours, as epithelial characteristics were highly associated with increased distant colonization after blood stream injections [68]. (ii) E-cadherin positive metastatic foci were found after injections of mesenchymal-like breast cancer cells, presenting a direct demonstration of need for E-cadherin expression [69]. Escape from primary tumour, gain of cell mobility and invasion may at first step be EMT-dependent, then cancer cells should undergo MET
in the secondary organ. The regulation of phenotype plasticity remains largely unknown but it can be hypothesized that while the tumour microenvironment promote the induction and continuation of EMT, circulating tumour cells revert to an epithelial state due to the loss of EMT-inducing signal, before entering into metastatic sites [70]. Nevertheless, Aokage and colleagues [71] showed that MET appeared after the tumour cells arrival at the metastatic site, and considered that local microenvironment or local resident cells contribute largely to the MET. Different histopathological analyses suggested very close contact between metastatic carcinoma cells and the neighbouring parenchyma cells, supporting a possible E-cadherin-dependent linkage [72–74]. This ability to create heterotypic E-cadherin adhesions and related survival signals is coherent with the dormancy of the tumour cells and its low metabolism inherent to this micrometastatic stage [75].

Nevertheless, there are some debates about the implication of EMT in cancer progression [76,77] as aggressive tumours may, in some cases, develop metastases in the absence of EMT-MET. A point-counterpoint review, in 2005, proclaimed that the biological machinery of normal and malignant cells is sufficient to account for the events and processes observed without needing to objective radical change in cell phenotype like EMT [78] suggesting that EMT is not always a prerequisite to metastasis and that tumours may undergo partial or incomplete EMT [68]. Indeed, mesenchymal cells derived from epithelial tumour cells are very difficult to distinguish from stromal cells or other tumour-associated fibroblasts. However, EMT was described at the invasive front of tumour as small aggregates of tumour cells extending from the tumour mass into adjacent stroma [79]. Cancer cells have a broad repertoire of invasion mechanisms, and cell-type-specific patterns of cell migration can be classified into single cell migration (amoeboid, mesenchymal) and collective migration modes (cell sheets, strands, tubes, clusters) [80]. The collective migrating cells form membrane protrusions, such as ruffles and pseudopods, use cell-matrix adhesion receptors and, in contrast to solitary migration, do not retract their cellular tails but rather exert pulling forces on adjacent adherent cells [81,82]. An other potential mechanism for tumour cell invasion and metastasis is the podoplanin-mediated remodelling of actin cytoskeleton and tumour invasion [83], also described in NSCLC [84].

3. EMT-Related MicroRNAs

MicroRNAs (miRNA) are highly conserved small single-stranded non-coding RNA of 21-23 nucleotides acting as post-transcriptional regulators of gene expression. They function to affect RNA stability and translation in order to negatively regulate gene expression [85]. MicroRNAs are transcribed from DNA by RNA polymerase II or III as a form of long primary transcripts (pri-miRNA) [86] which are then processed by the microprocessor complex containing RNase III enzyme Drosha and DGCR8 (DiGeorge syndrome chromosomal region 8) into shorter stem-loop-structured double-stranded RNA (hairpin precursor miR, pre-miR) [87]. Pre-miR are delocalized from nucleus to cytoplasm and processed into mature-miR by RNase enzyme III Dicer [88]. The RNA interference is finally efficient into the RNA-induced silencing complex (RISC) to target single-stranded complementary messenger-RNA (mRNA) for translation repression or mRNA degradation, by binding to the 3’ untranslated regions of their target genes [89]. The target mRNA could be blocked in case of partial complementarity or degraded in case of perfect complementarity [90]. Thus, the possible imperfect match offers the ability to regulate many genes.

In normal lung, the overall expression profile of miRNAs is 75% similar in mouse and human lung, indicating evolutionary conservation of miRNAs expression [91]. However, miRNAs expression profile varies along development and profiles differ between human foetal, post-natal and adult lung [91]. In adult lung tissues the 30 most highly expressed miRNAs were identified as [91]: miR-103, miR-99a, miR-15b, miR-150, miR-320, miR-23a, miR-200c, miR-195, miR-27b, miR-199a, miR-92, miR-29b, miR-30d, let-7g, miR-223, miR-199a, miR-30c, miR-142-3p, miR-125a, miR-26b, miR-29a, miR-126, miR-29c, miR-16, let-7b, miR-145, miR-21, let-7a, miR-30b and miR-26a. In parallel, tissue-specific
miR were found without any correspondence with the previous list [92]: miR-224, miR-137, miR-192, miR-886, miR-31, miR-92b, miR-10a, miR-625, miR-301a, miR-96 and let-7i.

Reports of miRNA implication in diseases began in the 2000s, with a first description that miRNAs were dysregulated in human B-cell chronic lymphocytic leukemia using a microarray containing miRNA probes [93]. MicroRNAs were then studied in many situations, hepatic viral infections [94], Alzheimer disease [95], cardiac hypertrophy [96], diabetes [97] and in various lung diseases such as chronic obstructive pulmonary disease, sarcoidosis, pulmonary fibrosis [98,99]. MicroRNAs have been shown to play a crucial part in cancer development and progression in the past decade, in various solid organ cancers. Half of miRNAs genes are located at fragile sites or genomic regions involved in cancer-related chromosomal abnormalities [100]. MicroRNAs were then characterized as “OncomiR” or “Tumour suppressor miR” depending on the suppressed target genes [101–103]. Finally, microRNAs functions studies showed their capacity to affect pathways regulating EMT [1,76,104]. The microRNAs regulatory network is highly complex and deeply integrated into cell functions. The different studies may be heterogeneous and difficult to compare, different models can be used including cancer tissues and cell lines. Moreover, despite tissue preservation, RNA studies remain shaky and submitted to numerous pitfalls before final interpretation. Two main technologies allow microRNAs analyses qPCR based and specific probes sets or high throughput sequencing. Concerning EMT, the main microRNAs involved are in one hand the miR-200 family and miR-205 that maintain the epithelial cell phenotype [104–108] and in the other hand, miR-21 is up-regulated in many cancers. It facilitates TGF-β-induced EMT [8] and was the first OncomiR to be identified. Based on comparison between tumour and normal tissue levels of expression, approximately 200 microRNAs were shown dysregulated in NSCLC [103]. MicroRNAs from the miR-200 family (miR-200a/200b/200c/141/429) have been shown to inhibit EMT, cell migration and invasion by targeting ZEB1 and ZEB2 mRNA, two repressors of E-cadherin expression [106]. Based on their chromosomal location, the miR-200 family can be split into two different gene clusters: miR-200/200b/429 (chromosome 1) and miR-200c/141 (chromosome 12) [106]. Loss of these genomic loci and subsequently loss of microRNAs expression was reported in mesenchymal cancer cell lines and linked to cancer progression including NSCLC [107]. Down-regulation of miR-200 family was also documented in cases with hypermethylation of the DNA locus [109,110]. Inversely, miR-200c has been shown to inhibit the metastasis in A549 NSCLC cell lines [111,112]. Bracken et al. showed that the promoter for the pri-miR (shared by miR-200a, miR-200b, and miR-429) is located within a 300-bp segment located 4 kb upstream of miR-200b. This promoter region is sufficient to confer expression in epithelial cells and is repressed in mesenchymal cells by ZEB1 and SIP1 through their binding to a conserved pair of ZEB-type E-box elements, located proximal to the transcription start site [113,114]. Therefore depending on extra cellular stimulations the miR-200/ZEB1/2 equilibrium may turn on epithelial or mesenchymal markers. Moreover, several other microRNAs were associated with NSCLC progression as miR-224 [115] or miR-1247 [116].

Several studies have indicated that microRNAs frequently form feedback loops, since they are regulated by transcription factors which they directly or indirectly target [117]. Siemens et al. showed that miR-34a could downregulate SNAIL as well as SLUG and ZEB1. Conversely, SNAIL can repress miR-34a by binding to E-box sequences in the miR-34a promoter thereby forming a double negative feedback loop blocking cell in a mesenchymal state [117,118].

Furthermore, in parallel to EMT regulation, microRNAs play crucial roles in carcinogenesis. Examples are (i) the negative regulatory loop between NF-κB and miR-146. In the highly metastatic human breast cancer cell line MDA-MB-231, lentiviral-mediated expression of miR-146a/b significantly downregulated the IL-1 receptor-associated kinase and the TNF receptor-associated factor 6, two key scaffold proteins in the IL-1 and Toll-like receptor signalling pathway, known to positively regulate NF-κB activity [119]. (ii) The tumour suppressor miR-34a targets CDK4/6, MET, HDAC1, E2F3 and Bcl-2 and induces cell cycle arrest and apoptosis [117].
4. MicroRNAs, EMT and NSCLC

In NSCLC, probably due to tumour heterogeneity and to different technical and analytical issues, it is difficult to find a common signature of miRNAs expression. Wang et al. [103] reviewed 4 studies comparing miRNAs profile in NSCLC tissues versus the corresponding non-cancerous lung tissues and pointed out that miRNAs identified in each study are different from the others [120–122]. However Zadran et al. [123], described a cancer-specific miRNAs signature for different solid organ cancers including lung, and Vosa et al. [124] presented the 30 most differentially expressed miRNAs in NSCLC. Supplementary Table S1 shows different published miRNAs signatures in NSCLC [120–125]. More than 150 miRNAs were identified as markers of NSCLC form 6 large studies. MiR-210, miR-143 and miR-205 were recurrently linked to NSCLC in 3 or 4 out of 6 studies. Three miRNAs (miR-195, miR-224 and miR-124a-1) are either up or downregulated and finally 130/153 miRNAs were associated to NSCLC in only 1 out of 6 studies. This illustrates the difficulties of validating relevant markers in clinics, due to the absence of specific miRNAs signature in NSCLC.

However miRNAs was evaluated as diagnostic tool, in sputum [126–128] or in plasma/serum [129] for the early detection of NSCLC. In plasma, or serum and/or exosome, different tools were elaborated, with various techniques reviewed by Hou et al. [130]. Several authors proposed single miRNA or multiple-miRNA panels useful for NSCLC screening. However, these studies remain to be validated given the heterogeneity of the normalization methods and the starting material used for RNA isolation [129–133].

To summarize published data concerning miRNAs and EMT in NSCLC, a systematic review of literature in Medline identified more than 75 articles based on cell lines studies (Table 1). Another subset of 37 articles was retained, based on studies on human NSCLC specimens leading to identify 35 miRNAs as modulator of EMT (Table 2). Figure 1 summarizes involved miRNAs in EMT in cancer.

### Table 1. List of EMT involved miRNAs based on NSCLC cell lines studies, with details on the involved pathways (green, promote EMT; red, suppress EMT; blue, controversial).

| MicroRNAs | Pathway | Cell Lines | References |
|-----------|---------|------------|------------|
| miR-10a   | XRN2    | H441, A549, HOP62 | [134] |
| miR-15b   | PEBP4   | A549       | [135] |
| miR-17    | TGF-β   | A549       | [136] |
| miR-23a   | E-cadherin | A549     | [137] |
| miR-26a   | EZH2    | SPC-A1, H1299 | [138] |
| miR-30a   | SNAI1   | A549, Calu1/3, H1299, H1395 | [139,140] |
| miR-34a   | NOTCH1  | H1299, H460 | [141] |
| miR-129a  | MCTS1   | H1299, SPC-A1, GLC-82, EPLCL-32M1, A549, H292, 16HBE, PT67 | [142] |
| miR-134   | ITGB1, MAGI2, FOXX1 | A549, H1299, A549, LC2/ad, PC3, PC9, RERF-LCKJ, RERF-LCMS, PC14, ABC-1 | [143–145] |
| miR-138   | GIT1, SEMA4C | A549, 95D, H23 | [146,147] |
| miR-145a-5p| TWIST1 | H1299 | [148] |
| miR-149   | FOXM1   | A549       | [149] |
| miR-151a-5p| TWIST1 | H1299 | [148] |
| miR-154   | ZEB2    | A549       | [150] |
| miR-155   | ZEB1    | HCC827     | [151] |
| miR-206   | PI3K/akt | A549, 95D | [152] |
| miR-211   | na      | H460, H838, H1299, H3255, HCC4006, HCC4011 | [153] |
| miR-222   | na      | H460, H838, H1299, H3255, HCC4006, HCC4011 | [153] |
| miR-337-3p| TWIST1  | H1299 | [148] |
| miR-374a  | Axl     | HCC827, Calu1 | [154] |
| miR-452   | BML1    | A549, H460 | [155] |
| miR-483a-5p| ALCAM  | A549, PC9 | [156] |
| miR-487b  | MAGI2   | A549       | [144] |
| miR-528   | ADAM9   | A549       | [157] |
| miR-543-3p| TWIST1  | H1299 | [148,158] |
| miR-544a  | Cadherina 1 | 95C, 95D | [159] |
| miR-548b  | Axl     | HCC827, Calu1 | [154] |
| miR-655   | MAGI2   | A549       | [144] |
| miR-1271  | FOXK2   | A549, H292, H1299, H358, H460 | [160] |
| miR-1246  | Stem cells | A549, HCC1588 | [161] |
| miR-1290  | Stem cells | A549, HCC1588 | [161] |
| let-7a    | HMGA2   | H1975, H1299, H1650 | [162] |
| let-7c    | Hedgehog | A549, H1299 | [163] |
Table 2. List of EMT involved miRNAs based on NSCLC tissue samples and patients’ series studies, with details on the involved pathways and the clinical impact (green, promote EMT; red, suppress EMT) (TKI, Tyrosine-Kinase Inhibitor).

| MicroRNAs | Pathways | Clinical Impact | References |
|-----------|----------|-----------------|------------|
| miR-16    | HDGF     | Cell growth and motility | [164] |
| miR-21    | STAT3, IL-6 | Carcinogenesis | [165] |
| miR-29b   | SPARC    | Cancer progression | [166] |
| miR-30    | MMP19    | Metastases | [167] |
| miR-30c   | E-cadherin, vimentin, SNAIL | Invasion | [168] |
| miR-31    | ERK1/2   | Lymph spread, survival | [169] |
| miR-33a   | TWIST1   | Metastases | [170] |
| miR-92b   | RECK     | Cell growth and motility | [171] |
| miR-96    | Fox2     | Invasion and metastases | [172] |
| miR-124   | CDH12, ZEB1 | Cell migration and invasion | [173,174] |
| miR-127   | feed-forward regulatory loop | TKI resistance | [175] |
| miR-132   | ZEB2     | Cell migration and invasion | [176] |
| miR-133a  | KLK8     | Cell migration and invasion | [177] |
| miR-133b  | Hippo signaling pathway | Metastases | [178] |
| miR-143   | CD44     | Cell migration and invasion | [179] |
| miR-145   | SMAD3    | Invasion | [180] |
| miR-146a  | IRS2     | Cancer progression | [181] |
| miR-146b  | ROCK1    | Lymph spread | [182] |
| miR-150   | p53      | Cell proliferation | [183] |
| miR-158b  | Fox2     | Invasion and metastases | [172] |
| miR-183   | Fox2     | Invasion and metastases | [172] |
| miR-184   | c-Myc    | Overall and disease-free survival | [184] |
| miR-193a  | WTI-E-cadherin axis + ERBB4/PK3R3/mTOR/S6K2 signaling pathway | Metastases | [185,186] |
| miR-196a  | HOXA5    | Cell proliferation, invasion | [187] |
| miR-196b  | NF-κB, Homeobox A9 | Cell invasion and migration | [188] |
| miR-200a  | ZEB1, Fox2 | Invasion and metastases | [172,178] |
| miR-200c  | E-cadherin, ETAR, NFκB | Invasion and metastases | [190–195] |
| miR-203   | SMAD3    | Invasion | [180] |
| miR-205   | CRIPTO1  | TKI resistance | [194] |
| miR-214   | Sufu     | Metastases | [195] |
| miR-338-3p| Sox4     | Metastases | [196] |
| miR-561   | FOXM1    | Cell proliferation and invasion | [197] |
| miR-575   | YAP1     | Neuroendocrine features | [198] |
| miR-451   | RAB14    | pTNM, Lymph spread | [199] |
| miR-489   | SUZ12    | Cell invasion | [200] |
| miR-490   | poly r(C)-binding protein 1 | Metastases, lymph spread | [201] |
| miR-589   | HDAC5    | Cell migration and invasion | [202] |
| miR-541   | TGFβ2    | Cancer progression | [203] |
| miR-638   | SOX2     | Cell proliferation and invasion | [204] |
To go further in the interpretation of the data, regulation of TWIST1 by miRNAs was investigated by Nairismägi et al. [148]. They identified 18 miRNAs targeting TWIST1’s 3’UTR region but only 3 were able to significantly repress TWIST1 translation: miR-145a-5p, miR-151-5p and in combination: miR-145a-5p + miR-151-5p and miR-151-5p + miR-337-3p. Among the many roles attributed to miRNAs in cancer, understanding their interaction with oncogenes and signalling pathways is of importance as it could lead to treatment strategies. In NSCLC, activation of the EGFR pathway plays a critical role in tumour development. A subset of miRNAs has been shown to interact with the EGFR pathway either as activators (miR-21, 24, 25 or miR-7) or repressors (miR-133) and may therefore modulate EGFR pathway activation. Concerning RAS activation and miRNAs in NSCLC, miR-31 was shown to target 6 regulators of the RAS/MAPK pathway and regulate lung epithelial cell growth. MiR-31 has been described to cooperate with RAS to drive lung tumorigenesis. Studies have revealed that miRNAs constitute a regulatory network in the post-transcriptional regulation of pathway genes. In parallel, tumour genetic background seems to impact on miRNAs profiles. Indeed, specific miRNAs profiles are associated to EGFR, KRAS or WT tumours [211]. In a high-throughput screening program in NSCLC, miR-155 was upregulated only in EGFR/KRAS negative group, miR-25 was upregulated only in EGFR positive group and miR-495 was upregulated only in KRAS positive adenocarcinomas [211].

We have previously reported an oncogenic cooperation between EGFR activation and TWIST1 reactivation in EGFR mutated NSCLC. Using NSCLC cell lines, Takeyama et al. showed that EGFR mutated cell lines had more epithelial characteristics as compared to non-EGFR mutated cell lines and that the mesenchymal state in the second group was related to ZEB1 upregulation [212]. It seems therefore that mutational status could drive specific EMT pathways.

For other pathways involved in NSCLC, experiments suggested that miR-19 induces EMT [213]. MiR-19 and miR-21 regulate PTEN levels [213]. High miR-19 levels were found in NSCLC cells and experiments suggest that PTEN is involved in miR-19-induced EMT, migration and invasion [213].

Inflammatory cytokines and hypoxia have been proven to promote EMT. NF-κB itself is regulated by miRNAs through different regulatory loops of which the mir-146/NF-κB was documented in A549 cell line [214]. Moreover, NF-κB-mediated inflammation was shown to lead to EMT due to decrease in miR-200c [191] and in nuclear stabilization of SNAIL1 [34]. Hypoxia directly triggers EMT through the ubiquitin C-terminal hydrolase-L1 (UCH-L1) and HIF-1α deubiquitination [215]. TWIST1 is a direct target of HIF1-α. In cancer cells, hypoxia was shown to reactivate TWIST1 [6], allowing cell to disseminate to a less hostile microenvironment [14,15]. Furthermore, hypoxia induces SNAIL in NSCLC [216]. Relations between ROS and EMT have been established [217,218]. ROS can activate NF-κB signalling and Wnt-β-catenin signalling pathway [217].

As seen, interaction loops between miRNAs and oncogenes or miRNAs and EMT transcription factors were largely described and seem cell and/or model dependent. It is sometimes hard to decipher whether miRNAs dysregulation is at the origin or is a consequence of the EMT process. Approximately half of miRNAs are associated with CpG islands [219] and several studies illustrated that methylation status could be responsible for the dysregulated expression of miRNAs in NSCLC [116,202,220,221]. Such a phenomenon was described for miR-200 inactivation under SNAIL1 control to maintain the mesenchymal phenotype [222]. In addition, histone acetylation may influence miRNAs expression [223]. Histone modifications were identified as the main mechanisms of miR-212 silencing in NSCLC [224]. DNA methylation and histone modifications are also largely associated with EMT regulation [225].

An emergent pathway in cancer is the involvement of Prion protein (PrP) [226]. Several studies reported overexpression of the PrP in cancer and particularly, links with EMT via direct influence of PrP on neural cell adhesion molecules (NCAM) [227], certain matrix metalloproteinases [228] and Fyn activation [229].

As a summary, Figure 2 illustrates the complex regulation of EMT in NSCLC.
Figure 2. Hallmarks of the complex regulation of EMT in NSCLC. The regulation of EMT in NSCLC is based on several intricate conditions and actors, detailed in the Section 4 (adapted from [24,44,111,116,148,191,202,206,207,216,220,221]).

5. Clinical Impact of EMT in NSCLC

EMT is largely involved in cancer development and in metastatic progression. For that it was frequently associated with prognosis [14,44,230–232]. The prognostic impact of miRNAs was investigated and some authors proposed prognostic miRNAs signature, in gastric and in NSCLC [233]. Using a cohort of 112 NSCLC patients, the last study identified a 5-miRNA-signature including 3 high-risk miRNAs (miR-137, miR-182*, and miR-372) and 2 protective miRNAs (miR-221 and let-7a). Another study identified a miRNAs profile counting only miR-155 and let-7a-2 [121]. The pooled results of a meta-analyse including 28 articles [234] revealed that high expression of miR-125b, miR-21 and miR-200c were negatively associated with survival. Conversely, high expression of miR-124, miR-365, miR-32, miR-148b, miR-146a and miR-375 were significantly associated with better prognosis [234]. However, the critical point with EMT is the associated chemo-resistance [235–238]. Therefore, understanding the mechanistic of EMT is important to assess treatment strategies for patients with NSCLC.

Upregulation or reactivation of inducing EMT transcription factors activates survival pathways (NF-κB, AKT), proliferation pathways (upregulation of EGFR and MET) and modulates the activity of Bcl-2 family members thereby favouring antiapoptotic signals [25]. Resistance to genotoxic agents such as anthracyclines, platinum-based drugs or spindle poison was associated to EMT. Data suggests that oxaliplatin-resistant colorectal cancer [239], gemcitabine-resistant tumour cells [240] tamoxifen-resistant breast cancer [241], gemcitabine-resistant pancreatic cancer, radiotherapy-resistant endometrial carcinoma [242] and radiotherapy-resistant ovarian cancer cells [243] harbour phenotypes of EMT [25]. Similar results were observed in NSCLC cell lines for cisplatin [244], docetaxel in
A549 and for the pemetrexed-cisplatin combination [245,246]. Moreover resistance to treatment in adjuvant setting was also reported [247]. Increased viability or drug resistance could be due to lower levels of ROS and subsequent better genome protection in cell undergoing EMT [25,248]. In NSCLC with EGFR mutations or ALK fusions, EMT was also related to resistance to tyrosine-kinase inhibitors (TKI) [249,250]. NSCLC lines expressing E-cadherin showed greater sensitivity to EGFR inhibition. In contrast, NSCLC lines expressing vimentin and/or fibronectin were insensitive to EGFR inhibition [39]. Data suggested that, in some cases, TGFβ activation is sufficient to induce TKI resistance and, in smokers population, SRC activation could trigger EMT and subsequent EGFR-TKI resistance [251]. Furthermore, EMT increases membrane transporters expression (ABC family, P-glycoprotein) leading to drug active efflux [246,252,253]. Finally EMT-induced decrease of ceramide was associated to chemo-resistance [254–256].

The association between EMT and stem-like phenotype in NSCLC cells was shown in several in vitro studies [257–259] but the data on this phenomenon in lung cancer patient samples are limited. Koren et al. showed that BMI1 and CD133 (cancer stem-cell markers) were coexpressed in a series of operated NSCLC, giving in vivo evidence of connection between EMT and cancer stem cells [260]. Such tumour subpopulation plays a role in drug resistant tumour cells with abilities of self-renewal, cancer initiation, and further maintenance of tumours [261].

MicroRNAs have been implicated in chemo-resistance as well as in chemo-sensitivity. As seen in the first parts of this review, miRNAs regulate pathways implicated in cell fate: proliferation, apoptosis and differentiation and thereby influence chemotherapy and radiotherapy responses. There are as many models in the literature as different contexts or situations describing a miRNA or a set of miRNAs related to treatment failure. Acquired chemo-resistance, to cisplatin, docetaxel and erlotinib in NSCLC [135,262] was related to up or downregulation of miRNAs linked to EMT: miR-140, miR-628, miR-135b, miR-200b/200c/141, miR-205, miR-197, miR-224, miR-34c, miR301a, miR-636, miR-518f [263]. In EGFR mutated tumours CpG island hypermethylation was shown to downregulated miR-200 family members in cells with gefitinib resistance and EMT features. More precisely, miR-200c downregulation was linked to the upregulation of LIN28B a protein favouring stem cell self-renewal [264]. Moreover several afatinib-resistant NSCLC cell lines also displayed EMT features and epigenetic silencing of miR-200c suggesting that miR-200 downregulation could be a common event in TKI acquired resistance [252].

Furthermore, an opposite point-of-view must be presented: some observations lead to consider the epithelial phenotype as drug-resistant. Byers et al. proposed a 76-gene EMT signature to classify NSCLC cell lines into distinct epithelial and mesenchymal groups [265]. Surprisingly, EGRF-mutated cell lines H1975 and H820, carrying the acquired-resistance mutation T790M, were classified as epithelial. Furthermore, they found a trend towards greater relative sensitivity in mesenchymal cells as compared to epithelial for cisplatin, gemcitabine and vinorelbine. This observation was also supported by the the work of Miow et al., who reported that ovarian cancer cell lines with an epithelial pattern were more resistant to cisplatin than those with a mesenchymal pattern [266]. This concept remains poorly documented and is largely counterbalanced by abundant literature on mesenchymal status-driven drug resistance. However it may be related with two distinct models of EMT: acquired phenotype of EMT following drug, growth factor or EMT-transcription factor treatment versus inherent phenotype of EMT related to the nature of the cancer cell [1,265,266].

Drug resistance and EMT have been clearly associated in different situations and genetic backgrounds but the mechanisms underlying drug resistance remain under investigation however some explanations could rely on miRNAs expression.

6. Therapies Targeting EMT

Inhibition of EMT could restore senescence and apoptosis capacity [46]. In a recent review, Malek et al. proposed 3 distinct strategies to target EMT through (a) extracellular inducers of EMT, (b) EMT-transcription factors and (c) downstream effectors of EMT inhibition [267].
First (a), inhibition of extracellular EMT-inducer pathways could rely on TGF-β blockade using rapamycin, 17-AAG [268], SB-431542 [269] or TGF-β receptor specific inhibitors such as EW-7195, EW-7203 and EW-7197 [270–273]. Only LY2157299 an oral TGF-βRI tyrosine kinase inhibitor reached clinical trials and is currently tested in several cancers, excluding NSCLC despite previous encouraging preclinical results [274]. Direct blockade of TGFβ using human TGFβ-antibody (fresolimumab) was not yet explored in NSCLC. Besides TGFβ blockade, interesting results were shown using LDN57444, a specific small molecule inhibitor, targeting ubiquitin carboxy-terminal hydrolase L1 (UCH-L1). LDN57444 was shown to downregulate HIF-1α, suppress EMT features and reduce the incidence of distant metastases [275,276]. Concerning extracellular EMT inducers, MMP as metastases-related cellular enzymes could appear as good candidates. However, MMP inhibitors failed in clinical trials likely due to the complexity of the metastatic process [277].

Second (b), inhibition of EMT transcription factors was analysed as a therapeutic option and illustrated by results based on TWIST1 [41,42,45,278–280]; PRMT1 [281] and SNAIL family and ZEB1/2 inhibition [20,282]. EMT-transcription factors are challenging therapeutic targets due to their heterogeneous expression and to the complexity of the EMT regulation network [283,284]. However, several agents were proved efficient in cell lines, including plant extracts: moscatilin [285], fucoidan [286], quercetin [287], thymoquinone [288], imipramine blue [289] and finally, in vitro and in vivo data on NSCLC suggest a potential impact of the harmala alkaloids to downregulate TWIST1 [267]. Targeting glycosylation pathways that regulate EMT transcription factors should be an interesting mean of treatment. Aberrant glycosylation was associated with carcinogenesis in many cancers including NSCLC [290,291] and inhibitors of one of the main glycosylation enzyme are in preclinical pipelines [292,293]. Moreover chromatin modulators such as drugs targeting histone methyltransferases (G9a and EZH2) and demethylases which contributes to EMT as E-cadherin repressors are promising epigenetic oncotargets [294,295]. Finally, histone deacetylation can be inhibited by HDAC inhibitors (butyrate, trichostatin A and Suberoylanilide hydroxamic acid which is the FDA-approved Vorinostat) and have been shown in preclinical studies to selectively target cancer cells by inducing apoptosis, cell cycle arrest, suppression of tumour angiogenesis, metastasis and invasion at least partially through upregulating E-cadherin [267,296,297].

Third (c), targeting the downstream effectors of EMT such as E-cadherin, N-cadherin, vimentin and HoxA9 may offer some possibilities [267]. MicroRNAs have emerged as a class of therapeutics targets. However there are some limitations due to the fact that miRNAs have typically many targets. This can either be harmful as it limits specificity but can also be interesting to consider if miRNAs blockage leads to the inhibition at different levels of a pathway, using a single agent. Therapeutic strategy could be either direct administration of anti-miRNA (antisens miRNA) to block OncomiR, or restoration of miRNAs expression to reactivate miRNAs with onco-suppressive functions [206,298–300]. Local delivery of miR-200 members into the tumour endothelium showed reduction of metastasis and angiogenesis in several experimental models of ovarian, lung, renal and basal-like breast cancers [301]. In NSCLC, enforced expression of miR-145 inhibited EMT and metastatic ability [208].

Nevertheless, inhibiting or reversing EMT could also lead to a serious adverse event: favouring MET and thus colonisation of metastatic sites by circulating tumour cells [67,302]. Moreover, the intra-tumour and inter-tumour heterogeneity in case of multiple sites, and the dynamic nature of epithelial plasticity in cancer suggests that to be efficient the strategy should be multimodal and not focusing only on a single EMT-related target. As examples, combination of chemotherapy and anti-miRNA strategies and also models of miRNA replacement therapy were tested in vitro and in mouse models [264,303]. Sato et al. showed that the introduction of miR-200c using pre-miR-200c caused LIN28B suppression in cells with acquired EGFR-TKI resistance that harbour ed EMT features (HCC4006 after chronic exposure to gefinitib) [264]. Van Roosbroeck et al. proposed the use of cisplatin and anti-miR-155 in a mouse model of athymic nude mice (intrapulmonary injections of A549 cells
stably infected with lentivirus containing a miR-155-overexpressing lentiviral vector) with significant results in term of primary tumour size and mediastinal lymph nodes [303].

Finally EMT is pointed out as a mechanism of resistance to immunotherapy and is involved in the shaping of the immune microenvironment. It was recently shown in NSCLC that tumours with EMT features expressed PDL1 and other immune checkpoints molecules and suggested that EMT should be further investigated as a predictor of response to immunotherapies [304]. Immunotherapy should then be considered as an anti-EMT therapy [305–307].

7. Conclusions

EMT is a highly regulated multistep process that is implicated in cancer progression through activation of proliferation pathways, loss of response to apoptotic signals, gain of stem cell properties, matrix remodelling and mobility. EMT involves various signalling pathways and crosstalk as well as a network of transcription factors. Upstream non-coding RNAs such as miRNAs have emerged as potent modulators of EMT. The physiopathology of the EMT process is highly dependent upon the cellular model, the environment and the EMT stimulating factors. Therefore cells undergoing EMT may express different markers. Moreover quantifying the degree of EMT in a tumour remains a challenging task due to its transient and reversible nature. However, some features such as loss of E-cadherin, reactivation of TWIST1, ZEB1 and SNAIL and downregulation of the miR-200 cluster could be common features of EMT in NSCLC.

Because of its link with metastasis and resistance to treatment, EMT has emerged as a useful prognosis and predictive marker but there is yet no clinical application in NSCLC. Our understanding of EMT is growing and may enable us to forward EMT characterization to the clinics. The development of methods to investigate molecular profiles or EMT signature using small amounts of tissues and FFPE sample will help validate EMT markers in clinical settings. Finally, EMT is a promising therapeutic target to overcome drug resistance in NSCLC in patients treated with chemotherapy, targeted therapies and immunotherapies. Because of the complexity of the EMT regulation network, the treatment will rely on integrative personalize care and high throughput molecular screenings.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6694/9/8/101/s1. Table S1: MicroRNA signatures in NSCLC [120–125].

Acknowledgments: Laura Spurrier (MD student) for English editing. No funding was received for this work.

Author Contributions: Hélène Blons, Pierre Laurent-Puig and Antoine Legras designed the review; Nicolas Pécuchet, Sandrine Imbeaud, Karine Pallier, Audrey Didelot, Hélène Roussel, Laure Gibault and Elizabeth Fabre contributed to literature review; Antoine Legras and Hélène Blons wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Kalluri, R.; Weinberg, R.A. The basics of epithelial-mesenchymal transition. J. Clin. Invest. 2009, 119, 1420–1428. [CrossRef] [PubMed]
2. Byrum, C.; Martindale, M. Gastrulation in the cnidaria and ctenophora. In Gastrulation; Stern CD: New York, NY, USA, 2004.
3. Thompson, E.W.; Haviv, I. The social aspects of EMT-MET plasticity. Nat. Med. 2011, 17, 1048–1049. [CrossRef] [PubMed]
4. Lim, J.; Thiery, J.P. Epithelial-mesenchymal transitions: insights from development. Dev. Camb. Engl. 2012, 139, 3471–3486. [CrossRef] [PubMed]
5. Thiery, J.P.; Acloque, H.; Huang, R.Y.; Nieto, M.A. Epithelial-mesenchymal transitions in development and disease. Cell 2009, 139, 871–890. [CrossRef] [PubMed]
6. Yang, J.; Weinberg, R.A. Epithelial-mesenchymal transition: At the crossroads of development and tumor metastasis. Dev. Cell 2008, 14, 818–829. [CrossRef] [PubMed]
7. Zaravinos, A. The Regulatory Role of MicroRNAs in EMT and Cancer. J. Oncol. 2015, 2015, 865816. [CrossRef] [PubMed]
8. Zavadil, J.; Böttinger, E.P. TGF-beta and epithelial-to-mesenchymal transitions. *Oncogene* 2005, 24, 5764–5774. [CrossRef] [PubMed]

9. Lo, H.-W.; Hsu, S.-C.; Xia, W.; Cao, X.; Shih, J.-Y.; Wei, Y.; Abubrushese, J.L.; Hortobagi, G.N.; Hung, M.-C. Epidermal growth factor receptor cooperates with signal transducer and activator of transcription 3 to induce epithelial-mesenchymal transition in cancer cells via up-regulation of TWIST gene expression. *Cancer Res.* 2007, 67, 9066–9076. [CrossRef] [PubMed]

10. Lee, J.M.; Dedhar, S.; Kalluri, R.; Thompson, E.W. The epithelial-mesenchymal transition: New insights in signaling, development, and disease. *J. Cell Biol.* 2006, 172, 973–981. [CrossRef] [PubMed]

11. Acevedo, V.D.; Gangula, R.D.; Freeman, K.W.; Li, R.; Zhang, Y.; Wang, F.; Ayala, G.E.; Peterson, L.E.; Ittmann, M.; Spencer, D.M. Inducible FGFR-1 activation leads to irreversible prostate adenocarcinoma and an epithelial-to-mesenchymal transition. *Cancer Cell* 2007, 12, 559–571. [CrossRef] [PubMed]

12. Savagner, P.; Yamada, K.M.; Thiery, J.P. The zinc-finger protein slug causes desmosome dissociation, an initial and necessary step for growth factor-induced epithelial-mesenchymal transition. *J. Cell Biol.* 1997, 137, 1403–1419. [CrossRef] [PubMed]

13. Graham, T.R.; Zhau, H.E.; Odero-Marah, V.A.; Osunkoya, A.O.; Kimbro, K.S.; Hahlbrock, C.; Pollet, I.; Karsan, A. Jagged1-mediated Notch activation induces epithelial-to-mesenchymal transition through Slug-induced repression of E-cadherin. *Cancer Res.* 2008, 68, 2479–2488. [CrossRef] [PubMed]

14. Yang, M.-H.; Wu, M.-Z.; Chiu, S.-H.; Chen, P.-M.; Chang, S.-Y.; Liu, C.-J.; Teng, S.-C.; Wu, K.-J. Direct regulation of TWIST by HIF-1alpha promotes metastasis. *Nat. Cell Biol.* 2008, 10, 295–305. [CrossRef] [PubMed]

15. Gort, E.H.; van Haften, G.; Verlaan, I.; Groot, A.J.; Plasterk, R.H.A.; Shvarts, A.; Suijkerbuijk, K.P.M.; van Laar, T.; van der Wall, E.; Raman, V.; et al. The TWIST1 oncogene is a direct target of hypoxia-inducible factor-2alpha. *Oncogene* 2008, 27, 1501–1510. [CrossRef] [PubMed]

16. Leong, K.G.; Niessen, K.; Kulic, I.; Raouf, A.; Aves, C.; Pollet, I.; Karsan, A. Jagged1-mediated Notch activation induces epithelial-to-mesenchymal transition through Slug-induced repression of E-cadherin. *J. Exp. Med.* 2007, 204, 2935–2948. [CrossRef] [PubMed]

17. Takai, E.; Tsukimoto, M.; Kojima, S. TGF-β1 downregulates COX-2 expression leading to decrease of PGE2 production in human lung cancer A549 cells, which is involved in fibrotic response to TGF-β1. *PLoS ONE* 2013, 8, e76346. [CrossRef] [PubMed]

18. Shintani, Y.; Maeda, M.; Chaika, N.; Johnson, K.R.; Wheelock, M.J. Collagen I promotes epithelial-to-mesenchymal transition in lung cancer cells via transforming growth factor-beta signaling. *Am. J. Respir. Cell Mol. Biol.* 2008, 38, 95–104. [CrossRef] [PubMed]

19. Zoltan-Jones, A.; Huang, L.; Ghattak, S.; Toole, B.P. Elevated hyaluronan production induces mesenchymal and transformed properties in epithelial cells. *J. Biol. Chem.* 2003, 278, 45801–45810. [CrossRef] [PubMed]

20. Tania, M.; Khan, M.A.; Fu, J. Epithelial to mesenchymal transition inducing transcription factors and metastatic cancer. *Tumour Biol.* J. Int. Soc. Oncodevelopmental Biol. Med. 2014, 35, 7335–7342. [CrossRef] [PubMed]

21. Yilmaz, M.; Christofori, G. EMT, the cytoskeleton, and cancer cell invasion. *Cancer Metastasis Rev.* 2009, 28, 15–33. [CrossRef] [PubMed]

22. Wang, Y.; Shi, J.; Chai, K.; Ying, X.; Zhou, B.P. The Role of Snail in EMT and Tumorigenesis. *Curr. Cancer Drug Targets* 2013, 13, 963–972. [CrossRef] [PubMed]

23. Zhang, P.; Sun, Y.; Ma, L. ZEB1: At the crossroads of epithelial-mesenchymal transition, metastasis and therapy resistance. *Cell Cycle* 2015, 14, 481–487. [CrossRef] [PubMed]

24. Gemmill, R.M.; Roche, J.; Potiron, V.A.; Nasarre, P.; Mitas, M.; Coldren, C.D.; Helfrich, B.A.; Garrett-Mayer, E.; Bunn, P.A.; Drabkin, H.A. ZEB1-responsive genes in non-small cell lung cancer. *Oncogene* 2008, 27, 9066–9076. [CrossRef] [PubMed]

25. Ansieau, S.; Morel, A.-P.; Hinkel, G.; Bastid, J.; Puisieux, A. TWISTing an embryonic transcription factor into an oncoprotein. *Oncogene* 2010, 29, 3173–3184. [CrossRef] [PubMed]

26. Yin, Z.; Xu, X.L.; Frasch, M. Regulation of the twist target gene tinman by modular cis-regulatory elements during early mesoderm development. *Dev. Camb. Engl.* 1997, 124, 4971–4982.
28. Pan, D.; Fujimoto, M.; Lopes, A.; Wang, Y.-X. Twist-1 is a PPARdelta-inducible, negative-feedback regulator of PGC-1alpha in brown fat metabolism. *Cell* 2009, 137, 73–86. [CrossRef] [PubMed]

29. Šošić, D.; Richardson, J.A.; Yu, K.; Ornitz, D.M.; Olson, E.N. Twist regulates cytokine gene expression through a negative feedback loop that represses NF-kappaB activity. *Cell* 2003, 112, 169–180. [CrossRef]

30. Sharif, M.N.; Sosic, D.; Rothlin, C.V.; Kelly, E.; Lemke, G.; Olson, E.N.; Ivashkiv, L.B. Twist mediates suppression of inflammation by type I IFNs and Axl. *J. Exp. Med.* 2006, 203, 1891–1901. [CrossRef] [PubMed]

31. Thuault, S.; Tan, E.-J.; Peinado, H.; Cano, A.; Heldin, C.-H.; Moustakas, A. HMGA2 and Smads co-regulate Snail1 expression during induction of epithelial-to-mesenchymal transition. *J. Biol. Chem.* 2008, 283, 33437–33446. [CrossRef] [PubMed]

32. Micalizzi, D.S.; Christensen, K.L.; Jedlicka, P.; Coletta, R.D.; Baron, A.E.; Harrell, J.C.; Horwitz, K.B.; Billheimer, D.; Heichman, K.A.; Welm, A.L.; et al. The Six1 homeoprotein induces human mammary carcinoma cells to undergo epithelial-mesenchymal transition and metastasis in mice through increasing TGF-beta signaling. *J. Clin. Invest.* 2009, 119, 2678–2690. [CrossRef] [PubMed]

33. Peinado, H.; Olmeda, D.; Cano, A. Snail, Zeb and bHLH factors in tumour progression: An alliance against the epithelial phenotype? *Nat. Rev. Cancer* 2007, 7, 415–428. [CrossRef] [PubMed]

34. Wu, Y.; Deng, J.; Rychahou, P.G.; Qu, S.; Evers, B.M.; Zhou, B.P. Stabilization of snail by NF-kappaB is required for inflammation-induced cell migration and invasion. *Cancer Cell* 2009, 15, 416–428. [CrossRef] [PubMed]

35. Yamashita, S.; Miyagi, C.; Fukada, T.; Kağara, N.; Che, Y.-S.; Hirano, T. Zinc transporter LIVI controls epithelial-mesenchymal transition in zebrafish gastrula organizer. *Nature* 2004, 429, 298–302. [CrossRef] [PubMed]

36. Ikenouchi, J.; Matsuda, M.; Furuse, M.; Tsukita, S. Regulation of tight junctions during the epithelium-mesenchyme transition: Direct repression of the gene expression of claudins/occludin by Snail. *J. Cell Sci.* 2003, 116, 1959–1967. [CrossRef] [PubMed]

37. Moreno-Bueno, G.; Portillo, F.; Cano, A. Transcriptional regulation of cell polarity in EMT and cancer. *Oncogene* 2008, 27, 6958–6969. [CrossRef] [PubMed]

38. Billottet, C.; Tuefferd, M.; Gentien, D.; Rapinat, A.; Thiery, J.-P.; Broët, P.; Jouanneau, J. Modulation of several waves of gene expression during FGF-1 induced epithelial-mesenchymal transition of carcinoma cells. *J. Cell. Biochem.* 2008, 104, 826–839. [CrossRef] [PubMed]

39. Xiao, D.; He, J. Epithelial mesenchymal transition and lung cancer. *J. Thorac. Dis.* 2010, 2, 154–159. [CrossRef] [PubMed]

40. Valsesia-Wittmann, S.; Magdeleine, M.; Dupasquier, S.; Garin, E.; Jallas, A.-C.; Combaret, V.; Krause, A.; Leissner, P.; Puisieux, A. Oncogenic cooperation between H-Twist and N-Myc overrides failsafe programs in cancer cells. *Cancer Cell* 2004, 6, 625–630. [CrossRef] [PubMed]

41. Ansieau, S.; Bastid, J.; Doreau, A.; Morel, A.-P.; Bouchet, B.P.; Thomas, C.; Fauvet, F.; Puisieux, I.; Doglioni, C.; Piccinin, S.; et al. Induction of EMT by twist proteins as a collateral effect of tumor-promoting inactivation of premature senescence. *Cancer Cell* 2008, 14, 79–89. [CrossRef] [PubMed]

42. Morel, A.-P.; Hinkal, G.W.; Thomas, C.; Fauvet, F.; Courtis-Cox, S; Wierinckx, A; Devouassou-Shisheboran, M.; Treilleux, I.; Tissier, A.; Gras, B.; et al. EMT inducers catalyze malignant transformation of mammary epithelial cells and drive tumorigenesis towards claudin-low tumors in transgenic mice. *PLoS Genet.* 2012, 8, e1002723. [CrossRef] [PubMed]

43. Puisieux, A.; Valsesia-Wittmann, S.; Ansieau, S. A twist for survival and cancer progression. *Br. J. Cancer* 2006, 94, 13–17. [CrossRef] [PubMed]

44. Pallier, K.; Cessot, A.; Côté, J.-F.; Just, P.-A.; Cazes, A.; Fabre, E.; Danel, C.; Riquet, M.; Devouassou-Shisheboran, M.; Ansieau, S.; Puisieux, A.; et al. TWIST1 a new determinant of epithelial to mesenchymal transition in EGFR mutated lung adenocarcinoma. *PLoS ONE* 2012, 7, e29954. [CrossRef] [PubMed]

45. Yang, J.; Mani, S.A.; Donaher, J.L.; Ramaswamy, S.; Itzykson, R.A.; Come, C.; Savagner, P.; Gitelman, I.; Richardson, A.; Weinberg, R.A. Twist, a master regulator of morphogenesis, plays an essential role in tumor metastasis. *Cell* 2004, 117, 927–939. [CrossRef] [PubMed]

46. Weinberg, R.A. Twisted epithelial-mesenchymal transition blocks senescence. *Nat. Cell Biol.* 2008, 10, 1021–1023. [CrossRef] [PubMed]
47. Hui, L.; Zhang, S.; Dong, X.; Tian, D.; Cui, Z.; Qiu, X. Prognostic significance of twist and N-cadherin expression in NSCLC. *PLoS ONE* 2013, 8, e62171. [CrossRef] [PubMed]

48. Lu, Z.; Ghosh, S.; Wang, Z.; Hunter, T. Downregulation of caveolin-1 function by EGF leads to the loss of E-cadherin, increased transcriptional activity of beta-catenin, and enhanced tumor cell invasion. *Cancer Cell* 2003, 4, 499–515. [CrossRef]

49. Lee, M.-Y.; Chou, C.-Y.; Tang, M.-J.; Shen, M.-R. Epithelial-mesenchymal transition in cervical cancer: Correlation with tumor progression, epidermal growth factor receptor overexpression, and snail up-regulation. *Clin. Cancer Res.* 2008, 14, 4743–4750. [CrossRef]

50. Tsoukalas, N.; Aravantinou-Fatorou, E.; Tolia, M.; Giaginis, C.; Galanopoulos, M.; Kikakou, M.; Kostakis, I.D.; Dana, E.; Vamvakaris, I.; Korogiannos, A.; et al. Epithelial-mesenchymal transition in non small-cell lung cancer. *Anticancer Res.* 2017, 37, 1773–1778. [CrossRef]

51. Milara, J.; Peiró, T.; Serrano, A.; Cortijo, J. Epithelial to mesenchymal transition is increased in patients with COPD and induced by cigarette smoke. *Thorax* 2013, 68, 410–420. [CrossRef] [PubMed]

52. Wang, Q.; Wang, Y.; Zhang, Y.; Zhang, Y.; Xiao, W. The role of uPAR in epithelial-mesenchymal transition in small airway epithelium of patients with chronic obstructive pulmonary disease. *Respir. Res.* 2013, 14, 67. [CrossRef] [PubMed]

53. Zhang, H.; Liu, H.; Borok, Z.; Davies, K.J.A.; Ursini, F.; Forman, H.J. Cigarette smoke extract stimulates epithelial-mesenchymal transition through Src activation. *Free Radic. Biol. Med.* 2012, 52, 1437–1442. [CrossRef] [PubMed]

54. Okubo, K.; Uenosono, Y.; Arigami, T.; Yanagita, S.; Matsushita, D.; Kijima, T.; Amatatsu, M.; Uchikado, Y.; Kijima, Y.; Maemura, K.; et al. Clinical significance of altering epithelial-mesenchymal transition in metastatic lymph nodes of gastric cancer. *Gastric Cancer* 2017. [CrossRef] [PubMed]

55. Wen, J.; Luo, K.-J.; Liu, Q.-W.; Wang, G.; Zhang, M.-F.; Xie, X.-Y.; Yang, H.; Fu, J.-H.; Hu, Y. The epithelial-mesenchymal transition phenotype of metastatic lymph nodes impacts the prognosis of esophageal squamous cell carcinoma patients. *Oncotarget* 2016, 7, 37581–37588. [CrossRef] [PubMed]

56. Lee, W.-Y.; Shin, D.-Y.; Kim, H.J.; Ko, Y.-H.; Kim, S.; Jeong, H.-S. Prognostic significance of epithelial-mesenchymal transition of extracapsular spread tumors in lymph node metastases of head and neck cancer. *Ann. Surg. Oncol.* 2014, 21, 1904–1911. [CrossRef] [PubMed]

57. Yu, H.; Simons, D.L.; Segall, I.; Carcamo-Cavazos, V.; Schwartz, E.J.; Yan, N.; Zuckerman, N.S.; Dirbas, F.M.; Johnson, D.L.; Holmes, S.P.; et al. PRC2/EED-EZH2 complex is up-regulated in breast cancer lymph node metastasis compared to primary tumor and correlates with tumor proliferation in situ. *PLoS ONE* 2012, 7, e51239. [CrossRef] [PubMed]

58. Shimamatsu, S.; Okamoto, T.; Haro, A.; Kitahara, H.; Kohno, M.; Morodomi, Y.; Tagawa, T.; Okano, S.; Oda, Y.; Maehara, Y. Prognostic Significance of Expression of the Epithelial-Mesenchymal Transition-Related Factor Brachyury in Intrathoracic Lymphatic Spread of Non-Small Cell Lung Cancer. *Ann. Surg. Oncol.* 2016, 23, 1012–1020. [CrossRef] [PubMed]

59. Kispert, A.; Herrmann, B.G. Immunohistochemical analysis of the Brachyury protein in wild-type and mutant mouse embryos. *Dev. Biol.* 1994, 161, 179–193. [CrossRef] [PubMed]

60. Larocca, C.; Cohen, J.R.; Fernandez, R.I.; Huang, B.; Hamilton, D.H.; Palena, C. An autocrine loop between TGF-β1 and the transcription factor brachyury controls the transition of human carcinoma cells into a mesenchymal phenotype. *Mol. Cancer Ther.* 2013, 12, 1805–1815. [CrossRef] [PubMed]

61. Su, J.-L.; Yang, P.-C.; Shih, J.-Y.; Yang, C.-Y.; Wei, L.-H.; Hsieh, C.-Y.; Chou, C.-H.; Jeng, Y.-M.; Wang, M.-Y.; Chang, K.-J.; et al. The VEGF-C/Flt-4 axis promotes invasion and metastasis of cancer cells. *Cancer Cell* 2006, 9, 209–223. [CrossRef] [PubMed]

62. Alitalo, A.; Detmar, M. Interaction of tumor cells and lymphatic vessels in cancer progression. *Oncogene* 2012, 31, 4499–4508. [CrossRef] [PubMed]

63. Adams, R.H.; Alitalo, K. Molecular regulation of angiogenesis and lymphangiogenesis. *Nat. Rev. Mol. Cell Biol.* 2007, 8, 464–478. [CrossRef] [PubMed]

64. Liersch, R.; Hirakawa, S.; Berdel, W.E.; Mesters, R.M.; Detmar, M. Induced lymphatic sinus hyperplasia in sentinel lymph nodes by VEGF-C as the earliest premetastatic indicator. *Int. J. Oncol.* 2012, 41, 2073–2078. [CrossRef] [PubMed]
65. Kilvaer, T.K.; Paulsen, E.-E.; Hald, S.M.; Wilsgaard, T.; Breunnes, R.M.; Busund, L.-T.; Donnem, T. Lymphangiogenic Markers and Their Impact on Nodal Metastasis and Survival in Non-Small Cell Lung Cancer—A Structured Review with Meta-Analysis. PloS ONE 2015, 10, e0132481. [CrossRef] [PubMed]

66. Zhou, L.; Yu, L.; Wu, S.; Feng, Z.; Song, W.; Gong, X. Clinicopathological significance of KAI1 expression and epithelial-mesenchymal transition in non-small cell lung cancer. World J. Surg. Oncol. 2015, 13, 234. [CrossRef] [PubMed]

67. Tsai, J.H.; Donaher, J.L.; Murphy, D.A.; Chau, S.; Yang, J. Spatiotemporal regulation of epithelial-mesenchymal transition is essential for squamous cell carcinoma metastasis. Cancer Cell 2012, 22, 725–736. [CrossRef] [PubMed]

68. Chaffer, C.L.; Brennan, J.P.; Slavin, J.L.; Blick, T.; Thompson, E.W.; Williams, E.D. Mesenchymal-to-epithelial transition facilitates bladder cancer metastasis. Cancer Res. 2006, 66, 11271–11278. [CrossRef] [PubMed]

69. Chao, Y.L.; Shepard, C.R.; Wells, A. Breast carcinoma cells re-express E-cadherin during mesenchymal to epithelial reverting transition. Mol. Cancer 2010, 9, 179. [CrossRef] [PubMed]

70. Frisch, S.M. The epithelial cell default-phenotype hypothesis and its implications for cancer. BioEssays News Rev. Mol. Cell. Dev. Biol. 1997, 19, 705–709. [CrossRef] [PubMed]

71. Aokage, K.; Ishii, G.; Ohtaki, Y.; Yamaguchi, Y.; Hishida, T.; Yoshida, J.; Nishimura, M.; Nagai, K.; Ochiai, A. Dynamic molecular changes associated with epithelial-mesenchymal transition and subsequent mesenchymal-epithelial transition in the early phase of metastatic tumor formation. Int. J. Cancer 2011, 128, 1585–1595. [CrossRef] [PubMed]

72. Rubin, M.A.; Mucci, N.R.; Figurski, J.; Fecko, A.; Pienta, K.J.; Day, M.L. E-cadherin expression in prostate cancer: A broad survey using high-density tissue microarray technology. Hum. Pathol. 2001, 32, 690–697. [CrossRef] [PubMed]

73. Kowalski, P.; Rubin, M.A.; Kleer, C.G. E-cadherin expression in primary carcinomas of the breast and its distant metastases. Breast Cancer Res. 2003, 5, R217–R222. [CrossRef] [PubMed]

74. Imai, T.; Horiuchi, A.; Shiozawa, T.; Osada, R.; Kikuchi, N.; Ohira, S.; Oka, K.; Konishi, I. Elevated expression of E-cadherin and alpha-, beta-, and gamma-catenins in metastatic lesions compared with primary epithelial ovarian carcinomas. Hum. Pathol. 2004, 35, 1469–1476. [CrossRef] [PubMed]

75. Wells, A.; Yates, C.; Shepard, C.R. E-cadherin as an indicator of mesenchymal to epithelial reverting transitions during the metastatic seeding of disseminated carcinomas. Clin. Exp. Metastasis 2008, 25, 621–628. [CrossRef] [PubMed]

76. Meng, F.; Wu, G. The rejuvenated scenario of epithelial-mesenchymal transition (EMT) and cancer metastasis. Cancer Metastasis Rev. 2012, 31, 455–467. [CrossRef] [PubMed]

77. Diepenbruck, M.; Christofori, G. Epithelial-mesenchymal transition (EMT) and metastasis: Yes, no, maybe? Curr. Opin. Cell Biol. 2016, 43, 7–13. [CrossRef] [PubMed]

78. Tarin, D.; Thompson, E.W.; Newgreen, D.F. The fallacy of epithelial mesenchymal transition in neoplasia. Cancer Res. 2005, 65, 5996–6001. [CrossRef] [PubMed]

80. Friedl, P. Tumour budding in colorectal carcinoma. Histopathology 2007, 50, 151–162. [CrossRef] [PubMed]

81. Wicki, A.; Christofori, G. The potential role of podoplanin in tumour invasion. Br. J. Cancer 2007, 96, 1–5. [CrossRef] [PubMed]

82. Friedl, P.; Hegerfeldt, Y.; Tusch, M. Collective cell migration in morphogenesis and cancer. Int. J. Dev. Biol. 2004, 48, 441–449. [CrossRef] [PubMed]

83. Wicki, A.; Christofori, G. Tumor invasion in the absence of epithelial-mesenchymal transition: Podoplanin-mediated remodeling of the actin cytoskeleton. Cancer Cell 2006, 9, 261–272. [CrossRef] [PubMed]

84. Van Rooij, E. The art of microRNA research. Circ. Res. 2011, 108, 219–234. [CrossRef] [PubMed]

85. Cullen, B.R. Transcription and processing of human microRNA precursors. Mol. Cell 2004, 16, 861–865. [CrossRef] [PubMed]
87. Denli, A.M.; Tops, B.B.J.; Plasterk, R.H.A.; Ketting, R.F.; Hannon, G.J. MicroRNAs as regulators of epithelial-mesenchymal transition. *Nature* 2004, 432, 231–235. [CrossRef] [PubMed]

88. Ketting, R.F.; Fischer, S.E.; Bernstein, E.; Sijen, T.; Hannon, G.J.; Plasterk, R.H. Dicer functions in RNA interference and in synthesis of small RNA involved in developmental timing in *C. elegans*. *Genes Dev.* 2001, 15, 2654–2659. [CrossRef] [PubMed]

89. Sontheimer, E.J. Assembly and function of RNA silencing complexes. *Nat. Rev. Mol. Cell Biol.* 2005, 6, 127–138. [CrossRef] [PubMed]

90. Gregory, R.I.; Chendrimada, T.P.; Cooch, N.; Shiekhattar, R. Human RISC couples microRNA biogenesis and posttranscriptional gene silencing. *Cell* 2005, 123, 631–640. [CrossRef] [PubMed]

91. Williams, A.E.; Moschos, S.A.; Perry, M.M.; Barnes, P.J.; Lindsay, M.A. Maternally imprinted microRNAs are differentially expressed during mouse and human lung development. *Dev. Dyn. Off. Publ. Am. Assoc. Anat.* 2007, 236, 572–580. [CrossRef] [PubMed]

92. Landgraf, P.; Rusu, M.; Sheridan, R.; Aissani, A.; Iovino, N.; Pfeffer, S.; Rice, A.; Kamphorst, A.O.; Landthaler, M.; et al. A mammalian microRNA expression atlas based on small RNA library sequencing. *Cell* 2007, 129, 1401–1414. [CrossRef] [PubMed]

93. Calin, G.A.; Liu, C.-G.; Sevignani, C.; Ferracin, M.; Felli, N.; Dumitru, C.D.; Shimizu, M.; Cimmino, A.; Zupo, S.; Dono, M.; et al. MicroRNA profiling reveals distinct signatures in B cell chronic lymphocytic leukemia. *Proc. Natl. Acad. Sci. USA* 2004, 101, 11755–11760. [CrossRef] [PubMed]

94. Gupta, A.; Swaminathan, G.; Martin-Garcia, J.; Navas-Martin, S. MicroRNAs, hepatitis C virus, and HCV/HIV-1 co-infection: New insights in pathogenesis and therapy. *Viruses* 2012, 4, 2485–2513. [CrossRef] [PubMed]

95. Cui, L.; Li, Y.; Ma, G.; Wang, Y.; Cai, Y.; Liu, S.; Chen, Y.; Li, J.; Xie, Y.; Liu, G.; et al. A functional polymorphism in the promoter region of microRNA-146a is associated with the risk of Alzheimer disease and the rate of cognitive decline in patients. *PLoS ONE* 2014, 9, e89019. [CrossRef] [PubMed]

96. Zhang, Z.; Li, J.; Liu, B.; Luo, C.; Dong, Q.; Zhao, L.; Zhong, Y.; Chen, W.; Chen, M.; Liu, S. MicroRNA-26 was decreased in rat cardiac hypertrophy model and may be a promising therapeutic target. *J. Cardiovasc. Pharmacol.* 2013, 62, 312–319. [CrossRef] [PubMed]

97. Karolina, D.S.; Armugam, A.; Iavintharan, S.; Kong, M.T.K.; Lim, S.C.; Sum, C.F.; Jeyaseelan, K. MicroRNA-144 impairs insulin signaling by inhibiting the expression of insulin receptor substrate 1 in type 2 diabetes mellitus. *PLoS ONE* 2011, 6, e22839. [CrossRef]

98. Ebrahimi, A.; Sadroddiny, E. MicroRNAs in lung diseases: Recent findings and their pathophysiological implications. *Pulm. Pharmacol. Ther.* 2015, 34, 55–63. [CrossRef] [PubMed]

99. Alipoor, S.D.; Adcock, I.M.; Garssen, J.; Mortaz, E.; Varahram, M.; Mirsaeidi, M.; Velayati, A. The roles of miRNAs as potential biomarkers in lung diseases. *Eur. J. Pharmacol.* 2016, 791, 395–404. [CrossRef] [PubMed]

100. Calin, G.A.; Sevignani, C.; Dumitru, C.D.; Hyslop, T.; Noch, E.; Yendamuri, S.; Shimizu, M.; Rattan, S.; Bullrich, F.; Negrini, M.; et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc. Natl. Acad. Sci. USA* 2004, 101, 2999–3004. [CrossRef] [PubMed]

101. Esquela-Kerscher, A.; Slack, F.J. Oncomirs-microRNAs with a role in cancer. *Nat. Rev. Cancer* 2006, 6, 259–269. [CrossRef] [PubMed]

102. Wang, D.; Qiu, C.; Zhang, H.; Wang, J.; Cui, Q.; Yin, Y. Human microRNA oncogenes and tumor suppressors show significantly different biological patterns: From functions to targets. *PLoS ONE* 2010, 5. [CrossRef] [PubMed]

103. Wang, Q.Z.; Xu, W.; Habib, N.; Xu, R. Potential uses of microRNA in lung cancer diagnosis, prognosis, and therapy. *Curr. Cancer Drug Targets* 2009, 9, 572–594. [CrossRef] [PubMed]

104. Gregory, P.A.; Bracken, C.P.; Bert, A.G.; Goodall, G.J. MicroRNAs as regulators of epithelial-mesenchymal transition. *Cell Cycle Georget. Tex* 2008, 7, 3112–3118. [CrossRef] [PubMed]

105. Korpal, M.; Lee, E.S.; Hsu, G.; Kang, Y. The miR-200 family inhibits epithelial-mesenchymal transition and cancer cell migration by direct targeting of E-cadherin transcriptional repressors ZEB1 and ZEB2. *J. Biol. Chem.* 2008, 283, 14910–14914. [CrossRef] [PubMed]

106. Park, S.-M.; Gaur, A.B.; Lengyel, E.; Peter, M.E. The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2. *Genes Dev.* 2008, 22, 894–907. [CrossRef] [PubMed]
Cancers 2017, 9, 101

107. Gregory, P.A.; Bert, A.G.; Paterson, E.L.; Barry, S.C.; Tsykin, A.; Farshid, G.; Vadas, M.A.; Khew-Goodall, Y.; Goodall, G.J. The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. Nat. Cell Biol. 2008, 10, 593–601. [CrossRef] [PubMed]

108. Paterson, E.L.; Kolesnikoff, N.; Gregory, P.A.; Bert, A.G.; Khew-Goodall, Y.; Goodall, G.J. The microRNA-200 family regulates epithelial to mesenchymal transition. Sci. World J. 2008, 8, 901–904. [CrossRef] [PubMed]

109. Díaz-Martin, J.; Díaz-López, A.; Moreno-Bueno, G.; Castilla, M.Á.; Rosa-Rosa, J.M.; Cano, A.; Palacios, J. A core microRNA signature associated with inducers of the epithelial-to-mesenchymal transition. J. Pathol. 2014, 232, 319–329. [CrossRef] [PubMed]

110. Davalos, V.; Moutinho, C.; Villanueva, A.; Boque, R.; Silva, P.; Carneiro, F.; Esteller, M. Dynamic epigenetic regulation of the microRNA-200 family mediates epithelial and mesenchymal transitions in human tumorigenesis. Oncogene 2012, 31, 2062–2074. [CrossRef] [PubMed]

111. Jiao, A.; Sui, M.; Zhang, L.; Sun, P.; Geng, D.; Zhang, W.; Wang, X.; Li, J. MicroRNA-200c inhibits the metastasis of non-small cell lung cancer cells by targeting ZEB2, an epithelial-mesenchymal transition regulator. Mol. Med. Rep. 2016, 13, 3349–3355. [CrossRef] [PubMed]

112. Roybal, J.D.; Zang, Y.; Ahn, Y.-H.; Yang, Y.; Gibbons, D.L.; Baird, B.N.; Alvarez, C.; Thilaganathan, N.; Liu, D.D.; Saintigny, P.; et al. miR-200 Inhibits Lung Adenocarcinoma Cell Invasion and Metastasis by Targeting Fli1/VEGFR1. Mol. Cancer Res. 2011, 9, 25–35. [CrossRef] [PubMed]

113. Bracken, C.P.; Gregory, P.A.; Kolesnikoff, N.; Bert, A.G.; Wang, J.; Shannon, M.F.; Goodall, G.J. A double-negative feedback loop between ZEB1-SIP1 and the microRNA-200 family regulates epithelial-mesenchymal transition. Cancer Res. 2008, 68, 7846–7854. [CrossRef] [PubMed]

114. Hill, L.; Browne, G.; Tulchinsky, E. ZEB/miR-200 feedback loop: At the crossroads of signal transduction in cancer. Int. J. Cancer 2013, 132, 745–754. [CrossRef] [PubMed]

115. Cui, R.; Meng, W.; Sun, H.-L.; Kim, T.; Ye, Z.; Fassan, M.; Jeon, Y.-J.; Li, B.; Vicentini, C.; Peng, Y.; et al. Silencing of miR-1247 by DNA methylation promoted nonsmall cell lung cancer. Mol. Cancer 2011, 10, 4256–4271. [CrossRef] [PubMed]

116. Zhang, J.; Fu, J.; Pan, Y.; Zhang, X.; Shen, L. Silencing of miR-1247 by DNA methylation promoted nonsmall-cell lung cancer cell invasion and migration by effects of STMN1. OncoTargets Ther. 2016, 9, 7297–7307. [CrossRef] [PubMed]

117. Chan, S.-H.; Wang, L.-H. Regulation of cancer metastasis by microRNAs. J. Biomed. Sci. 2015, 22, 9. [CrossRef] [PubMed]

118. Siemens, H.; Jackstadt, R.; Hünten, S.; Kaller, M.; Menssen, A.; Götz, U.; Hermeking, H. MiR-34 and SNAIL form a double-negative feedback loop to regulate epithelial-mesenchymal transitions. Cell Cycle Georget. Tex. 2011, 10, 4256–4271. [CrossRef] [PubMed]

119. Bhau Mikhail, D.; Scott, G.K.; Shokkur, S.; Patil, C.K.; Campisi, J.; Benz, C.C. Expression of microRNA-146 suppresses NF-kappaB activity with reduction of metastatic potential in breast cancer cells. Oncogene 2008, 27, 5643–5647. [CrossRef] [PubMed]

120. Volinia, S.; Calin, G.A.; Liu, C.-G.; Ambros, V.; Savino, V.; Petrocca, F.; Fais, V.; Sorrentino, S.; Zoppetti, G.; Roldo, C.; Ferracin, M.; et al. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc. Natl. Acad. Sci. 2006, 103, 2257–2261. [CrossRef] [PubMed]

121. Yanaihara, N.; Caplen, N.; Bowman, E.; Seike, M.; Kumamoto, K.; Yi, M.; Stephens, R.M.; Okamoto, A.; Yokota, J.; Tanaka, T.; et al. Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. Cancer Cell 2006, 9, 189–198. [CrossRef] [PubMed]

122. Peltier, H.J.; Latham, G.J. Normalization of microRNA expression levels in quantitative RT-PCR assays: Identification of suitable reference RNA targets in normal and cancerous human solid tissues. RNA 2008, 14, 844–852. [CrossRef] [PubMed]

123. Zadran, S.; Remacle, F.; Levine, R.D. MiRNA and mRNA cancer signatures determined by analysis of expression levels in large cohorts of patients. Proc. Natl. Acad. Sci. USA 2013, 110, 19160–19165. [CrossRef] [PubMed]

124. Vösa, U.; Vooder, T.; Kolde, R.; Fischer, K.; Välk, K.; Tönnissen, N.; Roosipuu, R.; Vilo, J.; Metspalu, A.; Annilo, T. Identification of miR-374a as a prognostic marker for survival in patients with early-stage nonsmall cell lung cancer. Genes. Chromosomes Cancer (2011), 50, 812–822. [CrossRef] [PubMed]
125. Cazzoli, R.; Buttitta, F.; Di Nicola, M.; Malatesta, S.; Marchetti, A.; Rom, W.N.; Pass, H.I. MicroRNAs derived from circulating exosomes as noninvasive biomarkers for screening and diagnosing lung cancer. J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer 2013, 8, 1156–1162. [CrossRef] [PubMed]

126. Su, Y.; Fang, H.; Jiang, F. Integrating DNA methylation and microRNA biomarkers in sputum for lung cancer detection. Clin. Epigenetics 2016, 8, 109. [CrossRef] [PubMed]

127. Razzak, R.; Bédard, E.L.R.; Kim, J.O.; Gazala, S.; Guo, L.; Ghosh, S.; Joy, A.; Nijjar, T.; Wong, E.; Roa, W.H. MicroRNA expression profiling of sputum for the detection of early and locally advanced non-small-cell lung cancer: A prospective case-control study. Curr. Oncol. Tor. Ont. 2016, 23, e86–e94. [CrossRef] [PubMed]

128. Xie, Y.; Todd, N.W.; Liu, Z.; Zhan, M.; Fang, H.; Peng, H.; Alattar, M.; Deepak, J.; Stass, S.A.; Jiang, F. Altered miRNA expression in sputum for diagnosis of non-small cell lung cancer. Lung Cancer Amst. Neth. 2010, 67, 170–176. [CrossRef] [PubMed]

129. Zhang, H.; Mao, F.; Shen, T.; Luo, Q.; Ding, Z.; Qian, L.; Huang, J. Plasma miR-145, miR-20a, miR-21 and miR-223 as novel biomarkers for screening early-stage non-small cell lung cancer. Oncol. Lett. 2017, 13, 669–676. [CrossRef] [PubMed]

130. Hou, J.; Meng, F.; Chan, L.W.C.; Cho, W.C.S.; Wong, S.C.C. Circulating Plasma MicroRNAs As Diagnostic Markers for NSCLC. Front. Genet. 2016, 7, 193. [CrossRef] [PubMed]

131. Giallombardo, M.; Reclusa, P.; Valentino, A.; Sirera, R.; Pauwels, P.; Rolfo, C. P2.07: Evaluation of different exosomal RNA isolation methods in nsccl liquid biopsies: Track: Biology and pathogenesis. J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer 2016, 11, S220–S221. [CrossRef] [PubMed]

132. Reclusa, P.; Giallombardo, M.; Castiglia, M.; Sorber, L.; Van Der Steen, N.; Pauwels, P.; Rolfo, C. P2.06: Exosomal miRNA analysis in non-small cell lung cancer: New liquid biomarker?: Track: Biology and pathogenesis. J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer 2016, 11, S219–S220. [CrossRef] [PubMed]

133. Rolfo, C.; Giallombardo, M.; Reclusa, P.; Sirera, R.; Peeters, M. Exosomes in lung cancer liquid biopsies: Two sides of the same coin? Lung Cancer Amst. Neth. 2017, 104, 134–135. [CrossRef] [PubMed]

134. Zhang, H.; Lu, Y.; Chen, E.; Li, X.; Lv, B.; Vikis, H.G.; Liu, P. XRN2 promotes EMT and metastasis through regulating maturation of miR-10a. Oncogene 2017. [CrossRef] [PubMed]

135. Zhao, Z.; Zhang, L.; Yao, Q.; Tao, Z. MiR-15b regulates cisplatin resistance and metastasis by targeting TGFbetaR2 in NSCLC. PLoS ONE 2014, 9, e94639. [CrossRef] [PubMed]

136. Cao, M.; Seike, M.; Soeno, C.; Mizutani, H.; Kitamura, K.; Minegishi, Y.; Noro, R.; Yoshimura, A.; Cai, L.; Gemma, A. MiR-23a regulates TGF-β-induced epithelial-mesenchymal transition by targeting E-cadherin in lung cancer cells. Int. J. Oncol. 2012, 41, 869–875. [CrossRef] [PubMed]

137. Chen, J.; Xu, Y.; Tao, L.; Pan, Y.; Zhang, K.; Wang, R.; Chen, L.-B.; Chu, X. MiRNA-26a Contributes to the Acquisition of Malignant Behaviors of Doctaxel-Resistant Lung Adenocarcinoma Cells through Targeting EZH2. Cell. Physiol. Biochem. Int. J. Exp. Cell. Physiol. Biochem. Pharmacol. 2017, 41, 583–597. [CrossRef] [PubMed]

138. Liu, K.; Guo, L.; Guo, Y.; Zhou, B.; Li, T.; Yang, H.; Yin, R.; Xi, T. AEG-1 3′-untranslated region functions as a ceRNA in inducing epithelial-mesenchymal transition of human non-small cell lung cancer by regulating miR-30a activity. Eur. J. Cell Biol. 2015, 94, 22–31. [CrossRef] [PubMed]

139. Kumarswamy, R.; Mudduluru, G.; Ceppi, P.; Muppala, S.; Kozlowski, M.; Niklinski, J.; Papotti, M.; Allgayer, H. MicroRNA-30a inhibits epithelial-to-mesenchymal transition by targeting Sna11 and is downregulated in non-small cell lung cancer. Int. J. Cancer 2012, 130, 2044–2053. [CrossRef] [PubMed]

140. Kang, J.; Kim, E.; Kim, W.; Seong, K.M.; Youn, H.; Kim, J.W.; Kim, J.; Youn, B. Rhamnetin and cirsiliol induce radiosensitization and inhibition of epithelial-mesenchymal transition (EMT) by miR-34a-mediated suppression of Notch-1 expression in non-small cell lung cancer cell lines. J. Biol. Chem. 2013, 288, 27343–27357. [CrossRef] [PubMed]

141. Liu, M.-X.; Zhou, K.-C.; Cao, Y. MCR51 overexpression, which is specifically inhibited by miR-129*, promotes the epithelial-mesenchymal transition and metastasis in non-small cell lung cancer. Mol. Cancer 2014, 13, 245. [CrossRef] [PubMed]

142. Qin, Q.; Wei, F.; Zhang, J.; Li, B. MiR-134 suppresses the migration and invasion of non-small cell lung cancer by targeting ITGB1. Oncol. Rep. 2017, 37, 823–830. [CrossRef] [PubMed]
144. Kitamura, K.; Seike, M.; Okano, T.; Matsuda, K.; Miyanaga, A.; Mizutani, H.; Noro, R.; Minegishi, Y.; Kubota, K.; Gemma, A. MiR-134/487b/655 cluster regulates TGF-β-induced epithelial-mesenchymal transition and drug resistance to gefitinib by targeting MAGI2 in lung adenocarcinoma cells. *Mol. Cancer Ther.* **2014**, *13*, 444–453. [CrossRef] [PubMed]

145. Li, J.; Wang, Y.; Luo, J.; Fu, Z.; Ying, J.; Yu, Y.; Yu, W. MiR-134 inhibits epithelial to mesenchymal transition by targeting FOXM1 in non-small cell lung cancer cells. *FEBS Lett.* **2012**, *586*, 3761–3765. [CrossRef] [PubMed]

146. Li, J.; Wang, Q.; Wen, R.; Liang, J.; Zhong, X.; Yang, W.; Su, D.; Tang, J. MiR-138 inhibits cell proliferation and reverses epithelial-mesenchymal transition in non-small cell lung cancer cells by targeting GIT1 and SEMA4C. *J. Cell. Mol. Med.* **2015**, *19*, 2793–2805. [CrossRef] [PubMed]

147. Jin, Z.; Guan, L.; Song, Y.; Xiang, G.-M.; Chen, S.-X.; Gao, B. MicroRNA-138 regulates chemoresistance in human non-small cell lung cancer via epithelial mesenchymal transition. *Eur. Rev. Med. Pharmacol. Sci.* **2016**, *20*, 1080–1086. [PubMed]

148. Nairismägi, M.-L.; Füchtbauer, A.; Labouriau, R.; Bramsen, J.B.; Füchtbauer, E.-M. The proto-oncogene TWIST1 is regulated by microRNAs. *PLoS ONE* **2013**, *8*, e66070. [CrossRef] [PubMed]

149. Ke, Y.; Zhao, W.; Xiong, J.; Cao, R. MiR-149 Inhibits Non-Small-Cell Lung Cancer Cells EMT by Targeting FOXM1. *Biochem. Res. Int.* **2013**, *2013*, 506731. [CrossRef] [PubMed]

150. Lin, X.; Yang, Z.; Zhang, P.; Liu, Y.; Shao, G. MiR-154 inhibits migration and invasion of human non-small cell lung cancer cell by targeting ZEB2. *Oncol. Lett.* **2016**, *12*, 301–306. [CrossRef] [PubMed]

151. Narita, M.; Shimura, E.; Nagasawa, A.; Aiuchi, T.; Suda, Y.; Hamada, Y.; Ikegami, D.; Iwasawa, C.; Arakawa, K.; Igarashi, K.; et al. Chronic treatment of non-small-cell lung cancer cells with gefitinib leads to an epigenetic loss of epithelial properties associated with reductions in microRNA-155 and -200c. *PLoS ONE* **2017**, *12*, e0172115. [CrossRef] [PubMed]

152. Chen, Q.; Jiao, D.; Wu, Y.; Chen, J.; Wang, J.; Tang, X.; Mou, H.; Hu, H.; Song, J.; Yan, J.; et al. MiR-206 inhibits cell proliferation and reverses epithelial-mesenchymal transition and drug resistance to gefitinib in lung adenocarcinoma cells. *Cancers* **2017**, *9*, 101. [CrossRef] [PubMed]

153. Yamashita, R.; Sato, M.; Kakumu, T.; Hase, T.; Yogo, N.; Maruyama, E.; Sekido, Y.; Kondo, M.; Hasegawa, Y. Epithelial and mesenchymal properties are associated with stemness and invasiveness of non-small cell lung cancer. *Cancer Res.* **2014**, *74*, 3031–3042. [CrossRef] [PubMed]

154. Wang, Y.; Xia, H.; Zhuang, Z.; Miao, L.; Chen, X.; Cai, H. Axl-altered microRNAs regulate tumorigenicity and gefitinib resistance in lung cancer. *Cell Death Dis.* **2014**, *5*, e1227. [CrossRef] [PubMed]

155. Zhang, Y.; Han, L.; Pang, J.; Wang, Y.; Feng, F.; Jiang, Q. Expression of microRNA-452 via adenoviral vector inhibits non-small cell lung cancer cells proliferation and metastasis. *Tumour Biol.* **2016**, *37*, 8259–8270. [CrossRef] [PubMed]

156. Song, Q.; Xu, Y.; Yang, C.; Chen, Z.; Jia, C.; Chen, J.; Zhang, Y.; Lai, P.; Fan, X.; Zhou, X.; et al. MiR-483-5p promotes invasion and metastasis of lung adenocarcinoma by targeting RhoGDI1 and ALCAM. *Cancers* **2017**, *9*, 1080–1086. [PubMed]

157. Van Kampen, J.G.M.; van Hooij, O.; Jansen, C.F.; Smit, F.P.; van Noort, P.I.; Schultz, I.; Schaapveld, R.Q.J.; Arakawa, K.; Igarashi, K.; et al. Chronic treatment of non-small-cell lung cancer cells with gefitinib leads to an epigenetic loss of epithelial properties associated with reductions in microRNA-155 and -200c. *PLoS ONE* **2013**, *8*, e66070. [CrossRef] [PubMed]

158. Alam, M.; Ahmad, R.; Rajabi, H.; Kufe, D. MUC1-C Induces the LIN28B →LET-7 →HMGA2 Axis to Regulate Self-Renewal in NSCLC. *Mol. Cancer Res.* **2015**, *13*, 449–460. [CrossRef] [PubMed]
163. Ahmad, A.; Maitah, M.Y.; Ginnebaugh, K.R.; Li, Y.; Bao, B.; Gadgeel, S.M.; Sarkar, F.H. Inhibition of Hedgehog signaling sensitizes NSCLC cells to standard therapies through modulation of EMT-regulating miRNAs. J. Hematol. Oncol. 2013, 6, 77. [CrossRef] [PubMed]

164. Ke, Y.; Zhao, W.; Xiong, J.; Cao, R. Downregulation of miR-16 promotes growth and motility by targeting HDGF in non-small cell lung cancer cells. FEBS Lett. 2013, 587, 3153–3157. [CrossRef] [PubMed]

165. Luo, F.; Xu, Y.; Ling, M.; Zhao, Y.; Xu, W.; Liang, X.; Jiang, R.; Wang, B.; Bian, Q.; Liu, Q. Arsenite evokes IL-6 secretion, autocrine regulation of STAT3 signaling, and miR-21 expression, processes involved in the EMT and malignant transformation of human bronchial epithelial cells. Toxicol. Appl. Pharmacol. 2013, 273, 27–34. [CrossRef] [PubMed]

166. Grant, J.L.; Fishbein, M.C.; Hong, L.-S.; Krysan, K.; Minna, J.D.; Shay, J.W.; Walser, T.C.; Dubinett, S.M. A novel molecular pathway for Snail-dependent, SPARC-mediated invasion in non-small cell lung cancer pathogenesis. Cancer Prev. Res. 2014, 7, 150–160. [CrossRef] [PubMed]

167. Yu, G.; Herazo-Maya, J.D.; Nukui, T.; Romkes, M.; Parwani, A.; Juan-Guardela, B.M.; Robertson, J.; Gauldie, J.; Siegfried, J.M.; Kaminski, N.; et al. MicroRNA-30c promotes invasion by inducing epithelial-mesenchymal transition in non-small cell lung cancer. Mol. Med. Rep. 2014, 10, 2575–2579. [CrossRef] [PubMed]

168. Zhong, Z.; Xia, Y.; Wang, P.; Liu, B.; Chen, Y. Inhibition of miR-92b suppresses nonsmall cell lung cancer cells growth and motility by targeting RECK. Mol. Cell. Biochem. 2014, 387, 171–176. [CrossRef] [PubMed]

169. Li, Z.; Wang, X.; Li, W.; Wu, L.; Chang, L.; Chen, H. MiRNA-124 modulates lung carcinoma cell migration and invasion. Int. J. Clin. Pharmacol. Ther. 2016, 54, 603–612. [CrossRef] [PubMed]

170. Shi, H.; Ji, Y.; Zhang, D.; Liu, Y.; Fang, P. MiR-135a inhibits migration and invasion and regulates EMT-related marker genes by targeting KLF8 in lung cancer cells. Biochem. Biophys. Res. Commun. 2015, 465, 125–130. [CrossRef] [PubMed]

171. Lin, C.-W.; Chang, Y.-L.; Chang, Y.-C.; Lin, J.-C.; Chen, C.-C.; Pan, S.-H.; Wu, C.-T.; Chen, H.-Y.; Yang, S.-C.; Hong, T.-M.; et al. MicroRNA-135b promotes lung cancer metastasis by regulating multiple targets in the Hippo pathway and LZTS1. Nat. Commun. 2013, 4, 1877. [CrossRef] [PubMed]
180. Hu, H.; Xu, Z.; Li, C.; Xu, C.; Lei, Z.; Zhang, H.-T.; Zhao, J. MiR-145 and miR-203 represses TGF-β-induced epithelial-mesenchymal transition and invasion by inhibiting SMAD3 in non-small cell lung cancer cells. *Lung Cancer Anst. Neth.* 2016, 97, 87–94. [CrossRef] [PubMed]

181. Park, D.H.; Jeon, H.S.; Lee, S.Y.; Choi, Y.Y.; Lee, H.W.; Yoon, S.; Lee, J.C.; Yoon, Y.S.; Kim, D.S.; Na, M.J.; et al. MicroRNA-146a inhibits epithelial mesenchymal transition in non-small cell lung cancer by targeting insulin receptor substrate 2. *Int. J. Oncol.* 2015, 47, 1545–1553. [CrossRef] [PubMed]

182. Li, J.; Song, Y.; Wang, Y.; Luo, J.; Yu, W. MicroRNA-148a suppresses epithelial-to-mesenchymal transition by targeting ROCK1 in non-small cell lung cancer cells. *Mol. Cell. Biochem.* 2013, 380, 277–282. [CrossRef] [PubMed]

183. Zhang, N.; Wei, X.; Xu, L. MiR-150 promotes the proliferation of lung cancer cells by targeting P53. *FEBS Lett.* 2013, 587, 2346–2351. [CrossRef] [PubMed]

184. Lin, T.-C.; Lin, P.-L.; Cheng, Y.-W.; Wu, T.-C.; Chou, M.-C.; Chen, C.-Y.; Lee, H. MicroRNA-184 Deregulated Promotes Tumor Malignancy and Poor Outcomes in Non-Small Cell Lung Cancer via Targeting CDC25A and c-Myc. *Ann. Surg. Oncol.* 2015, 22 (Suppl. 3), S1532–S1539. [CrossRef] [PubMed]

185. Chen, J.; Gao, S.; Wang, C.; Wang, Z.; Zhang, H.; Huang, K.; Zhou, B.; Li, H.; Yu, Z.; Wu, J.; et al. Eratum to: Pathologically decreased expression of miR-193a contributes to metastasis by targeting WT1-E-cadherin axis in non-small cell lung cancers. *J. Exp. Clin. Cancer Res.* 2017, 36, 31. [CrossRef] [PubMed]

186. Yu, T.; Li, J.; Yan, M.; Liu, L.; Lin, H.; Zhao, F.; Sun, L.; Zhang, Y.; Cui, Y.; Zhang, F.; et al. MicroRNA-193a-3p and -5p suppress the metastasis of human non-small-cell lung cancer by downregulating the ERBB4/PIK3R3/mTOR/S6K2 signaling pathway. *Oncogene* 2015, 34, 413–423. [CrossRef] [PubMed]

187. Liu, X.; Lu, K.; Wang, K.; Sun, M.; Zhang, E.; Yang, J.; Yin, D.; Liu, Z.; Zhou, J.; Liu, Z.; et al. MicroRNA-196a promotes non-small cell lung cancer cell proliferation and invasion through targeting HOXA5. *BMC Cancer* 2012, 12, 348. [CrossRef] [PubMed]

188. Yu, S.-L.; Lee, D.C.; Sohn, H.A.; Lee, S.Y.; Jeon, H.S.; Lee, J.H.; Park, C.G.; Lee, H.Y.; Yeom, Y.I.; Son, J.W.; et al. Homeobox A9 directly targeted by miR-196 regulates aggressiveness through nuclear Factor-kappa B activity in non-small cell lung cancer cells. *Mol. Carcinog.* 2016, 55, 1915–1926. [CrossRef] [PubMed]

189. Chen, L.; Gibbons, D.L.; Goswami, S.; Cortez, M.A.; Ahn, Y.-H.; Byers, L.A.; Zhang, X.; Yi, X.; Dwyer, D.; Lin, W.; et al. Metastasis is regulated via microRNA-200/ZEB1 axis control of tumour cell PD-L1 expression and intratumoral immunosuppression. *Nat. Commun.* 2014, 5, 5241. [CrossRef] [PubMed]

190. Ceppi, P.; Mudduluru, G.; Kumarswamy, R.; Rapa, I.; Scagliotti, G.V.; Papotti, M.; Allgayer, H. Loss of microRNA-184 expression is associated with epithelial-mesenchymal transition and metastasis in lung adenocarcinoma by targeting the suppressor-of-fused protein (Sufu). *Neoplasma* 2015, 64, 353–360. [CrossRef] [PubMed]

191. Zhao, J.; Xu, Y.; Li, Y.; Xu, W.; Luo, F.; Wang, B.; Pang, Y.; Xiang, Q.; Zhou, J.; Wang, X.; et al. NF-κB-mediated inflammation leading to EMT via miR-200c is involved in cell transformation induced by cigarette smoke extract. *Toxicol. Sci. Off. J. Soc. Toxicol.* 2013, 135, 265–276. [CrossRef] [PubMed]

192. Zhao, J.; Zhao, Y.; Wang, Z.; Xuan, Y.; Luo, Y.; Jiao, W. Loss expression of micro ribonucleic acid (miRNA)-200c induces adverse post-surgical prognosis of advanced stage non-small cell lung carcinoma and its potential relationship with ETAR messenger RNA. *Thorac. Cancer* 2015, 6, 421–426. [CrossRef] [PubMed]

193. Tejero, R.; Navarro, A.; Campayo, M.; Viñoles, N.; Marrades, R.M.; Cordeiro, A.; Ruiz-Martínez, M.; Santassusagna, S.; Molins, L.; Ramírez, J.; et al. MiR-141 and miR-200c as markers of overall survival in early stage non-small cell lung cancer adenocarcinoma. *PloS ONE* 2014, 9, e101899. [CrossRef] [PubMed]

194. Park, K.-S.; Raffeld, M.; Moon, Y.W.; Xi, L.; Bianco, C.; Pham, T.; Lee, L.C.; Mitsudomi, T.; Yatabe, Y.; Okamoto, I.; et al. CRIPTO1 expression in EGFR-mutant NSCLC elicits intrinsic EGFR-inhibitor resistance. *J. Clin. Invest.* 2014, 124, 3003–3015. [CrossRef] [PubMed]

195. Long, H.; Wang, Z.; Chen, J.; Xiang, T.; Li, Q.; Diao, X.; Zhu, B. MicroRNA-214 promotes epithelial-mesenchymal transition and metastasis in lung adenocarcinoma by targeting the suppressor-of-fused protein (Sufu). *Oncotarget* 2015, 6, 38705–38718. [CrossRef] [PubMed]

196. Li, Y.; Chen, P.; Zu, L.; Liu, B.; Wang, M.; Zhou, Q. Eratum: MicroRNA-338-3p suppresses metastasis of lung cancer cells by targeting the EMT regulator Sox4. *Am. J. Cancer Res.* 2016, 6, 1582. [PubMed]

197. Hou, X.W.; Sun, X.; Yu, Y.; Zhao, H.M.; Yang, Z.J.; Wang, X.; Cao, X.C. MiR-361-5p suppresses lung cancer cell lines progression by targeting FOXM1. *Neoplasma* 2017, 64. [CrossRef] [PubMed]
198. Nishikawa, E.; Osada, H.; Okazaki, Y.; Arima, C.; Tomida, S.; Tatematsu, Y.; Taguchi, A.; Shimada, Y.; Yanagisawa, K.; Yatabe, Y.; et al. MiR-375 is activated by ASH1 and inhibits YAP1 in a lineage-dependent manner in lung cancer. *Cancer Res.* **2011**, *71*, 6165–6173. [CrossRef] [PubMed]

199. Wang, R.; Wang, Z.-X.; Yang, J.-S.; Pan, X.; De, W.; Chen, L.-B. MicroRNA-451 functions as a tumor suppressor in human non-small cell lung cancer by targeting ras-related protein 14 (RAB14). *Oncogene* **2011**, *30*, 2644–2658. [CrossRef] [PubMed]

200. Xie, Z.; Cai, L.; Li, R.; Zheng, J.; Wu, H.; Yang, X.; Li, H.; Wang, Z. Down-regulation of miR-489 contributes to NSCLC cell invasion through targeting SUZ12. *Tumour Biol. J. Int. Soc. Oncodevelopmental Biol. Med.* **2015**, *36*, 6497–6505. [CrossRef] [PubMed]

201. Li, J.; Feng, Q.; Wei, X.; Yu, Y. MicroRNA-490 regulates lung cancer metastasis by targeting poly r(C)-binding protein 1. *Tumour Biol. J. Int. Soc. Oncodevelopmental Biol. Med.* **2016**, *37*, 15221–15228. [CrossRef] [PubMed]

202. Liu, C.; Lv, D.; Li, M.; Zhang, X.; Sun, G.; Bai, Y.; Chang, D. Hypermethylation of miRNA-589 promoter leads to upregulation of HDAC5 which promotes malignancy in non-small cell lung cancer. *Int. J. Oncol.* **2017**, *50*, 2079–2090. [CrossRef] [PubMed]

203. Lu, Y.-J.; Liu, R.-Y.; Hu, K.; Wang, Y. MiR-541-3p reverses cancer progression by directly targeting TGIF2 in non-small cell lung cancer. *Tumour Biol. J. Int. Soc. Oncodevelopmental Biol. Med.* **2016**, *37*, 12685–12695. [CrossRef] [PubMed]

204. Xia, Y.; Wu, Y.; Liu, B.; Wang, P.; Chen, Y. Downregulation of miR-638 promotes invasion and proliferation by regulating SOX2 and induces EMT in NSCLC. *FEBS Lett.* **2014**, *588*, 2238–2245. [CrossRef] [PubMed]

205. Behbahani, G.D.; Ghahhari, N.M.; Javidi, M.A.; Molan, A.F.; Feizi, N.; Babashah, S. MicroRNA-Mediated Post-Transcriptional Regulation of Epithelial to Mesenchymal Transition in Cancer. *Pathol. Oncol. Res. POR* **2017**, *23*, 1–12. [CrossRef] [PubMed]

206. Guo, F.; Parker Kerrigan, B.C.; Yang, D.; Hu, L.; Shmulevich, I.; Sood, A.K.; Xue, F.; Zhang, W. Post-transcriptional regulatory network of epithelial-to-mesenchymal and mesenchymal-to-epithelial transitions. *J. Hematol. Oncol. J. Hematol. Oncol.* **2014**, *7*, 19. [CrossRef] [PubMed]

207. Saitoh, M. Epithelial-mesenchymal transition is regulated at post-transcriptional levels by transforming growth factor-β signaling during tumor progression. *Cancer Sci.* **2015**, *106*, 481–488. [CrossRef] [PubMed]

208. Garg, M. Targeting microRNAs in epithelial-to-mesenchymal transition-induced cancer stem cells: Therapeutic approaches in cancer. *Expert Opin. Ther. Targets* **2015**, *19*, 285–297. [CrossRef] [PubMed]

209. Lin, C.-W.; Kao, S.-H.; Yang, P.-C. The miRNAs and epithelial-mesenchymal transition in cancers. *Curr. Pharm. Des.* **2014**, *20*, 5309–5318. [CrossRef] [PubMed]

210. Yan, J.; Gumireddy, K.; Li, A.; Huang, Q. Regulation of mesenchymal phenotype by MicroRNAs in cancer. *Curr. Cancer Drug Targets 2013*, *13*, 930–934. [CrossRef] [PubMed]

211. Dacic, S.; Kelly, L.; Shuai, Y.; Nikiforova, M.N. MiRNA expression profiling of lung adenocarcinomas: Correlation with mutational status. *Mod. Pathol. Off. J. U. S. Can. Acad. Pathol. Inc* **2010**, *23*, 1577–1582. [CrossRef] [PubMed]

212. Takeyama, Y.; Sato, M.; Horio, M.; Hase, T.; Yoshida, K.; Yokoyama, T.; Nakashima, H.; Hashimoto, N.; Sekido, Y.; Gazdar, A.F.; et al. Knockdown of ZEB1, a master epithelial-to-mesenchymal transition (EMT) gene, suppresses anchorage-independent cell growth of lung cancer cells. *Cancer Lett.* **2010**, *296*, 216–224. [CrossRef] [PubMed]

213. Li, J.; Yang, S.; Yan, W.; Yang, J.; Qin, Y.-J.; Lin, X.-L.; Xie, R.-Y.; Wang, S.-C.; Jin, W.; Gao, F.; et al. MicroRNA-19 triggers epithelial-mesenchymal transition of lung cancer cells accompanied by growth inhibition. *Lab. Invest. J. Tech. Methods Pathol.* **2015**, *95*, 1056–1070. [CrossRef] [PubMed]

214. Perry, M.M.; Williams, A.E.; Tsitsiou, E.; Larner-Svensson, H.M.; Lindsay, M.A. Divergent intracellular pathways regulate interleukin-1beta-induced miR-146a and miR-146b expression and chemokine release in human alveolar epithelial cells. *FEBS Lett.* **2009**, *583*, 3349–3355. [CrossRef] [PubMed]

215. Marie-Egyptienne, D.T.; Lohse, I.; Hill, R.P. Cancer stem cells, the epithelial to mesenchymal transition (EMT) and radioresistance: Potential role of hypoxia. *Cancer Lett.* **2013**, *341*, 63–72. [CrossRef] [PubMed]

216. Hung, J.-J.; Yang, M.-H.; Hsu, H.-S.; Hsu, W.-H.; Liu, J.-S.; Wu, K.-J. Prognostic significance of hypoxia-inducible factor-alpha, TWIST1 and Snail expression in resectable non-small cell lung cancer. *Thorax* **2009**, *64*, 1082–1089. [CrossRef] [PubMed]
217. Cannito, S.; Novo, E.; di Bonzo, L.V.; Busletta, C.; Colombatto, S.; Parola, M. Epithelial-mesenchymal transition: From molecular mechanisms, redox regulation to implications in human health and disease. *Antioxid. Redox Signal.* 2010, 12, 1383–1430. [CrossRef] [PubMed]

218. Giannoni, E.; Parri, M.; Chiarugi, P. EMT and oxidative stress: A bidirectional interplay affecting tumor malignancy. *Antioxid. Redox Signal.* 2012, 16, 1248–1263. [CrossRef] [PubMed]

219. Weber, B.; Stresemann, C.; Brueckner, B.; Lyko, F. Methylation of human microRNA genes in normal and neoplastic cells. *Cell Cycle Georget. Tex.* 2007, 6, 1001–1005. [CrossRef] [PubMed]

220. Xia, W.; Chen, Q.; Wang, J.; Mao, Q.; Dong, G.; Shi, R.; Zheng, Y.; Xu, L.; Jiang, F. DNA methylation mediated silencing of microRNA-145 is a potential prognostic marker in patients with lung adenocarcinoma. *Sci. Rep.* 2015, 5, 16901. [CrossRef] [PubMed]

221. Watanabe, K.; Amano, Y.; Ishikawa, R.; Sunohara, M.; Kage, H.; Ichinose, J.; Sano, A.; Nakajima, J.; Fukayama, M.; Yatomi, Y.; et al. Histone methylation-mediated silencing of miR-139 enhances invasion of non-small-cell lung cancer. *Cancer Med.* 2015, 4, 1573–1582. [CrossRef] [PubMed]

222. Díaz-López, A.; Díaz-Martin, J.; Moreno-Bueno, G.; Cuevas, E.P.; Santos, V.; Olmeda, D.; Portillo, F.; Palacios, J.; Cano, A. Zeb1 and Snail1 engage miR-200f transcriptional and epigenetic regulation during EMT. *Int. J. Cancer* 2015, 136, E62–E73. [CrossRef] [PubMed]

223. Chen, C.-Q.; Chen, C.-S.; Chen, J.-J.; Zhou, L.-P.; Xu, H.-L.; Jin, W.-W.; Wu, J.-B.; Gao, S.-M. Histone deacetylases inhibitor trichostatin A increases the expression of Dleu2/miR-15a/16-1 via HDAC3 in non-small-cell lung cancer. *Mol. Cell. Biochem.* 2013, 383, 137–148. [CrossRef] [PubMed]

224. Incoronato, M.; Urso, L.; Portela, A.; Laukkanen, M.O.; Soini, Y.; Quintavalle, C.; Keller, S.; Esteller, M.; Condorelli, G. Epigenetic regulation of miR-212 expression in lung cancer. *PLoS ONE* 2011, 6, e27722. [CrossRef] [PubMed]

225. Huangyang, P.; Shang, Y. Epigenetic regulation of epithelial to mesenchymal transition. *Curr. Cancer Drug Targets* 2013, 13, 973–985. [CrossRef] [PubMed]

226. Mehrabian, M.; Ehsani, S.; Schmitt-Ulms, G. An emerging role of the cellular prion protein as a modulator of a morphogenetic program underlying epithelial-to-mesenchymal transition. *Front. Cell Dev. Biol.* 2014, 2, 53. [CrossRef] [PubMed]

227. Evseenko, D.; Zhu, Y.; Schenke-Layland, K.; Kuo, J.; Latour, B.; Ge, S.; Dravid, G.; Li, X.; MacLellan, W.R.; et al. Mapping the first stages of mesoderm commitment during differentiation of human embryonic stem cells. *Proc. Natl. Acad. Sci. USA* 2010, 107, 13742–13747. [CrossRef] [PubMed]

228. Pan, Y.; Zhao, L.; Liang, J.; Liu, J.; Shi, Y.; Liu, N.; Zhang, G.; Jin, H.; Gao, J.; Xie, H.; et al. Cellular prion protein promotes invasion and metastasis of gastric cancer. *FASEB J.* 2006, 20, 1886–1888. [CrossRef] [PubMed]

229. Mouillet-Richard, S.; Ermonval, M.; Chebassier, C.; Laplanche, J.L.; Lehmann, S.; Launay, J.M.; Kellermann, O. Signal transduction through prion protein. *Science* 2000, 289, 1925–1928. [CrossRef] [PubMed]

230. Martin, T.A.; Goyal, A.; Watkins, G.; Jiang, W.G. Expression of the transcription factors snail, slug, and twist and their clinical significance in human breast cancer. *Ann. Surg. Oncol.* 2005, 12, 488–496. [CrossRef] [PubMed]

231. Kwok, W.K.; Ling, M.-T.; Lee, T.-W.; Lau, T.C.M.; Zhou, C.; Zhang, X.; Chua, C.W.; Chan, K.W.; Chan, F.L.; Glackin, C.; et al. Up-regulation of TWIST in prostate cancer and its implication as a therapeutic target. *Cancer Res.* 2005, 65, 5153–5162. [CrossRef] [PubMed]

232. Hosono, S.; Kajiyama, H.; Terauchi, M.; Shibata, K.; Ino, K.; Nawa, A.; Kikkawa, F. Expression of Twist increases the risk for recurrence and for poor survival in epithelial ovarian carcinoma patients. *Br. J. Cancer* 2007, 96, 314–320. [CrossRef] [PubMed]

233. Yu, S.-L.; Chen, H.-Y.; Chang, G.-C.; Chen, C.-Y.; Chen, H.-W.; Singh, S.; Cheng, C.-L.; Yu, C.-J.; Lee, Y.-C.; Chen, H.-S.; et al. MicroRNA signature predicts survival and relapse in lung cancer. *Cancer Cell* 2008, 13, 48–57. [CrossRef] [PubMed]

234. Zhan, B.; Lu, D.; Luo, P.; Wang, B. Prognostic Value of Expression of MicroRNAs in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. *Clin. Lab.* 2016, 62, 2203–2211. [CrossRef] [PubMed]

235. Shibue, T.; Weinberg, R.A. EMT, CSCs, and drug resistance: The mechanistic link and clinical implications. *Nat. Rev. Clin. Oncol.* 2017. [CrossRef] [PubMed]

236. Heery, R.; Finn, S.P.; Cuffe, S.; Gray, S.G. Long non-coding RNAs: Key regulators of epithelial-mesenchymal transition, tumour drug resistance and cancer stem cells. *Cancers* 2017, 9, 38. [CrossRef] [PubMed]
237. Brozovic, A. The relationship between platinum drug resistance and epithelial-mesenchymal transition. *Arch. Toxicol.* 2017, 91, 605–619. [CrossRef] [PubMed]

238. Du, B.; Shim, J.S. Targeting epithelial-mesenchymal transition (EMT) to overcome drug resistance in cancer. *Molecules* 2016, 21, 965. [CrossRef] [PubMed]

239. Yang, A.D.; Fan, F.; Camp, E.R.; van Buren, G.; Liu, W.; Somcio, R.; Gray, M.J.; Cheng, H.; Hoff, P.M.; Ellis, L.M. Chronic oxaliplatin resistance induces epithelial-to-mesenchymal transition in colorectal cancer cell lines. *Clin. Cancer Res.* 2006, 12, 4147–4153. [CrossRef] [PubMed]

240. Shah, A.N.; Summy, J.M.; Zhang, J.; Park, S.I.; Parikh, N.U.; Gallick, G.E. Development and characterization of gemcitabine-resistant pancreatic tumors. *Ann. Surg. Oncol.* 2007, 14, 3629–3637. [CrossRef] [PubMed]

241. Hiscox, S.; Jiang, W.G.; Obermeier, K.; Taylor, K.; Morgan, L.; Burmi, R.; Barrow, D.; Nicholson, R.I. Tamoxifen resistance in MCF7 cells promotes EMT-like behaviour and involves modulation of beta-catenin phosphorylation. *Int. J. Cancer* 2006, 118, 290–301. [CrossRef] [PubMed]

242. Tsukamoto, H.; Shibata, K.; Kajiyama, H.; Terauchi, M.; Nawa, A.; Kikkawa, F. Irradiation-induced epithelial-mesenchymal transition (EMT) related to invasive potential in endometrial carcinoma cells. *Gynecol. Oncol.* 2007, 107, 500–504. [CrossRef] [PubMed]

243. Kurrey, N.K.; Jalgaonkar, S.P.; Joglekar, A.V.; Ghanate, A.D.; Chaskar, P.D.; Doiphode, R.Y.; Bapat, S.A. Snail and slug mediate radioresistance and chemoresistance by antagonizing p53-mediated apoptosis and acquiring a stem-like phenotype in ovarian cancer cells. *Stem Cells* 2009, 27, 2059–2068. [CrossRef] [PubMed]

244. Barr, M.P.; Gray, S.G.; Hoffmann, A.C.; Hilger, R.A.; Thomale, J.; O’Flaherty, J.D.; Fennell, D.A.; Richard, D.; O’Leary, J.; O’Byrne, K.J. Generation and characterization of cisplatin-resistant non-small cell lung cancer cell lines displaying a stem-like signature. *PloS ONE* 2013, 8, e54193. [CrossRef] [PubMed]

245. Rho, J.K.; Choi, Y.J.; Lee, J.K.; Ryoo, B.-Y.; Na, I.I.; Yang, S.H.; Kim, C.H.; Lee, J.C. Epithelial to mesenchymal transition derived from repeated exposure to gefitinib determines the sensitivity to EGFR inhibitors in A549, a non-small cell lung cancer cell line. *Lung Cancer Amst. Neth.* 2009, 63, 219–226. [CrossRef] [PubMed]

246. Shen, W.; Pang, H.; Liu, J.; Zhou, J.; Zhang, F.; Liu, L.; Ma, N.; Zhang, N.; Zhang, H.; Liu, L. Epithelial-mesenchymal transition contributes to docetaxel resistance in human non-small cell lung cancer. *Oncol. Res.* 2014, 22, 47–55. [CrossRef] [PubMed]

247. Gao, W.; Lu, X.; Liu, L.; Xu, J.; Feng, D.; Shu, Y. MiRNA-21: A biomarker predictive for platinum-based adjuvant chemotherapy response in patients with non-small cell lung cancer. *Cancer Biol. Ther.* 2012, 13, 330–340. [CrossRef] [PubMed]

248. Diehn, M.; Cho, R.W.; Lobo, N.A.; Kalisky, T.; Dorie, M.J.; Kulp, A.N.; Qian, D.; Lam, J.S.; Ailles, L.E.; Wong, M.; et al. Association of reactive oxygen species levels and radioresistance in cancer stem cells. *Nature* 2009, 458, 780–783. [CrossRef] [PubMed]

249. Yauch, R.L.; Januario, T.; Eberhard, D.A.; Cavet, G.; Zhu, W.; Fu, L.; Pham, T.Q.; Soriano, R.; Stinson, J.; Seshagiri, S.; et al. Epithelial versus mesenchymal phenotype determines in vitro sensitivity and predicts clinical activity of erlotinib in lung cancer patients. *Clin. Cancer Res.* 2005, 11, 8686–8698. [CrossRef] [PubMed]

250. Thomson, S.; Buck, E.; Petti, F.; Griffin, G.; Brown, E.; Rammarine, N.; Iwata, K.K.; Gibson, N.; Haley, J.D. Epithelial to mesenchymal transition is a determinant of sensitivity of non-small-cell lung carcinoma cell lines and xenografts to epidermal growth factor receptor inhibition. *Cancer Res.* 2005, 65, 9455–9462. [CrossRef] [PubMed]

251. Li, D.; Zhang, L.; Zhou, J.; Chen, H. Cigarette smoke extract exposure induces EGFR-TKI resistance in EGFR-mutated NSCLC via mediating Src activation and EMT. *Lung Cancer Amst. Neth.* 2016, 93, 35–42. [CrossRef] [PubMed]

252. Hashida, S.; Yamamoto, H.; Shien, K.; Miyoshi, Y.; Ohtsuka, T.; Suzawa, K.; Watanabe, M.; Maki, Y.; Soh, J.; Asano, H.; et al. Acquisition of cancer stem cell-like properties in non-small cell lung cancer with acquired resistance to afatinib. *Cancer Sci.* 2015, 106, 1377–1384. [CrossRef] [PubMed]

253. Sugano, T.; Seike, M.; Noro, R.; Soeno, C.; Chiba, M.; Zou, F.; Nakamichi, S.; Nishijima, N.; Matsumoto, M.; Miyanaga, A.; et al. Inhibition of ABCB1 Overcomes Cancer Stem Cell-like Properties and Acquired Resistance to MET Inhibitors in Non-Small Cell Lung Cancer. *Mol. Cancer Ther.* 2015, 14, 2433–2440. [CrossRef] [PubMed]
254. Zhu, X.; Du, X.; Deng, X.; Yi, H.; Cui, S.; Liu, W.; Shen, A.; Cui, Z. C6 ceramide sensitizes pemetrexed-induced apoptosis and cytotoxicity in osteosarcoma cells. *Biochem. Biophys. Res. Commun.* 2014, 452, 72–78. [CrossRef] [PubMed]

255. Brizuela, L.; Ader, I.; Mazerolles, C.; Bocquet, M.; Malaval, B.; Cuvillier, O. First evidence of sphingosine 1-phosphate lyase protein expression and activity downregulation in human neoplasm: Implication for resistance to therapeutics in prostate cancer. *Mol. Cancer Ther.* 2012, 11, 1841–1851. [CrossRef] [PubMed]

256. Edmond, V.; Dufour, P.; Pouiroux, G.; Shoji, K.; Malleter, M.; Fouqué, A.; Tazuin, S.; Rimokh, R.; Sergent, O.; Penna, A.; et al. Downregulation of ceramide synthase-6 during epithelial-to-mesenchymal transition reduces plasma membrane fluidity and cancer cell motility. *Oncogene* 2015, 34, 996–1005. [CrossRef] [PubMed]

257. Gomez-Casal, R.; Bhattacharya, C.; Ganesh, N.; Bailey, L.; Basse, P.; Gibson, M.; Epperly, M.; Levinia, V. Non-small cell lung cancer cells survived ionizing radiation treatment display cancer stem cell and epithelial-mesenchymal transition phenotypes. *Mol. Cancer* 2013, 12, 94. [CrossRef] [PubMed]

258. Shien, K.; Toyooka, S.; Yamamoto, H.; Soh, J.; Jida, M.; Thu, K.L.; Hashida, S.; Maki, Y.; Ichihara, E.; Asano, H.; et al. Acquired resistance to EGFR inhibitors is associated with a manifestation of stem cell-like properties in cancer cells. *Cancer Res.* 2013, 73, 3051–3061. [CrossRef] [PubMed]

259. Akunuru, S.; James Zhai, Q.; Zheng, Y. Non-small cell lung cancer stem/progenitor cells are enriched in multiple distinct phenotypic subpopulations and exhibit plasticity. *Cell Death Dis.* 2012, 3, e352. [CrossRef] [PubMed]

260. Koren, A.; Rijavec, M.; Kern, I.; Sodja, E.; Korosec, P.; Cufer, T. BMI1, ALDH1A1, and CD133 Transcripts Connect Epithelial-Mesenchymal Transition to Cancer Stem Cells in Lung Carcinoma. *Stem Cells Int.* 2016, 2016, 9714315. [CrossRef] [PubMed]

261. Suresh, R.; Ali, S.; Ahmad, A.; Philip, P.A.; Sarkar, F.H. The Role of Cancer Stem Cells in Recurrent and Drug-Resistant Lung Cancer. *Adv. Exp. Med. Biol.* 2016, 890, 57–74. [CrossRef] [PubMed]

262. Cui, S.-Y.; Huang, J.-Y.; Chen, Y.-T.; Song, H.-Z.; Feng, B.; Huang, G.-C.; Wang, R.; Chen, L.-B.; De, W. Let-7c governs the acquisition of chemo- or radioresistance and epithelial-to-mesenchymal transition phenotypes in docetaxel-resistant lung adenocarcinoma. *Mol. Cancer Res.* 2013, 11, 699–713. [CrossRef] [PubMed]

263. Bryant, J.L.; Britson, J.; Balko, J.M.; Willian, M.; Timmons, R.; Frolov, A.; Black, E.P. A microRNA gene expression signature predicts response to erlotinib in epithelial cancer cell lines and targets EMT. *Br. J. Cancer* 2012, 106, 148–156. [CrossRef] [PubMed]

264. Sato, H.; Shien, K.; Tomida, S.; Okayasu, K.; Suzawa, K.; Hashida, S.; Torigoe, H.; Watanabe, M.; Yamamoto, H.; Soh, J.; et al. Targeting the miR-200c/LIN28B axis in acquired EGFR-TKI resistance non-small cell lung cancer cells harboring EMT features. *Sci. Rep.* 2017, 7, 40847. [CrossRef] [PubMed]

265. Byers, L.A.; Diao, L.; Wang, J.; Saintigny, P.; Girard, L.; Peyton, M.; Shen, L.; Fan, Y.; Giri, U.; Tumula, P.K.; et al. An epithelial-mesenchymal transition gene signature predicts resistance to EGFR and PI3K inhibitors and identifies Axl as a therapeutic target for overcoming EGFR inhibitor resistance. *Clin. Cancer Res.* 2013, 19, 279–290. [CrossRef] [PubMed]

266. Miow, Q.H.; Tan, T.Z.; Ye, J.; Lau, J.A.; Yokomizo, T.; Thiery, J.-P.; Mori, S. Epithelial-mesenchymal status renders differential responses to cisplatin in ovarian cancer. *Oncogene* 2015, 34, 1899–1907. [CrossRef] [PubMed]

267. Malek, R.; Wang, H.; Taparra, K.; Tran, P.T. Therapeutic Targeting of Epithelial Plasticity Programs: Focus on the Epithelial-Mesenchymal Transition. *Cells Tissues Organs* 2017, 203, 114–127. [CrossRef] [PubMed]

268. Reka, A.K.; Kuick, R.; Kurpati, H.; Standiford, T.J.; Ommen, G.S.; Keshamouni, V.G. Identifying inhibitors of epithelial-mesenchymal transition by connectivity map-based systems approach. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* 2011, 6, 1784–1792. [CrossRef] [PubMed]

269. Halder, S.K.; Beauchamp, R.D.; Datta, P.K. A specific inhibitor of TGF-beta receptor kinase, SB-431542, as a potent antitumor agent for human cancers. *Neoplasia* 2005, 7, 509–521. [PubMed]

270. Nagaraj, N.S.; Datta, P.K. Targeting the transforming growth factor-beta signaling pathway in mammalian epithelial cells. *Cancer Sci.* 2011, 102, 1889–1896. [CrossRef] [PubMed]

271. Park, C.-Y.; Kim, D.-K.; Sheen, Y.Y. EW-7203, a novel small molecule inhibitor of transforming growth factor-beta (TGF-beta) type I receptor/activin receptor-like kinase-5, blocks TGF-beta1-mediated epithelial-to-mesenchymal transition in mammary epithelial cells. *Cancer Sci.* 2011, 102, 1889–1896. [CrossRef] [PubMed]
272. Park, C.-Y.; Son, J.-Y.; Jin, C.H.; Nam, J.-S.; Kim, D.-K.; Sheen, Y.Y. EW-7195, a novel inhibitor of ALK5 kinase inhibits EMT and breast cancer metastasis to lung. *Eur. J. Cancer Oxf. Engl.* 1990 **2011**, 47, 2642–2653. [CrossRef] [PubMed]

273. Son, J.Y.; Park, S.-Y.; Kim, S.-J.; Lee, S.J.; Park, S.-A.; Kim, M.-J.; Kim, S.W.; Kim, D.-K.; Nam, J.-S.; Sheen, Y.Y. EW-7197, a novel ALK-5 kinase inhibitor, potently inhibits breast to lung metastasis. *Mol. Cancer Ther.* **2014**, 13, 1704–1716. [CrossRef] [PubMed]

274. Bueno, L.; de Alwis, D.P.; Pitou, C.; Yingling, J.; Lahn, M.; Glatt, S.; Trocóniz, I.F. Semi-mechanistic modelling of the tumour growth inhibitory effects of LY2157299, a new type I receptor TGF-beta kinase antagonist, in mice. *Eur. J. Cancer Oxf. Engl.* 1990 **2008**, 44, 142–150. [CrossRef]

275. Jang, M.J.; Baek, S.H.; Kim, J.H. UCH-L1 promotes cancer metastasis in prostate cancer cells through EMT inhibition. *Cancer Lett.* **2011**, 302, 128–135. [CrossRef] [PubMed]

276. Goto, Y.; Yeom, C.J.; Zhu, Y.; Morinibu, A.; Shinomiya, K.; Kobayashi, M.; Hirota, K.; Itasaka, S.; Yoshimura, M.; et al. UCHL1 provides diagnostic and antimetastatic strategies due to its deubiquitinating effect on HIF-1α. *Nat. Commun.* **2015**, 6, 6153. [CrossRef] [PubMed]

277. Sparano, J.A.; Bernardo, P.; Stephenson, P.; Gradishar, W.J.; Ingle, J.N.; Zucker, S.; Davidson, N.E. Randomized phase III trial of marimastat versus placebo in patients with metastatic breast cancer who have responding or stable disease after first-line chemotherapy: Eastern Cooperative Oncology Group trial E2196. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2004**, 22, 4683–4690. [CrossRef] [PubMed]

278. Tran, P.T.; Shroff, E.H.; Burns, T.F.; Thiyagarajan, S.; Das, S.T.; Zabuawala, T.; Chen, J.; Cho, Y.-J.; Luong, R.; Park, C.-Y.; Son, J.-Y.; Jin, C.H.; Nam, J.-S.; Kim, D.-K.; Sheen, Y.Y. EW-7195, a novel inhibitor of ALK5 kinase inhibits EMT and breast cancer metastasis to lung. *Cancer Lett.* **2011**, 302, 128–135. [CrossRef] [PubMed]

279. Burns, T.F.; Dobromilskaya, I.; Murphy, S.C.; Gajula, R.P.; Thiyagarajan, S.; Chatley, S.N.H.; Aziz, K.; Rudin, P.T.; Tran, P.T.; Port, J.D.; Winn, R.A.; et al. PRMT1 Is a Novel Regulator of Epithelial-Mesenchymal-Transition in Non-small Cell Lung Cancer. *J. Biol. Chem.* **2015**, 290, 13479–13489. [CrossRef] [PubMed]

280. Da Silva, S.D.; Alouai-Jamali, M.A.; Soares, F.A.; Carraro, D.M.; Glatt, S.; Troc

281. Voulgari, A.; Pintzas, A. Epithelial-mesenchymal transition in cancer metastasis: Mechanisms, markers and strategies to overcome drug resistance in the clinic. *Biochim. Biophys. Acta* **2009**, 1796, 75–90. [CrossRef] [PubMed]

282. Li, H.; Wang, H.; Wang, F.; Gu, Q.; Xu, X. Snail involves in the transforming growth factor β1-mediated epithelial-mesenchymal transition of retinal pigment epithelial cells. *PLoS ONE* **2011**, 6, e23322. [CrossRef] [PubMed]

283. Pergande, M.R.; Borgia, J.A.; DeGregori, J.; Port, J.D.; Winn, R.A.; et al. PRMT1 Is a Novel Regulator of Epithelial-Mesenchymal-Transition in Non-small Cell Lung Cancer. *J. Biol. Chem.* **2015**, 290, 13479–13489. [CrossRef] [PubMed]

284. Iwatsuki, M.; Mimori, K.; Yokobori, T.; Ishi, H.; Beppu, T.; Nakamori, S.; Baba, H.; Mori, M. Epithelial-mesenchymal transition in cancer development and its clinical significance. *Cancer Sci.* **2013**, 104, 128–135. [CrossRef] [PubMed]

285. Li, H.; Wang, H.; Wang, F.; Gu, Q.; Xu, X. Snail involves in the transforming growth factor β1-mediated epithelial-mesenchymal transition of retinal pigment epithelial cells. *PLoS ONE* **2011**, 6, e23322. [CrossRef] [PubMed]

286. Hsu, H.-Y.; Lin, T.-Y.; Hwang, P.-A.; Tseng, L.-M.; Chen, R.-H.; Tsao, S.-M.; Hsu, J. Fucoidan induces changes in the epithelial to mesenchymal transition and decreases metastasis by enhancing ubiquitin-dependent TGFβ receptor degradation in breast cancer. *Carcinogenesis* **2013**, 34, 874–884. [CrossRef] [PubMed]

287. Chang, W.-W.; Hu, F.-W.; Yu, C.-C.; Wang, H.-H.; Feng, H.-P.; Lan, C.; Tsai, L.-L.; Chang, Y.-C. Quercetin in elimination of tumor initiating stem-like and mesenchymal transformation property in head and neck cancer. *Head Neck* **2013**, 35, 413–419. [CrossRef] [PubMed]

288. Khan, M.A.; Tania, M.; Wei, C.; Mei, Z.; Fu, S.; Cheng, J.; Xu, J.; Fu, J. Thymoquinone inhibits cancer metastasis by downregulating TWIST1 expression to reduce epithelial to mesenchymal transition. *Oncotarget* **2015**, 6, 19580–19591. [CrossRef] [PubMed]
Cancers 2017, 9, 101

290. Lemjabbar-Alaoui, H.; McKinney, A.; Yang, Y.-W.; Tran, V.M.; Phillips, J.J. Glycosylation alterations in lung and brain cancer. *Adv. Cancer Res.* 2015, 126, 305–344. [CrossRef] [PubMed]

291. Mi, W.; Gu, Y.; Han, C.; Liu, H.; Fan, Q.; Zhang, X.; Cong, Q.; Yu, W. O-GlcNAcylation is a novel regulator of lung and colon cancer malignancy. *Biochim. Biophys. Acta* 2011, 1812, 514–519. [CrossRef] [PubMed]

292. Trapannone, R.; Rafie, K.; van Aalten, D.M.F. O-GlcNAc transferase inhibitors: Current tools and future challenges. *Biochem. Soc. Trans.* 2016, 44, 88–93. [CrossRef] [PubMed]

293. Ma, Z.; Vocadlo, D.J.; Vosseller, K. Hyper-O-GlcNAcylation is anti-apoptotic and maintains constitutive NF-κB activity in pancreatic cancer cells. *J. Biol. Chem.* 2013, 288, 15121–15130. [CrossRef] [PubMed]

294. Wagner, T.; Jung, M. New lysine methyltransferase drug targets in cancer. *Nat. Biotechnol.* 2012, 30, 622–623. [CrossRef] [PubMed]

295. Yuan, Y.; Wang, Q.; Paulk, J.; Kubicek, S.; Kemp, M.M.; Adams, D.J.; Shamji, A.F.; Wagner, B.K.; Schreiber, S.L. A small-molecule probe of the histone methyltransferase G9a induces cellular senescence in pancreatic adenocarcinoma. *ACS Chem. Biol.* 2012, 7, 1152–1157. [CrossRef] [PubMed]

296. Takai, N.; Desmond, J.C.; Kumagai, T.; Gui, D.; Said, J.W.; Whittaker, S.; Miyakawa, I.; Koeffler, H.P. Histone deacetylase inhibitors have a profound antigrowth activity in endometrial cancer cells. *Clin. Cancer Res.* 2004, 10, 1141–1149. [CrossRef] [PubMed]

297. Ma, X.; Ezzeldin, H.H.; Diasio, R.B. Histone deacetylase inhibitors: Current status and overview of recent clinical trials. *Drugs* 2009, 69, 1911–1934. [CrossRef] [PubMed]

298. Krützfeldt, J.; Rajewsky, N.; Braich, R.; Rajeev, K.G.; Tuschl, T.; Manoharan, M.; Stoffel, M. Silencing of microRNAs in vivo with “antagomirs”. *Nature* 2005, 438, 685–689. [CrossRef] [PubMed]

299. Rupaimoole, R.; Han, H.-D.; Lopez-Berestein, G.; Sood, A.K. MicroRNA therapeutics: Principles, expectations, and challenges. *Chin. J. Cancer* 2011, 30, 368–370. [CrossRef] [PubMed]

300. Su, C.-M.; Lee, W.-H.; Wu, A.T.H.; Lin, Y.-K.; Wang, L.-S.; Wu, C.-H.; Yeh, C.-T. Pterostilbene inhibits triple-negative breast cancer metastasis via inducing microRNA-205 expression and negatively modulates epithelial-to-mesenchymal transition. *J. Nutr. Biochem.* 2015, 26, 675–685. [CrossRef] [PubMed]

301. Pecot, C.V.; Rupaimoole, R.; Yang, D.; Akbani, R.; Ivan, C.; Lu, C.; Wu, S.; Han, H.-D.; Shah, M.Y.; Rodriguez-Aguayo, C.; Bottsford-Miller, J.; et al. Tumour angiogenesis regulation by the miR-200 family. *Nat. Commun.* 2013, 4, 2427. [CrossRef] [PubMed]

302. Ocana, O.H.; Corcoles, R.; Fabra, A.; Moreno-Bueno, G.; Acloque, H.; Vega, S.; Barrallo-Gimeno, A.; Cano, A.; Nieto, M.A. Metastatic colonization requires the repression of the epithelial-mesenchymal transition inducer Prrx1. *Cancer Cell* 2012, 22, 709–724. [CrossRef] [PubMed]

303. Van Roosbroeck, K.; Fanini, F.; Setoyama, T.; Ivan, C.; Rodriguez-Aguayo, C.; Fuentes-Mattei, E.; Xiao, L.; Vannini, I.; Redis, R.S.; D’Abundo, L.; et al. Combining Anti-Mir-155 with Chemotherapy for the Treatment of Lung Cancers. *Clin. Cancer Res.* 2017, 23, 2891–2904. [CrossRef] [PubMed]

304. Lou, Y.; Diao, L.; Cuentas, E.R.P.; Denning, W.L.; Chen, L.; Fan, Y.H.; Byers, L.A.; Wang, J.; Papadimitrakopoulou, V.A.; Behrens, C.; et al. Epithelial-mesenchymal transition is associated with a distinct tumor microenvironment including elevation of inflammatory signals and multiple immune checkpoints in lung adenocarcinoma. *Clin. Cancer Res.* 2016, 22, 3630–3642. [CrossRef] [PubMed]

305. Ardian, A.; Gameiro, S.R.; Palena, C.; Hamilton, D.H.; Kwilas, A.; King, T.H.; Schlom, J.; Hodge, J.W. Vaccine-mediated immunotherapy directed against a transcription factor driving the metastatic process. *Cancer Res.* 2014, 74, 1945–1957. [CrossRef] [PubMed]

306. Hamilton, D.H.; Litzinger, M.T.; Jales, A.; Huang, B.; Fernando, R.I.; Hodge, J.W.; Ardiani, A.; Apelian, D.; Schlom, J.; Palena, C. Immunological targeting of tumor cells undergoing an epithelial-mesenchymal transition via a recombinant brachyury-yeast vaccine. *Oncotarget* 2013, 4, 1777–1790. [CrossRef] [PubMed]

307. Palena, C.; Hamilton, D.H. Immune targeting of tumor epithelial-mesenchymal transition via brachyury-based vaccines. *Adv. Cancer Res.* 2015, 128, 69–93. [CrossRef] [PubMed]

© 2017 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).