Cancer is the uncontrollable growth of cells that can come from any organ or body tissue and often appears as a tumor or mass in the body. Cancer is the second leading cause of death for people in the United States; 152.5 people for every 100,000 US residents died of cancer in the year 2017. Most cancer-related deaths are a product of a process called metastasis, in which a secondary cancerous location forms from the initial site of cancer. The severity and frequency of metastasis vary based on the type of cancer; however, it follows a general sequential order. Cancer cells penetrate neighboring tissue, go through intravasation (cancer cells infiltrate blood or lymphatic vessels through basement membranes), extravasation (cancerous cells move into tissues from blood), and finally, colonize and metastasize in a secondary location. Cancer can be treated in a variety of ways though there is not a proven cure for any cancer. Chemotherapy, in which the drug aims to slow the dividing of cancerous cells by inducing DNA breakage, is a key player in the development and maintenance of cancer stem cells, catalyzing increased chemoresistance and metastasis. The Wnt signaling pathway can sustain these CS-LCs with β-Cat present in the pathway. In this review, we summarize the current knowledge surrounding the Wnt signaling pathway as well as its crosstalk with other pathways and their implications for cancer cell plasticity.

**Keywords:** Chemoresistance, crosstalk, lung cancer, plasticity, tumorigenesis, Wnt signaling

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sistance of cancer cells seem to be the result of the ability of cells to reversible interconvert into different phenotypes, a process known as cell plasticity. In this article, we review mechanisms of plasticity, especially in lung cancer, focusing on the role of the Wnt signaling pathway and the crosstalk with other important signaling pathways responsible for the maintenance of plasticity in general.

**Lung Cancer**

Lung cancer is the uncontrollable growth of cells in one or both lungs. Globally, it is the most common and deadliest cancer: in 2012, 12.9% of cancer-related deaths were caused by lung cancer. Annually, around 1.6 million people die from different forms of lung cancer. Lung cancer often spreads to other regions of the body through the blood or lymphatic systems to catalyze the development of secondary tumors. This process is called metastasis. Lung cancer is often caused by exposure to air pollutants, consumption of alcohol, and, most often, smoking. Most patients diagnosed with lung cancer reported being current or former smokers. Undoubtedly, the emergence of the lung cancer epidemic during the twentieth century was fueled by the rise of smoking. Lung cancer is a heterogeneous malignancy, meaning multiple types of cancer exist. Lung cancer can be divided into two main subsets: small cell lung cancer (SCLC) and nonsmall cell lung cancer (NSCLC). SCLC represents approximately 15% of lung cancer cases while NSCLC accounts for around 85%. SCLC is frequently diagnosed in heavy smokers and presents at later stages. These tumors are believed to arise from neuroendocrine cells present in lung endothelial cells due to the expression of neuroendocrine markers such as chromogranin and synaptophysin. NSCLC is less associated with smoking and tends to have a delayed expression of symptoms. The microscopic divisions of NSCLC include adenocarcinoma and squamous cell carcinoma, with the presence of specific DNA mutations allowing further molecular stratification. There are several smaller types that account for less than 5% of diagnoses. Small cell and large cell carcinomas are other subdivisions of NSCLC and SCLC; they account for around 20% and 10% of cases, respectively. Adenocarcinoma and squamous cell carcinoma are more prevalent, with adenocarcinoma being the most diagnosed type of lung cancer. Adenocarcinomas are usually located at the edge of the lung and metastasize early. In contrast, squamous cell carcinomas generally metastasize later but are located centrally inside the bronchi. There is a multitude of tests available for diagnosing lung cancer although these tools are often not sensitive enough to make a diagnosis early. Only 10%–15% of patients are diagnosed at an early stage while 75% are diagnosed at an advanced stage.

**Cell Plasticity**

Cancer cells and stem cells in general exhibit a characteristic called plasticity. Stem cell plasticity is the ability of adult tissue-specific cells to reversibly adopt a new identity. Plasticity also refers to phenotypic potential in which cells take on a broader set of phenotypes of the differentiated cells for their original tissues. Plasticity is useful in regenerative medicine because tissues such as bone marrow have shown the ability to restore heart, skin, and liver function in multiple cases. This ability to convert from one tissue to another is based on differentiation potential. More differentiated cells can differentiate between complex and simple cell types based on conditions present in their surrounding niche. Differentiation occurs when stem cells with broad potential are placed in an environment with sufficient inductive signals, which cause a developmental change in the affected cell. For example, plasticity allows progenitors and enterocytes in the intestinal lining to de-differentiate to intestinal stem cells through the Wnt signaling pathway. Overall, plasticity serves three main functions: mature cells can dedifferentiate into more specific cells of the same lineage, mature cells can transdifferentiate into other mature cells, and progenitor cells can convert to other types of progenitors. Transdifferentiation refers to individual cells changing their identity in response to a change in environmental conditions or injury. Metaplasia is the term that denotes the change of identity of an entire tissue. In humans, only a little is known about the mechanism of metaplasia. Metaplasia is reversible, especially when the source of injury stops. For instance, in patients with lung cancer, excessive tobacco use may cause metaplasia, but quitting may allow the damage to reverse.

Plasticity causes issues because different phenotypes respond uniquely to the same treatment or environment. This is especially problematic with cancerous cells because there are few proven treatments that combat even a single phenotype. The plasticity of normal cells is a physiological process; plasticity of cancer cells allows further invasion and negatively affects the infected. Cancer cell plasticity helps cells survive treatment and change surroundings to spread.

**Mechanisms of Plasticity**

At present, the underlying mechanism of cell plasticity is not fully understood and is clearly cell-type dependent. The plasticity of T cells (cells present in the immune response), specifically TH17 cells, is often influenced by the presence of cytokines such as IL-6 and TGF-β. These cytokines are present in dendritic cells which are cells exposed to the outside environment. Their specific role in T cell plasticity is still unclear; however, it can be speculated that their influence on...
T cell differentiation is dependent on their environment.\(^{[23]}\) The plasticity of Schwann cells is valuable in the peripheral nervous system; Schwann cells myelinate axons to form the myelin sheath. Schwann cells can repair damage after nerve injury because of their plastic ability.\(^{[24]}\) There are four main transcriptional regulators that allow this: c-Jun, Notch, Zeb2, and NF-κB. These regulators influence functional recovery, remyelination, and axonal regeneration.\(^{[24]}\) There are many regulators present across different types of cells. In lung cancer specifically, Wnt is a major glycoprotein that is a part of a larger signaling pathway. Its expression plays a role in cancer metastasis, chemoresistance, and tumorigenesis. The pathway contains tumor suppressors, phosphoryl groups, and various proteins that alter characteristics as the components of the pathway interact with each other in different ways. The Wnt pathway transduces signals through the Frizzled (FZD) and low-density lipoprotein receptor-related protein (LRP) receptors (Fig. 1) in the Wnt/β-catenin and Wnt/stabilization of proteins (STOP) signaling cascade.\(^{[25]}\) The primary receptors of the Wnt/β-catenin pathway are seven transmembrane FZDs while LRPs are coreceptors.\(^{[26]}\) This is true for the canonical and noncanonical pathways. Both the canonical and noncanonical Wnt/β-catenin cascades have implications in plasticity due to their role in the creation and maintenance of CSCs.\(^{[25]}\) Wnt ligands are required to activate the pathway; the Wnt/β-catenin pathway is impressively complex as there is a multitude of different Wnt ligands and receptors. Activation occurs when a Wnt ligand binds to both receptors, initiating the phosphorylation of LRP6 and consequently the degradation of β-catenin as it exits the destruction complex.\(^{[26]}\)

**Cancer Cell Plasticity**

Cancer cell plasticity includes the interconversion of cancer cells into various subtypes or entirely different cells through transdifferentiation. Cancer cells being plastic also allows them to phenotypically transition to be more prepared for the challenges that accompany metastasis. Plasticity allows cancer cells to survive in difficult microenvironments while still being resistant to treatment by acquiring stem cell-like characteristics and other functional adaptations through dedifferentiation.\(^{[26]}\) Cancer cell plasticity occurs for a variety of reasons, including the presence of secreted nanoparticles deemed exosomes and the extracellular matrix (ECM) comprising immune cells, fibroblasts, adipocytes, and endothelial cells, and a noncellular component, which is a network of polymeric proteins and accessory molecules.\(^{[27,28]}\) Exosomes can transport lipids, proteins, and nucleic acids. Their contents have been known to promote cancer progression, therapeutic treatment resistance, and tumor heterogeneity. The RNA in exosomes has been found to promote cancer therapy resistance in cancer stem-like cells, which furthers the influence of plasticity.\(^{[27]}\) The ECM creates biomechanical and biochemical contexts that influence cell plasticity and vice versa. The ECM in conjunction with other cell types, including an array of cytokines and other secreted and membrane-bound factors found in the tumor stroma promotes cancer cell plasticity.\(^{[28]}\) There are multiple types of plasticity. One of the most understood types of plasticity is the epithelial-to-mesenchymal transition (EMT). Epithelial cells make up the lining of hollow organs as well as the outer layer of the human body. Epithelial cells interact with one another through tight junctions, adherens junctions, and

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**Figure 1.** The Wnt signaling pathway. Left panel: The Wnt protein is absent, and therefore β-catenin (β-Cat) is not present in the nucleus. Right Panel: Wnt binds to the low-density lipoprotein (LDL) receptor-related protein (LRP), thereby prompting the translocation of β-Cat into the nucleus and cytoplasm from the destruction complex. The Axin is also removed from the destruction complex. β-Cat binds a transcription factor, such as TCF/LEF in DNA and initiates transcription of genes/proteins.

APC: Antigen-presenting cell; FRZ: response regulator protein; DSH: Disheveled protein; P: Phosphate.
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Desmosomes to establish an apical–basal polarity.\textsuperscript{[29]} Apical–basal polarity allows cells to respond to their microenvironment; the apical membrane faces the lumen of internal cavities while the basolateral membrane faces the opposite.\textsuperscript{[30]} Mesenchymal cells have a front–rear axis polarity, while epithelial cells have an apical–basal polarity.\textsuperscript{[30]} EMT changes the shape and molecular structure of cells through the loss of apical–basal polarity and disassembly of epithelial cell junctions.\textsuperscript{[22]} Tight junctions are located at the lateral side of cell membranes close to the apical surface; tight junctions are broken down after epithelial cells lose apical–basal polarity.\textsuperscript{[29,32]} Adherens junctions exist adjacent to tight junctions in the basolateral compartments of epithelial cells. E-cadherin characterizes adherens junctions by binding to β-catenin which attaches to the actin cytoskeleton. The cytoskeleton is responsible for the shape of the cell. Its reorganization is partly caused by the loss of E-cadherin and is a major event in EMT.\textsuperscript{[29]} Desmosomes are adhesive junctions that contain cadherins connected to cell cytoskeletons. A decrease in desmosome presence is associated with EMT, but it is still unknown where it fits sequentially.\textsuperscript{[29,32]} All of these components of epithelial cells allow them to transition to mesenchymal cells during EMT. This process is fully reversible: mesenchymal cells can revert to epithelial cells or exist in a partial state known as partial EMT.\textsuperscript{[22]} EMT occurs when epithelial cells become mesenchymal following the breakdown of cell–cell junctions and rearrangement of elements of the cytoskeleton.\textsuperscript{[22]} This transition increases the invasiveness of cancer cells and the rate of metastasis through decreased expression of E-cadherin and therefore increased expression of N-cadherin.\textsuperscript{[29,31]} N-cadherin and vimentin are mesenchymal genes. Their expression indicates the mesenchymal identity of the cell and increases cell migration. EMT is a regular cell process as well as one of the cancer cells. The migration of cancer cells promotes tumorigenesis and metastasis.\textsuperscript{[33]}

Numerous types of cancers exhibit plasticity at various degrees. There are myriad reasons why cells can be plastic, and they differ between types and subtypes of cancer. For example, increased stemness of cells is a large contributor to lung cancer cell plasticity. Lung cancer stem cells (LCSCs) utilize the expression of many signaling pathways,\textsuperscript{[34]} including Wnt/β-catenin, Notch, and sonic hedgehog (Shh), which will be discussed later in the article.

**Plasticity of Lung Cancer Cells**

The plasticity of lung cancer cells allows for their unfortunate survival in response to cancer treatments. Lung cancer contains a subpopulation of cancer stem cells (CSCs) which are highly resistant to anticancer drugs and are a major catalyst for tumor recurrence.\textsuperscript{[34]} According to the stemness phenotype model, cancer cells can increase their stemness depending on the surrounding microenvironment, interconversion between phenotypically CSCs exists, and CSCs and non-CSCs can convert to each other.\textsuperscript{[34,35]} Differentiated lung cancer cells can dedifferentiate into CSCs, induce new tumor growth, and strengthen primary cancer sites.\textsuperscript{[19]} One strain of SCLC, the cell line NCI-H446 exhibited the ability to differentiate to neurons, adipocytes, and osteocytes as well.\textsuperscript{[34]} The plasticity of LCSCs and NCSCs has been supported by in vitro studies; however, there is more research to be done on the ability of interconversion in the human body.\textsuperscript{[19]} Cells in the lungs differentiate from other cell types in response to injury, exposure to toxins, or cell ablation.\textsuperscript{[36]} For instance, cuboidal or columnar epithelial cells in the airways and alveoli transition to the stratified squamous epithelium in response to consistent injury caused by environmental conditions. This is deemed metaplasia. This transformation can make cells more susceptible to becoming carcinoma.\textsuperscript{[20]}

**Mechanisms of Plasticity in Lung Cancer: Wnt**

Secreted, cysteine-rich glycoproteins, known as the Wnt family, act as ligands for many receptors in the human body as well as play a role in cell survival, organ formation, and stem cell renewal.\textsuperscript{[37]} Wnts are responsible for cell-to-cell communication dependent on contact or over a short distance. Wnt and β-Cat go together. Without Wnt signaling present, β-Cat is bound to the Axin and antigen-presenting cell (APC), phosphorylated by protein kinases, and ubiquitylated by enzymes.\textsuperscript{[38]} When Wnt is deactivated, Axin is stabilized by its phosphoryl group, provided by the GSK-3 protein (also found in the destruction complex). When the pathway is activated, the Axin is dephosphorylated, allowing the phosphorylation of β-Cat and the degradation of APC. This degradation is important because APC is classified as a tumor suppressor. When Wnt is on and APC is reduced, tumorigenesis is more likely to occur.\textsuperscript{[39]} The E3 ligase SIAH prevents β-Cat from being eliminated by proteasomes, while APC is attacked by these proteasomes.\textsuperscript{[38,39]} Wnt employs both autocrine (self-targeting) and paracrine (targets nearby cells) signaling to promote intracellular transport. Activation of the Wnt pathway increases resistance to chemotherapy drugs such as cisplatin, a wide spectrum drug that is effective in the treatment of many cancers.\textsuperscript{[40]} Understanding the regulation of signaling pathways is crucial in the development of treatment. Unfortunately, there is almost always more than one pathway involved in the expression of certain genes or characteristics. Wnt is a major pathway when it comes to lung cancer, but there is a multitude in action. The interactions among different elements of each pathway causing a response different from that of a singular pathway are referred to as crosstalk.\textsuperscript{[41]}
Crosstalk between the Wnt Signaling Pathway and Other Pathways and Proteins

Though the Wnt pathway alone has an influence on plasticity, the crosstalk of Wnt and other pathways while expressing target proteins does as well. Table 1 shows examples of proteins and signaling pathways known to crosstalk with the Wnt pathways associated with chemoresistance, tumorigenesis, and metastasis. For instance, the Notch pathway crosstalks with Wnt in many cancers and various malignancies. In NSCLC, Notch crosstalk with Wnt signaling pathways allows the maintenance of CSCs. As the pathways interact, they upregulate or deregulate genes and proteins in the pathway of others. For example, Wnt ligands upregulate JAG and NOTCH2 genes to enhance Notch signaling but repress Notch signaling pathways by the upregulation of NUMB and Prospero homeobox 1 protein. On the other hand, Notch ligands signal the upregulation of NRARP to enhance β-catenin/LEF1 signaling within the Wnt pathway. Repression of Wnt/β-catenin signaling occurs when the gene OLFM4 is upregulated. Notch and Wnt ligands converge on BMI1 and TCF7 to support slow-cycling CSCs (exhibit increased chemoresistance and tumorigenicity in vivo and take part in metastatic dormancy) and on CCND1 and MYC genes to increase tumor proliferation. This combination of upregulation and downregulation contributes to overall increased chemoresistance, tumor progression, and metastasis in NSCLC (Notch pathways are inactive in SCLC).[^42] Another example of Wnt crosstalk exists in pituitary adenomas (benign tumors). Crosstalk between the Shh and Wnt signaling pathways is mediated by the sex-determining region Y box 2 (SOX2) to increase pituitary adenoma cell proliferation. Though separately Shh and Wnt activation both contribute to tumorigenesis, crosstalk is unable to occur without SOX2 mediation. The inhibition of SOX2 gene is required to mediate crosstalk between Shh and Wnt[^43].

| Pathway                  | CR        | Tg        | Met       | Wnt crosstalk |
|--------------------------|-----------|-----------|-----------|---------------|
| Wnt                      | ↑ CR[^46] | ↑ Tg[^47] | ↑ Met[^48] | Yes – pituitary adenoma[^43] |
| Sonic hedgehog (Shh)     | ↑ CR[^49,50] | ↑ Tg[^51] | ↑ Met[^52] | Yes – breast cancer, non-small-cell lung cancer, and hematological malignancies[^42] |
| c-Jun                    | ↑ CR[^53] | ↑ Tg[^54] | ↑ Met[^55] | Yes – colorectal cancer (c-Jun gene)[^54] |
| Notch                    | ↑ CR[^56] | ↑ Tg[^57] | ↑ Met[^58] | Gene required to mediate crosstalk between Shh and Wnt[^43] |
| SOX2 gene                | ↑ CR[^59] | ↑ Tg[^59,60] | ↑ Met[^61] | Protein involved with IGF-1 signaling crosstalk with Wnt[^62] prostate cancer |
| Egr-1 protein            | ↑ CR[^62] | ↑ Tg[^63] | ↑ Met[^64] | No results |
| CDKN1C                   | ↑ CR[^65] | ↑ Tg[^66] | ↑ Met[^67] | Yes – colon cancer in mice[^67] |
| p38 MAPK                 | ↑ CR[^68] | ↑ Tg[^69] | ↑ Met[^70] | Does not explicitly say crosstalk |
| AKT                      | ↑ CR[^71] | ↑ Tg[^72] | ↑ Met[^73] | Yes – head and neck cancer[^71] |
| PTEN                     | ↓ CR[^74] | ↓ Tg[^75] | ↓ Met[^76] | Yes – lung cancer[^46] |
| AMPK                     | ↑ CR[^77] | ↓ Tg[^78] | ↓ Met[^79] | Yes[^78] |
| eGFR                     | ↑ CR[^80] | ↑ Tg[^81] | ↑ Met[^82] | Yes – non-small cell lung cancer[^82] |
| TLR                      | ↑ CR[^83] | ↑ Tg[^84] | ↑ Met[^85] | ? |
| Ras                      | ↑ CR[^86] | ↑ Tg[^87] | ↑ Met[^88] | Yes – prostate cancer bone metastasis[^89] |
| NANOG                    | ↑ CR[^89] | ↑ Tg[^90] | ↑ Met[^91] | **List as a gene that is involved in liver cancer cell regulation and hepatocellular carcinoma prognosis[^90]** |
| PI3K                     | ↑ CR[^91] | ↑ Tg[^92] | ↑ Met[^93] | Yes – head and neck cancer[^71] |
| RB                       | ↑ CR[^94] | ↑ Tg[^95] | ↑ Met[^96] | ? |

Many of these proteins affect or are being affected by crosstalk with the Wnt signaling pathway in the lung as well as in other types of cancers (last column). ↑: Increase, ↓: Decrease, ?: Lack of sufficient information to draw a conclusion.
SOX2 disrupts the crosstalk, thereby decreasing tumor cell reproduction. The Hippo pathway is another pathway that undergoes crosstalk with Wnt. Their crosstalk occurs in gastrointestinal cancers. Wnt handles maintaining tissue and embryonic homeostasis while Hippo controls organ growth and tissue development. However, when the pathways interact with one another, cancerous cells experience increased self-renewal, growth, and survival through the alteration of proto-oncogenes and tumor suppressor genes. Activation of yes-associated protein (YAP) and TAZ (WW domain-containing transcription factor) in the Hippo signaling pathway leads to cancer metastasis and proliferation while activation of β-Cat in the Wnt signaling pathway leads to increased tumorigenesis. Together, interactions between YAP1 and β-Cat promote the expression of downstream genes, leading to cell proliferation and growth of intestinal tumors. TAZ in the Hippo pathway also has implications for the downregulation of β-Cat. When TAZ is reduced, less β-Cat is accumulated in the nucleus as less can be released from the destruction complex in the Wnt signaling pathway.

Wnt Inhibitors

The Wnt signaling pathway is one of the major oncogenic pathways in many cancers; however, its inhibition is limited by a lack of effective and supported compounds. The majority of proteins have not yet been consistent in whether or not they inhibit or facilitate the Wnt signaling pathway. Therefore, “inhibitor” proteins are usually referred to as Wnt regulators. There are two types of regulation of the pathway: the first binds to Wnt ligands so they cannot bind to receptors, and the other binds to LRP to prevent Wnt ligands from binding. Wnt pathway activation is related to lung cancer progression and chemoresistance. It is important to look into the development of drugs that can consistently inhibit the Wnt signaling pathway because proteins often exhibit inconsistencies as previously discussed. Inhibitor drugs such as LGK974, a novel orally bioavailable cancer therapeutic in Phase I clinical trials, have had positive results in downregulating the Wnt pathway and suppressing lung cancer growth. In vivo trials have produced positive results in mice, but human trials are yet to be concretely supported. In other types of cancer, LGK974 has been effective in downregulating Wnt genes as well as genes in the Notch signaling pathway, both of which have implications for chemoresistance and tumorigenesis of cancer cells. These trials have been performed in vivo and in vitro. Wnt and Notch also crosstalk. LGK974 can inhibit genes in both pathways, thereby efficiently minimizing cancerous growth.

Conclusion

The Wnt signaling pathway is a key regulator of phenotypic plasticity in lung cancer cells and is being extensively investigated as a promising target for anticancer drugs. Its extensive crosstalk with proteins involved in the regulation of other multiple pathways provides a complex regulatory network affecting key processes important for tumorigenesis, metastasis, and chemoresistance. Combination chemotherapy targeting simultaneously multiple Wnt crosstalking pathways may be a more effective strategy than targeting only multiple targets of a single transduction pathway. At present, not all the examples of crosstalk shown in Table 1 have been identified in lung cancer cells but their existence in other types of cancer suggests that they may be present in lung cancer cells as well. The recognition of these mediators and understanding of how different pathways strengthen the negative traits of lung cancer cells are critical for the development of novel and more effective therapies.

Disclosures

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