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Review

Akt/mTOR Activation in Lung Cancer Tumorigenic Regulators and Their Potential Value as Biomarkers

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Simple Summary: Key breakthroughs in evidence gathered from genetic and epigenetic data from lung cancer patient samples are related to dissimilar levels of gene expression both in the initial biopsy and upon therapeutic running protocols. Cancer stressful cell survival and growth involves phenotypic changes known as the EMT (epithelial-to-mesenchymal transition) to allow the key transition from an epithelial (polarized) state to a mesenchymal one (fibroblast-like). From a molecular point of view, several cell regulators and dependent cascades, such as proteins, miRNAs, growth factors, among others, support each of these states. Most, if not all, malignant steps are triggered by extracellular growth factor–membrane interaction that, at an intracellular level, initiates the tumorigenic PI3K/Akt tyrosine kinase pathway. Aside from this axis malignant potential, the resulting downstream cascades are full of molecular states that, once identified, could represent druggable targets and/or predictive tools. Surgery, radiation, chemotherapy and develop immunotherapies are already a pluralist approach devoted to target lung tumor's heterogeneity. Yet, and not surprisingly, inconstant therapeutic outcomes have been associated with different cancer epigenetic signatures. As such, the patients' positive stratification associated with high-grade malignancy is tricky, but highly needed as it can offer decision support to health professionals to manage and predict the lung cancer patient's therapeutic outcomes.

Abstract: The high incidence and modest therapeutic outcomes of lung cancer have prompted the identification of cell molecular targets/biomarkers within the complex networks of interactions involved in cell malignancy. Most of the EMT-related regulatory mediators underline patients' biologic variations, therapeutic refractory events, and tumor cell heterogeneity. Patient stratification based on the understanding of the relevant pathways, such as the PI3K/Akt axis crucial in EMT initiation, could favorably alter disease management. Significant clinical advantage could be expected when overexpressed Akt tyrosine kinase (Akt2) is addressed as a malignant biomarker to guide clinical management decisions, improving prognosis in lung cancer patients. Moreover, one should not miss the opportunity of using it as a druggable target aiming at the inhibition of the downstream complexity that underlies cell proliferation and survival, expression of stemness markers and drug resistance. The value of mTOR, as a downstream target of Akt, and the further activation of EMT transcription factors Twist, Snail and Zeb1 are revisited in this review. An in-depth state-of-the-art assessment provides evidence of its role in the mechanistic inhibition of epithelial markers, such as E-cadherin and miR-200, while inducing the expression of the mesenchymal ones, such as vimentin, N-cadherin, and miR-21. Lastly, evidence suggesting another transcription factor, FOXM1, as the link between the PI3K/Akt and Wnt/β-catenin pathways, prompting cell metabolism through the regulation of p70S6K, is analyzed. A more realistic approach is advised to address unmet clinical needs and support decision making at a clinical level. Taking into consideration several complex intracellular interactions might further improve patient stratification and result in better outcomes.

Keywords: lung cancer; Akt; EMT; miR-21; miR-200; mTOR; Twist; β-catenin; FOXM1

1. Introduction

With 2.21 million new cases being diagnosed every year, lung cancer is still the leading cause of cancer-related deaths (1.80 million deaths in 2020) [1]. New realms of decision flexibility against resistant forms of lung cancer phenotypic assessment, subpopulation identification and emerging appropriate stage-specific biomarkers are being investigated. In 2021, the WHO (World Health Organization) updated the conventional lung cancer classification prioritizing the utilization of molecular tools to classify tumor properties and stage, thus revealing potential biomarkers and possible drug targets [2]. The bottleneck in the conventional classification of lung cancer into non-small cell lung cancer (NSCLC) (about 80–85%) and into small cell lung cancer (SCLC) (around 20–15%) is related with misdiagnosed cells epigenetic signatures [3,4].

Emerging bioanalytical tools are crucial to correlate cell's tumorigenesis with the cell's proteomic signature. In the specific case of NSCLC, researchers have made it possible to divide this type of lung cancer into 222 different molecular subtypes based on the "driver" mutations that arise in oncogenes crucial for sustaining the tumorigenic potential of cancer cells, such as AKT, EGFR (Epidermal Growth Factor Receptor), KRAS, PIK3CA and PD-1 [5]. The latter has emerged as a key checkpoint of interest due to both the frequency of programmed death ligand-1 (PD-L1) expression in lung cancer as well as observed clinical activity using PD-1 pathway inhibitors [6]. Most EMT (epithelial-to-mesenchymal transition)-related signaling molecules overlap with those involved in the extrinsic induction of PD-L1, so it is difficult to differentiate both [7]. In a recent paper published by our group, we support this mutation-based classification of lung cancer, but emphasize the importance of a more specific molecular-basis understanding of tumor growth and progression to better classify lung cancer patients to improve key areas, such as diagnosis and patient sub-population response to treatment, making lung cancer a "cell-specific disease" instead of a "tissue-specific disease" [8].

In this paper, the focus on harmed cell machinery behind tumorigenesis is mainly devoted to understanding the EMT regulators in lung cancer irrespective of the diagnosed histological type, understanding its unique role and clinical potential. As outlined above, Akt has proven to be a core player in cell survival responses. The focus lies on its role in the PI3K/Akt axis that activates the downstream effector mTOR, which, in turn, opens the door to several of its downstream targets malignant programs, such as Twist, Snail, Slug, or even miR-21 [9,10]. This is accomplished when cancer cells suppress their epithelial markers, such as E-cadherin or miR-200, to activate mesenchymal ones, such as vimentin, Snail, or Twist [11]. In this review, we provide evidence for some of the players on lung cancer tumorigenesis that can be valuable tools in lung cancer patients' stratification.

2. PI3K/Akt/mTOR Implication in Lung Cancer Molecular Machinery

Akt, also known as protein kinase B (PKB), is a 57-kDa serine/threonine kinase that, according to functional proteomic analysis, is a molecular "workhorse" implicated in cell tumorigenesis, namely, cell growth, proliferation, metabolism, and stem-like properties, including drug resistance [12,13] (Figure 1). Gener et al. (2019) demonstrated that the inhibition of Akt downregulated invasion and cell migration, while also inhibiting cancer stem cell (CSC) survival in low attachment conditions in mesenchymal-like breast cancer cell lines (MDA-MB-231, SKBR3 and MDA-MB-468) [14].
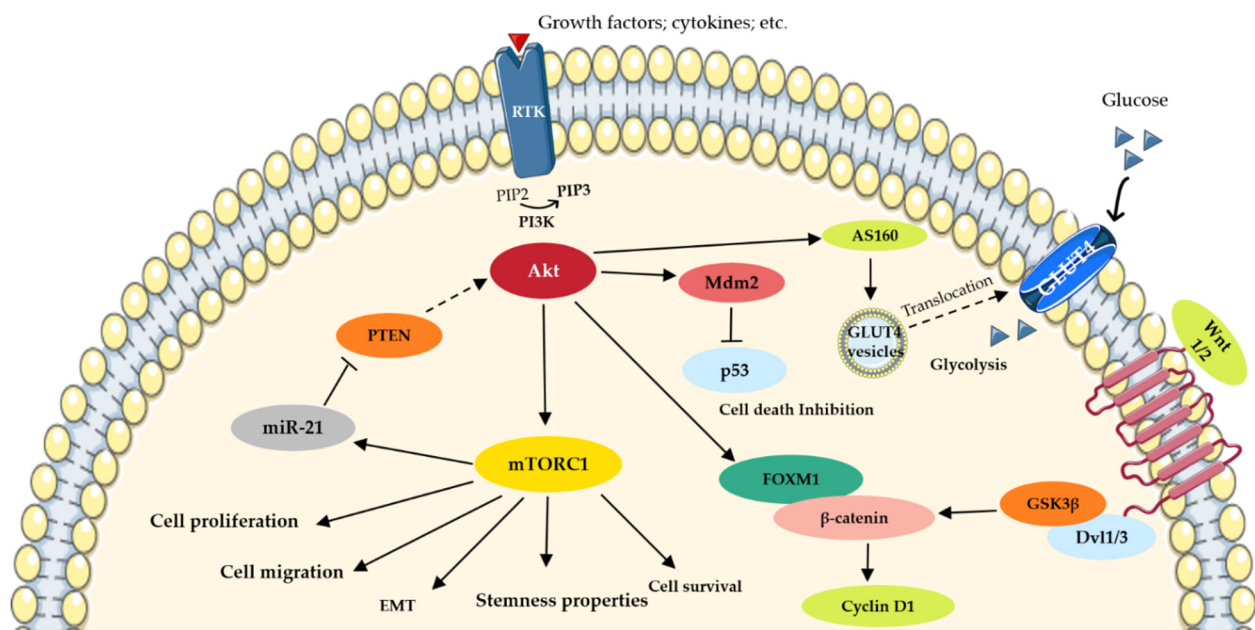
Figure 1. Different roles of Akt/mTOR axis in the development of cancer cells. As the core kinase in the PI3K/Akt signaling pathway, Akt is responsible for phosphorylating its downstream targets, such as mTORC1, that in turn will activate its downstream targets to sustain all the moleuclar processes involved in tumorigenesis, such as EMT, cell migration, cell proliferation, and stemness properties. More details related to these processes can be observed in Figure 2. Moreover, Akt activates AS160 to maintain a continued elevated metabolic rate, as well as Mdm2 to inhibit tumor suppressor p53 expression, leading to inhibition of cell death. Phosphorylation of Akt activates FOXM1 that functions as a chaperone to help β-catenin to translocate into the nucleus, and activate genes associated with cell proliferation.
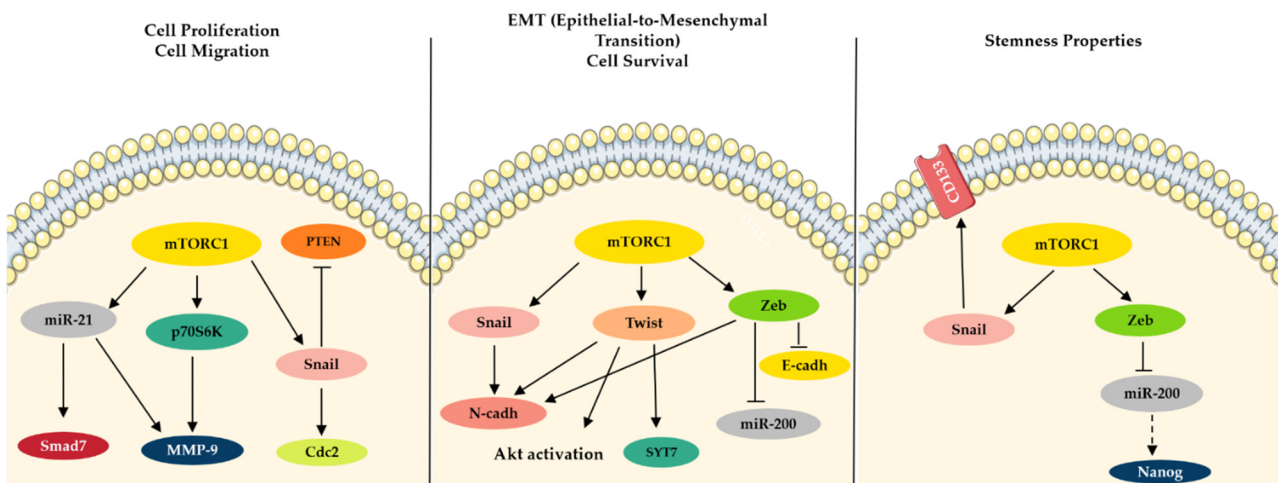

Figure 2. Role of Akt/mTOR signaling axis in lung cancer tumorigenesis. After the phosphorylation of mTORC1, due to Akt activation, this kinase will phosphorylate its downstream targets that have multiple roles in tumorigenesis. For example, the activation of transcription factors Twist, Snail and Zeb (representing Zeb1 and Zeb2 family members) results in the sustained stimulation of EMT, and consequently, inhibits the expression of E-cadherin (E-cadh) and miR-200, but increases the expression of N-cadherin (N-cadh) and SYT7. Some of these transcription factors, such as Snail, are also responsible for inducing cell proliferation and survival due to activation of Smad7, MMP-9 or Cdc2. Overexpression of miR-21 enhances cell proliferation and migration. Both Snail and Zeb are responsible for activating the expression of stemness markers, such as CD133 receptor and Nanog, respectively.

This kinase is frequently studied as an integral component of the PI3K/Akt signaling pathway, triggered by different extracellular stimuli such as, cytokines, growth factors, and nutrients [15]. At the intracellular level, the activation of the p110 catalytic subunit of PI3K (Phosphoinositide 3-kinase) is necessary to transmute phosphatidylinositol 4,5-bisphosphate (PIP$_2$) into phosphatidylinositol 3,4,5-trisphosphate (PIP$_3$) [9]. The latter binds to the PH (Pleckstrin homology) domain of this kinase to recruit Akt from the cytoplasm to the membrane and induces a conformational change important to allow PDK1 (Phosphoinositide-dependent kinase-1)-mediated phosphorylation at threonine 308 residue (Thr308) in Akt's catalytic domain [9,16–18]. This is the rate-limiting step in the complex PI3K/Akt activation process [13]. From this point onwards, phosphorylation at serine 473 residue (Ser473) in the carboxyl-terminal hydrophobic motif of Akt, by another yet incompletely defined mTORC2-dependent process, allows the full activation of Akt [13,15,19,20]. Translocation to the membrane and, consequent phosphorylation, are the two critical steps that allow Akt activation [15].

At this point, intracellular Akt inactivates tumor suppressor TSC1/TSC2 (Tuberous Sclerosis Complex 1/2) to allow mTOR activation [9,13], corroborated by the results obtained by Oh and colleagues (2012), where the expression of mTORC1 correlated with phosphorylation levels of Akt in samples from patients with NSCLC, and were associated with a worst prognosis [21].

Akts's downstream target mTOR, a 288.892 kDa serine/threonine that belongs to PI3K-related kinases (PIKK) [22], is an integral part of two structurally and functionally distinct complexes: mTOR complexes 1 and 2 (mTORC1 and mTORC2) [22,23]. Apart from mTOR, both complexes contain mLST8 (mammalian lethal with SEC13 protein 8). While mTORC1 contains Raptor (Regulatory protein associated with mTOR), PRAS40 (proline rich Akt substrate of 40 kDa) and DEPTOR (DEP domain containing mTOR interacting protein), mTORC2 comprises a mammalian stress-activated MAP kinase-interacting protein 1 (mSin1), Protor 1 (Protein observed with Rictor 1), and a rapamycin-insensitive companion (Rictor) [16,22–24], being, therefore, resistant to rapamycin, whereas mTORC1 is inhibited by it [13,24].

Within both complexes, mTOR regulates cell growth, cell proliferation, cell motility, protein synthesis and transcription through a cascade of phosphorylation, leading to the target activation, such as S6K and 4E-BP1 [22]. Data from several studies have shown that the activation of mTOR is associated with worse prognosis in different types of cancer [25–27], including lymph node metastasis [27] and drug resistance [28–30] (Figure 1). Nevertheless, the cellular localization of mTOR was associated with different outcomes in gastric cancer patients; cytoplasmic phosphorylated mTOR was associated with tumor progression and poor survival, whereas nuclear mTOR seems to have the opposite effect [26]. Even though samples of patients with triple negative breast cancer (TNBC) demonstrated a higher frequency of nuclear phosphorylated mTOR and a positive correlation between Ki67, GLUT1 and GLUT3 (Glucose transporter type 1 and 3), no direct link to prognosis was discovered [25]. To date, the evidence has revealed that, although mTOR overexpression is critical for tumorigenesis progression, it may not be useful as a standalone prognosis marker for certain types of cancer patients.

The activation of PI3K/Akt/mTOR signaling pathway is involved in S100A4-induced cell viability, migration, and VEGF (vascular endothelial growth factor) upregulation and E-cadherin downregulation [31]. In NSCLC cells, it also increased the expression of PD-L1 [32]. In these cases, patients possessed significant differences in the expression of some of the players involved in cancer tumorigenesis, which could be helpful for patient's stratification.

Surprisingly, the inhibition of mTORC1 shifted the activation of the PI3K/Akt pathway towards Ras/MAPK, enhancing the activation of both Akt and ERK, as a drug resistance mechanism [33], and the expression of EGFR [34]. Altogether, both studies have shown the possible role of Akt/mTOR axis as a disease biomarker; however, the regulation by the interconnection of different signaling pathways jeopardizes its use as a druggable target.

3. Tumor Cells Attain Mesenchymal Traits through Akt/mTOR-Induced EMT Activation

The major outcome of the Akt-dependent inhibition of TSC1/2 and the consequent activation of mTORC1 is cytoskeleton remodeling and EMT [13,16,35,36]. EMT is a molecular process that, in normal circumstances, occurs during the embryonic development and in tissue homeostasis. However, cancer cells use this process to transition from an epithelial (and immobile) phenotype to a mesenchymal-like one (mobile) to migrate to other organs. This process is initiated by the inhibition of epithelial markers, such as E-cadherin and claudins, followed by the expression of mesenchymal markers, such as vimentin or N-cadherin, to result in a migratory phenotype. The reverse transition (mesenchymal-to-epithelial: MET) has also been observed during cancer development, to prompt the attachment of cancer cells at the new site [37,38]. Still, both mechanisms are regulated by the same assembly of EMT-inducing proteins, such as transcription factors (Snail, Twist and Zeb) and micro-RNAs (miRNAs) (miR-200 and miR-21) [39–41]. Since all EMT-inducing factors have been linked to other tumorigenic features, such as acquisition of stem-like properties, drug and apoptosis resistance, and altered metabolism [37,38,42], one can hypothesize that EMT can be the main mechanism from which all other tumorigenic features originate.

3.1. Twist, Snail and Zeb Transcription Factors at the Crossroads of EMT

The most important EMT-inducing transcription factor Twist is a 21 kDa member of the basic helix-loop helix protein family (bHLH). Overexpressed in different types of cancer, once phosphorylated by mTORC1, it activates other genes (such as Snail and Zeb) and miRNAs (such as miR-200 or miR-21) to maintain the mesenchymal properties [43,44]. However, most importantly, Twist is responsible for activating Akt by binding to the E-box elements of this kinase [44,45], and downregulating E-cadherin expression [46,47]. Although the activation of Twist is mostly linked to the PI3K/Akt pathway, in breast cancer samples, it has been associated with Wnt signaling [48,49]. The overexpression of this transcription factor has been associated with poor prognosis, survival [50–53], lymph node metastasis and tumor stage [54] in patients with lung cancer.

Additionally, the expression of Twist has also been associated with the expression of mesenchymal markers, tumor progression and invasion [54–57]. Long-term exposure of A549 and H157 lung cancer cells to NNK (nicotine-derived nitrosamine ketone) induced migration and invasion, through increased mRNA levels of Twist and N-cadherin accompanied by decreased expression of E-cadherin [58] (Figure 1). The association between transcription factor Twist and mesenchymal marker N-cadherin expression was further supported by the reduced expression of N-cadherin and jammed cellular invasion, as a consequence of Twist knockdown in A549 cells [53]. Furthermore, diminished Twist expression leads to an increased sensitivity to Taxol, by downregulating Bcl-2/Bax ratio [59]. According to the work of Wang et al. (2018), the co-expression of high levels Twist and transcription factor Snail were associated with the low expression of E-cadherin in patients with lung cancer [50]. Recently, it was demonstrated that the expression of Snail inhibits the expression of cofilin-1, which is negatively associated with Twist expression in normal lung tissues [57].

As already mentioned, Snail is another transcription factor associated with EMT that represses PTEN by binding to its promoter, resulting in the sustained activation of PI3K/Akt pathway [60]. Snail is a zinc finger transcription factor whose family includes Snail1, Slug and Scratch protein members. The post-transcriptional regulation of Snail is dependent of GSK3β (glycogen synthase kinase 3β) phosphorylation on two serine-rich regions; the first one allows Snail to be exported into the cytoplasm and, once in the cytoplasm, the second phosphorylation leads to its ubiquitination by β-Trcp (β-Transducin Repeat Containing E3 Ubiquitin Protein Ligase) [60,61]. Recently, it was demonstrated that USP37 binds to Snail to prevent its ubiquitination [62]. Similar to the other EMT-inducing transcription factors, Snail expression is associated with tumor grade and poor survival in cancer patients [63–65].

The overexpression of Snail results in the increased phosphorylation of ERK, which is predominantly localized in the nucleus of MCF-7 breast cancer cells [66], and transactivated FOXK1's promoter activity [67]. Quin and coworkers (2021) demonstrated that the knockdown of Snail resulted in EMT reversion by downregulating mesenchymal proteins vimentin and N-cadherin, while upregulating E-cadherin in H1975 lung cancer cells [68]. Additionally, it also leads to decreased proliferation by activating the G2/M checkpoint protein Cdc2 and PCNA (proliferating cell nuclear antigen) expression [69] (Figure 2), followed by sensitization to cisplatin-induced apoptosis, due to the activation of the JNK/mitochondrial pathway [70]. These results strengthen the potential value of combining two transcription factors, such as Twist and Snail, as prognostic markers for patients with lung cancer, particularly in stage I NSCLC [52].

Moreover, the existence of a dynamic Slug/Snail interaction modulates the expression of phospholipase D in MDA-MB-231 and MCF-7 cells, with Slug acting as an activator and Snail as a repressor of gene and protein expression [71]. Interestingly, the combined overexpression of Slug and Snail generated CD133$^+$/CD44$^+$ cells with stem-like properties [65] (Figure 2). Even though Snail has been mostly associated with tumor cells, it was observed an interaction between Snail and neutrophils to recruit them into the tumor microenvironment [72]. Similarly, Guo et al. (2021) associated Zeb1 expression to the induction of CD47$^+$ cancer cells and macrophage polarization on the tumor microenvironment [73].

The Zeb family, apart from Twist and Snail, are another zinc finger protein family that act as transcription factors responsible for inducing EMT, composed by Zeb1 and Zeb2. As expected, the increased expression of Zeb1 and Zeb2 is associated with tumor progression, organ metastization, and tumor grade [11,74]. The overexpression of mesenchymal markers has been associated with the expression of Zeb1 in different types of cancer [75–78]. As an example, nuclear and cytoplasmic N-cadherin were associated with Zeb-1 and Zeb2 expression, respectively [76]. This observation was supported by the identification of 141 genes, such as vimentin, N-cadherin and Twist, which positively correlated with Zeb1 [77].

Even though Zeb1's activation can be induced by the PI3K/Akt pathway, Sigh and colleagues (2011) reported that the manipulation of Wnt signaling altered Zeb1 without affecting Akt phosphorylation [79], suggesting that the Akt-mediated regulation of Zeb1 is either upstream of or distinct from the Wnt pathway. This result was corroborated by Liu et al. (2014), in which Notch3 upregulation increased Zeb1 expression in NSCLC bone metastization [80] by repressing the expression of members of the miR-200 family [81]. More importantly, Zeb1 expression did not oscillate during cell cycle progression, and was negatively correlated with miR-200 levels in TNBC [78] (Figure 2).

Altogether, these data suggest that any of the mentioned transcription factors can be a potential druggable target, though Zeb family protein appears to be the better candidate given its role in lung tumorigenesis. Most importantly, if using EMT-induced transcription factors for potential biomarkers, more than one should be selected.

3.2. Akt/mTOR/p70S6K Drives Cancer Cell Survival and Proliferation

Two of the proposed cancer's hallmarks are intrinsically interconnected: cell survival and its consequent cell proliferation, and the ablation of cell death programs [82,83]. The regulation of these molecular processes is only accomplished by the activation of the PI3K/Akt/mTOR signaling pathway, due to the regulation of both pro-survival and anti-apoptotic proteins, such as p27, p21 and CDK1 [16,84]. Phosphorylation levels of Akt have been shown to oscillate during the cell cycle, similarly to cyclin A expression, but are inversely correlated with Cdt1 (Chromatin licensing and DNA replication factor 1) expression levels. However, the depletion of cyclin A2 or Cdk2 (Cyclin dependent kinase 2) decreased Akt phosphorylation, with no observable impact on the Akt upstream effectors PDK1 and mTORC2, as well as cell cycle progression [85], suggesting that the phosphorylation of Akt can be influenced by the cell cycle without being directly dependent on it.

Furthermore, Akt phosphorylation on serine residue 83 negatively regulates apoptosis signal-regulating kinase 1 (ASK1) [86], as well as the phosphorylation of Mdm2 [15], thus

resulting in apoptosis inhibition and, consequently, stimulating cell proliferation and survival. Mdm2 is a negative regulator of tumor suppressor p53 expression by mediating the ubiquitination of p53. This in turn disturbs the balance between pro-survival and pro-apoptotic proteins, resulting in resistance to apoptosis mediated by chemotherapeutic agents [9]. It was observed that Akt enables the nuclear localization of Mdm2 in breast cancer MCF-7 cells, indicating that this step is critical for the inhibition of p53. In addition, the loss of p53, after the blockade of PI3K/Akt signaling, resulted in a decreased cellular level of p21 [87].

Another kinase involved in the two previously mentioned molecular processes is p70S6K (also designated ribosomal protein S6 kinase beta-1) and is phosphorylated as the result of Akt/mTOR signaling axis activation [88–90] (Table 1). The inhibition of p70S6K with PF-4708671 resulted in significant delays in cell cycle progression in the G0/G1 phase in NSCLC cell lines [91]. Co-treatment of A549 cells with OZ-011 and cisplatin diminished mTOR/p70S6K activation and downstream targets STAT3, Survivin and cyclin D1 [92]. Similar results were obtained by Li and coworkers (2020) where the downregulation of p70S6K expression enhanced the effects of erlotinib and reverted EMT [93]. Moreover, p70S6K has also been described as a transcriptional activator of MMP-9 synthesis [94], thus contributing to the progression of EMT and cancer metastization. Evidence that decreased the phosphorylation levels of Ak and two of its downstream targets (mTOR and p706SK) resulted in the reduced expression of MMP-9 in lung [95] and breast cancer cells [96], which support the crosstalk between p70S6K and PI3K/Akt/mTOR pathway.

To sustain active cell survival as well as other tumorigenic mechanisms, cancer cells need to adapt their metabolism, such as glycolysis, lipids, and amino acid metabolism [23,97]. To achieve this, cancer cells overexpress glucose membrane transporters, such as GLUT4 [98]. AS160 (Akt substrate of 160 kDa) is an important substrate of Akt that, once phosphorylated, interacts with 14-3-3, thus suppressing the inhibitory activity of AS160 on GLUT4 traffic in different cell types [98–100] (Figure 1) (Table 1). RUVBL2 is a cytosolic binding AS160 protein that, once depleted, impairs the insulin-stimulated GLUT4 translocation and the consequent glucose uptake by decreasing AS160 phosphorylation [101]. Additional observations that AS160 modulated the expression of p21 [102] and Ki-67 [103] suggest a possible role of AS160 in the regulation of cell cycle.

Table 1. Synthesis of the potential biomarkers in lung tumorigenesis. This table summarizes the intervenient players in the PI3K/Akt/mTOR signaling pathway in lung cancer that could be useful for patient's stratification and, consequently, selecting the best treatment for each patient.

Cell Regulators	Downstream Target	Upstream Effector	References
Akt	mTOR	PI3K	[8,10,14,15,19]
	FOXM1		[104–108]
mTORC1	p70S6K	Akt	[20,21]
	Twist		[42,43]
	Snail		[46,53]
	Zeb (1/2)		[70–74]
FOXM1	Cyclin D1		[109–111]
Mdm2	p53		[10,112]
AS160	GLTU4		[113–116]
GSK3β	β-catenin	Wnt1/2	[117–119]
miR-21	PTEN	mTORC1	[120,121]
	Smad7		[113,114]
p70S6K	MMP-9		[122–124]
Snail	N-cadherin		[53,64]
	CD133		[125,126]
Twist	Akt		[40,41]
	N-cadherin		[49,54]
Zeb (1/2)	E-cadherin		[76,77]
	miR-200		[89–92,96]
miR-200	Nanog	Zeb (1/2)	[77,90]

3.3. Role of miRNAs as Cell Regulators

miRNAs (19–25 nucleotides) are short non-coding endogenous RNA molecules with the ability to control gene expression primarily by inhibiting protein translation or by degrading targeted mRNAs. Implicated in EMT are miR-200 and miR-21, though with opposite roles. While the first is reported to be inhibited during tumorigenesis, miR-21 is overexpressed, and their concentration in biological samples, such a urine or blood, can be used as prognostic markers in cancer patients [127–129].

miR-200 family is composed of five members (miR-200a, miR-200b, miR-200c, miR-141 and miR-429), divided into two functional groups: group I (miR-200b, miR-200c, and miR-429) and group II (miR-200a and miR-141) [120,121,130,131]. The inhibition of miR-200 has been reported to be controlled by Zeb1 [120,130,132,133] in a negative feedback loop that comprises Zeb1, miR-200 and E-cadherin [134–137], thus resulting in the acquisition of a mesenchymal-like phenotype. This negative correlation has been associated with resistance to nintedanib in A549 cells [138], and Nanog expression in CRC cells [139] (Figure 2). These data further prove our suggestion that Zeb could be the best candidate as a biomarker due to its ability to regulate the expression of miR-200.

Similar results were obtained by Title and coworkers (2018) in vivo [135]. Apart from this, Diaz-Riascos and colleagues (2019) observed a positive relation between miR-200 and E-cadherin expression in pancreatic ductal adenocarcinoma (PDAC) [134]. Treating cells with DAC (Decitabine) interfered with the miR-200/Zeb1 feedback loop and inhibited TGF-β-induced EMT in PC9 lung cancer cells [140]. However, Kundu et al. (2015) discovered that Foxf2 was able to repress both miR-200 and E-cadherin in a Zeb1-independent mechanism [141]. Furthermore, miR-200b inhibited Akt activation and ERK1/2 by targeting

one of its substrates p70S6K [142]. This result appears to be in accordance with previous studies were Akt expression was regulated by miR-200, with the activation of p70S6K as an intermediate player [112,143].

However, studies have demonstrated that different expression levels of each member of this family may lead to a different survival outcome [120,130,132,133]. As an example, a meta-analysis performed by Huang and colleagues (2019) revealed that high blood levels of miR-141 were associated with unfavorable patient survival, while high tissue levels of miR-141 were linked to a better outcome [144]. Similarly, Fontana and coworkers (*2021*) verified an increased expression of miR-200 in breast cancer tissues when compared to normal ones, and an association of the decreased expression of miR-141-3p/miR-200a-3p with HER2-amplified breast cancer subtypes, such as TNBC or Luminal B [145].

Conversely, miR-21 activity has been described as an oncogene [129,146,147]. Different studies have reported that high levels of miR-21 are associated with a worse prognosis, chemotherapy outcome, tumor stage, and survival outcome, especially in lung cancer [122–124,148,149]. Marin and colleagues (2020) detected an upregulation of miR-21 in NSCLC tumor cells, and a negative relation between miR-21 and PTEN expression [113] (Figure 1). Similarly, in a recent study, exosomal miR-21 was responsible for downregulating the expression of tumor suppressor proteins, such as PTEN and PDCD4 (Programmed Cell Death 4) [114], and the overexpression of mesenchymal markers, such as N-cadherin and vimentin, and β-catenin nuclear translocation was associated with the miR-21/LZTFL1 feedback loop [149] (Table 1), suggesting that miR-21 (over)expression can trigger EMT. Consequently, miR-21 induced EGFR-TKI (AG1478) resistance in NSCLC cells and the consequent activation of the PI3K/Akt pathway [115,116]. To test the dependency of miR-21 activation of this signaling pathway, Zhou and coworkers (2018) hindered the expression of this miRNA, and observed a blockade in Akt phosphorylation, resulting in inhibition of the PI3K/Akt signaling pathway, followed by the induction of apoptosis through a caspase-dependent mechanism [150], and increased sensitivity to radiotherapy [151].

New roles for miR-21 are emerging as research progresses in this field. Recently findings proved its role in controlling migration and proliferation, due to the regulation of the expression of Smad7 [152,153] and MMP-9 (metalloproteinase-9) [153] (Figure 2). According to the work of Sahraei et al. (2019), three cohorts of stage I NSCLC patients possessed an elevated expression of miR-21 in CD68^{+} tumor-associated macrophages [154]. In addition, tumor-associated fibroblasts expressed miR-21 to induce proliferation of cancer cells through the secretion of calumenin [155]. These results also suggest a possible regulation of miR-21 in the immune and fibroblast tumor-associated cells, being therefore an outputted potential disease stage biomarker.

4. FOXM1/ β-Catenin/GSK3β Feedback Loop: Intersection between PI3K/Akt and Wnt Signaling Pathways?

Similar to the PI3K/Akt pathway, the Wnt pathway is also involved in different biological aspects of cancer development, such as EMT, resistance to cell death, invasion and proliferation [156,157]. β-catenin is the central molecule in this pathway and controls the switch off of the Wnt pathway [157]. In situations of low activity ("off-state"), β-catenin is degraded by a destruction complex composed of APC (Adenomatous polyposis coli), AXIN (Axis inhibitor), CK1α (casein kinase 1α) and GSK3β. APC and AXIN function as scaffold proteins in this complex, and both CK1α and GSK3β require AXIN to phosphorylate β-catenin, thus allowing its cytoplasmic accumulation and nuclear translocation [157–159]. The activation of this pathway leads to the activation of Disheveled (DVL) protein, which in turn is able to inhibit the activity of GSK3β [160,161] and, consequently, translocate β-catenin into the nucleus due to the disassembly of the destruction complex [156,159]. FOXM1, among other proteins, has been described to be an important chaperone to mediate this translocation and the nuclear retention of β-catenin [159].

That being said, it comes as no surprise that several studies have demonstrated a negative relation between the overexpression of β-catenin, tumor stage, patient survival

and metastization in lung cancer cells [162–164]. This is accomplished when β-catenin forms a complex with E-cadherin [165,166] and decreases TIMP-2 (tissue inhibitor of metalloproteinases 2) expression to allow an EGF- or IGF1- (Insulin Growth Factor 1) induced EMT [167]. The latter was corroborated by Nakayama et al. (2014) by demonstrating that β-catenin is upregulated and translocated into the nucleus in lung cancer cells that harbor EGFR mutants, specifically EGFR-T790 mutants, and this is required for lung tumor formation [168]. The expression of β-catenin was also accompanied by the activation of Dvl proteins and the Wnt pathway. Dvl-1 and Dvl-3 proteins were overexpressed in brain metastasis tissues in 87.1% and 90.3% of the analyzed samples, respectively, and in 25% of these samples, a nuclear co-localization of Dvl proteins and β-catenin was observed [169]. Dvl-3 was overexpressed in 75% of all NSCLC freshly resected samples, accompanied by a higher expression of Wnt-1 or Wnt-2 [170]. Furthermore, anomalous Wnt-1 expression was associated with the overexpression of other downstream targets of the Wnt signaling pathway, apart from β-catenin, such as c-Myc and cyclin D1 in lung cancer [171] (Figure 1). β-catenin is also involved in the abrogation of apoptosis by forming a complex with NF-κB components (p65 and p50), leading to the inhibition of its targeted gene expression, but also by inhibiting the expression of Fas [172].

As previously mentioned, GSK3β is a crucial member of the Wnt/β-catenin pathway, forming a complex with CK1, AXIN, and APC [104,105]. GSK3β is a serine/threonine protein kinase, ubiquitously expressed in vertebrates [106] that acts as a tumor suppressor by phosphorylating different targets that act upstream and downstream of the PI3K/Akt pathway, including Rictor and PTEN [105–107], and as a negative regulator of EMT [104,105]. In normal conditions, this kinase is active in cells, but its dysregulated expression contributes to tumor progression [105]. Like the other two members of this feedback loop, the higher expression of GSK3β was associated with advanced lung cancer stages [108–110] and poor patient survival [173]. The inhibition of GSK3β blocked cells in the G0/G1 phase [108,111], induced apoptosis [111,174,175] and decreased the expression of mesenchymal proteins, such as Slug, by CHIP (C terminal Hsp70 binding protein)-mediated degradation in NSCLC [176]. The pharmacological modulation of GSK3β promoted p53-mediated apoptosis in A549 lung cancer cells [177]. However, Kazi and coworkers (2018) observed that the inhibition of GSK3β neither upregulated β-catenin or c-Myc expression nor induces apoptosis [178], suggesting the existence of other downstream targets for GSK3β. Recently, Li and colleagues (2021) observed that the upregulation of TIPE3 (Tumor necrosis factor-α-induced protein) promoted progression in human NSCLC by the activation of β-catenin, Snail1, and Slug, via the activation of Akt/ERK1/2/GSK3β signaling axis [117].

One of chaperones of β-catenin in the Wnt signaling pathway, FOXM1, is a member of the Forkhead Box (Fox) transcription factor family. It has four splice variants (FOXM1A, FOXM1B, FOXM1C and FOXM1D), with the first being the only one that is reported to be inactive [118,119,179]. It is a significant predictor of poor prognosis [180], tumor stage and lymph node metastasis in NSCLC patients [181]. Interestingly, SCLC cell lines possessed higher FOXM1 expression levels than any other cancer cell lines and normal tissues, according to the work of Liang et al. (2021) [182]. Similar results were observed after chemotherapy treatments, such as IR [183] and cisplatin [184,185], where it induced an upregulation of FOXM1 and, consequently, drug resistance.

The activity of this transcription factor is mainly associated with cell cycle regulation, to the point where it is upregulated through all cell cycle [179]. For example, FOXM1 downregulation, through the inhibition of one of its upstream factors (FAM188B), results in the decreased expression of CDK1, cyclin 1, aurora kinase B, and CDK2, all of which are responsible for controlling cell cycle and survival [186–188], specifically in G2/M and G1/S transition phases [189] (Figure 1). In lung carcinomas, FOXM1 is also able to induce EMT by transactivating Snail promoter activity [190], Zeb1, vimentin and the downregulation of E-cadherin [191], due to the activation of the Akt/p70S6K pathway [192]. However, the blocking of the PI3K/Akt pathway had the opposite effect, leading to the inhibition of

FOXM1 expression and reversed drug resistance in NSCLC cells [193]. Therefore, targeting either FOXM1 or GSK3β as a standalone marker may not be the best approach in lung cancer, but it can have the opposite outcome if used in combination with one of the already mentioned players of the Akt/mTOR axis.

5. Membrane Expression of CD133, a Stemness Marker in Lung Cancer

In the past decades, several studies have identified and tried to understand the connection between EMT-associated processes and the existence of CSC (cancer stem cells) on the tumor microenvironment. CSCs are cancer cells that possess characteristics normally associated with stem cells, specifically the ability to originate all cell types in a tumor, and their self-renewal ability. Their existence in tumor has been associated with drug resistance [42,194]. Although most of these studies have been performed in breast cancer, increasing evidence suggests that this can be a common process in all types of cancer, including lung cancer [195].

As previously mentioned, Akt has not only been associated with survival of CSC, but also with the expression of membrane receptors that confer stem-like properties to cancer cells [14]. CD133 is the most recently membrane receptor to be associated with stem properties in cancer cells [196]. CD133, also known as prominin 1 (PROM1), is a 97 kDa penta-span transmembrane glycoprotein localized in cholesterol-based lipid microdomains. In normal tissues, CD133 is not a stem cell marker and plays a role in morphogenesis [196,197]. Nuclear CD133 expression was correlated with poor survival [198], lymph node metastasis [199], and capillary formation due to the expression of VEGFR-2 (vascular endothelial growth factor receptor 2) [200] in NSCLC cancer patients. However, according to Salnikov et al. (2010), CD133 positivity did not correlate with the expression of angiogenic factors, such as VEGF, in NSCLC tissues [201], suggesting that CD133 expression could be more useful to predict the efficacy of anticancer therapy in NSCLC. Melatonin treatment reduced the expression of the CSC marker CD133, as the resulting inhibition of PLC, ERK/p38 and β-catenin signaling pathways [202], whereas the inhibition of mTOR upregulated CD133 expression in gastrointestinal cancer cells [203].

Several studies reported an enrichment in CD133^{+} cells in NSCLC patients after treatment that overexpressed the ABC transporter ABCG2, CXCR4^{+} [204,205], and ALDH [206]. These cells also expressed Oct-4 [207,208] that, when treated with Octa-4 siRNA, resulted in the downregulation of ABCG2 expression and increased chemosensitivity [207]. Moreover, the existence of a CD133^{+}/CXCR4^{+} phenotype was associated with chemoresistance and high metastatic potential [204,205]. This may be due to a higher expression of vimentin and the EMT-inducing transcriptions factors Snail, Slug and Twist. Silencing CD133 decreased CXCR4 mRNA and protein levels, indicating a possible CD133-dependent regulation of CXCR4 [209]. A similar CD133^{+}/CD44^{+} subpopulation was identified by Su and colleagues (2016), where the metastatic potential was regulated by the Wnt/β-catenin/FOXM1/Twist signaling axis [210]. This population demonstrated resistance to 5-FU and increased sphere-forming activity [211]. That said, this receptor could be used as a prognostic marker in association with other receptors.

6. Conclusions

Even though the potential of biomarkers has just started to be exploited, its development has already been initiated. Cancer therapies have significantly improved throughout the years; however, lung cancer continues to be one of the main causes of death worldwide, suggesting that the existing therapies are still ineffective for some lung cancer patients. This may be due to different expression patterns of tumorigenic proteins that result in tumor heterogeneity. A key molecular process responsible for this heterogeneity is EMT by which cancer cells suppress their epithelial proteins, such as E-cadherin, to activate mesenchymal ones, such as Zeb1, Snail, or Twist, to potentiate their metastatic potential. This process is activated by Akt, a core kinase in the PI3K/Akt signaling pathway, which has been associated with multiple tumorigenic processes, such as stemness properties, cell

migration and invasion, drug resistance or cell death apoptosis. As mediators of such key molecular key events and, eventually modifiers of gene expression, these players can be used as predictive tools of a patient's outcome to a certain therapy or as decision-making tools in the early diagnosis of lung cancer.

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