Non-small cell lung cancer and non-traditional management: A review

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Abstract

Lung cancer is the leading cause of cancer death in men and women in the United States. Non-Small Cell Lung cancer is the most common among all types of lung cancer. Late diagnosis and lack of effective management leads to poor prognosis. Recent research has discovered over expression of MUC5AC and its interaction with integrin beta4 that facilitates spread of cancer at a fast rate. Interventions that can suppress the overexpression of MUC5AC have shown promising results to slow down the progress of lung cancer. Although many pharmacological interventions are still under investigation and development, some herbs like Ginkgo biloba and ginger has shown its effectiveness in suppressing MUC5AC gene overexpression. Further study and FDA approval will help to handle this health problem easily and effectively without significant financial burden and side effects.

Lung cancers can start in the cells lining the bronchi and parts of the lung such as the bronchioles or alveoli. Lung cancers are thought to start as areas of pre-cancerous changes in the lung. The first changes in the genes (DNA) inside the lung cells may cause the cells to grow faster. These cells may look a bit abnormal if seen under a microscope, but at this point they do not form a mass or tumor. They cannot be seen on an x-ray and they do not cause symptoms.

Over time, the abnormal cells may acquire other gene changes, which cause them to progress to true cancer. As a cancer develops, the cancer cells may make chemicals that cause new blood vessels to form nearby. These blood vessels nourish the cancer cells, which can continue to grow and form a tumor large enough to be seen on imaging tests such as x-rays.

At some point, cells from the cancer may break away from the original tumor and spread (metastasize) to other parts of the body. Lung cancer is often a life-threatening disease because it tends to spread in this way even before it can be detected on an imaging test such as a chest x-ray.

Non-Small Cell Lung Cancer is the most common type of lung cancer. Statistics for lung cancer include both small cell and non-small cell lung cancer. In 2015, an estimated 221,200 adults (115,610 men and 105,590 women) in the United States will be diagnosed with lung cancer. Lung cancer is the second most common cancer and the leading cause of cancer death for men and women. It is estimated that 158,040 (86,380 men and 71,660 women) deaths from this disease will occur this year (American Cancer Society, 2015).

About 85% to 90% of lung cancers are non-small cell lung cancer (NSCLC). There are 3 main subtypes of NSCLC. The cells in these subtypes differ in size, shape, and chemical make-up when looked at under a microscope. But they are grouped together because the approach to treatment and prognosis (outlook) are often very similar.

Squamous cell (epidermoid) carcinoma: About 25% to 30% of all lung cancers are squamous cell carcinomas. These cancers start in early versions of squamous cells, which are flat cells that line the inside of the airways in the lungs. They are often linked to a history of smoking and tend to be found in the middle of the lungs, near a bronchus.

Adenocarcinoma: About 40% of lung cancers are adenocarcinomas. These cancers start in early versions of the cells that would normally secrete substances such as mucus. This type of lung cancer occurs mainly in current or former smokers, but it is also the most common type of lung cancer seen in non-smokers. It is more common in women than in men, and it is more likely to occur in younger people than other types of lung cancer.

Adenocarcinoma is usually found in outer parts of the lung. It tends to grow slower than other types of lung cancer, and is more likely to be found before it has spread outside of the lung. People with a type of adenocarcinoma tend to have a better outlook (prognosis) than those with other types lung cancer.

Lung cancer at molecular level

MUC5AC is a secretory mucin aberrantly expressed in various cancers. In lung cancer, MUC5AC is overexpressed in both primary and metastatic lesions. Its role overexpression of MUC5AC is still not understood. A recent study by Lakshmanan et al. was aimed at evaluating mechanistic role of MUC5AC on metastasis of lung cancer cells [1]. Clinically, the overexpression of MUC5AC was observed in lung cancer patient tissues and was associated with poor survival. In addition, the overexpression of MUC5AC was also observed in genetically engineered mouse lung adenocarcinoma tissues (KrasG12D; Trp53R172H/+; AdCre) in comparison with normal lung tissues. This

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study also showed that MUC5AC knockdown resulted in significantly decreased migration in two lung cancer cell lines (A549 and H1437) as compared with scramble cells. Expression of integrins (α5, β1, β3, β4 and β5) was decreased in MUC5AC knockdown cells [1]. Although both integrins and MUC5AC have a von Willebrand factor domain, MUC5AC strongly interacted only with integrin β4. The co-localization of MUC5AC and integrin β4 was observed both in A549 lung cancer cells as well as genetically engineered mouse adenocarcinoma tissues. Activated integrins recruit focal adhesion kinase (FAK) that mediates metastatic downstream signaling pathways. Phosphorylation of FAK (Y397) was decreased in MUC5AC knockdown cells. MUC5AC/β4/FAK-mediated lung cancer cell migration was confirmed through experiments utilizing a phosphorylation (Y397)–specific FAK inhibitor. This study concluded that overexpression of MUC5AC is a poor prognostic marker in lung cancer. MUC5AC interacts with integrin β4 that mediates phosphorylation of FAK at Y397 leading to lung cancer cell migration.

Excessive mucus production has been linked to many of the pathologic features of respiratory diseases, including obstruction of the airways, decline in lung function, increased rates of mortality, and increased infections. The mucins, MUC5AC and MUC5B, contribute to the viscoelastic properties of mucus, and are found at elevated levels in the airways of individuals with chronic respiratory diseases. The T helper type 2 cell cytokine, IL-13, is known to regulate MUC5AC expression in goblet cells of the airways, although much less is known about the regulation of MUC5B expression. In a study to further understand the mediators of MUC5AC and MUC5B expression, neuregulin (NRG) 1β1 was identified as novel regulator of goblet cell formation in primary cultures of human bronchial epithelial cells (HBECs) [2]. NRG1β1 increased expression of MUC5AC and MUC5B proteins in a time- and dose-dependent fashion in HBEC cultures. NRG1β1-induced expression of MUC5AC and MUC5B was shown to involve v-erb-b2 erythroblastic leukemia viral oncogene homolog (ErbB) and ErbB3 receptors, but not ErbB4 receptors. Treatment of HBECs with inhibitors of p38 mitogen-activated protein kinase, extracellular signal–regulated kinase1/2, and phosphatidylinositol 3-kinase indicated that these kinases were involved in NRG1β1-induced MUC5AC and MUC5B expression. Additionally, NRG1β1 was shown to induce the phosphorylation of the ErbB2 receptor, AKT, and extracellular signal–regulated kinase 1/2. NRG1β1 protein was found increased in the airways of antigen-challenged mice, together with increases in MUC5AC and MUC5B message. Together, these data indicate that NRG1β1 is a novel mediator of MUC5AC and MUC5B expression in HBECs, and may represent a novel therapeutic target for mucus hypersecretion in respiratory diseases and MUC5AC interaction with integrin in lung carcinomas.

These studies open the door for many other studies that can focus on down regulating MUC5AC and inhibiting the interaction of MUC5AC and integrin β4. Integrins are heterodimers composed of alpha and beta subunits that are noncovalently associated transmembrane glycoprotein receptors. Different combinations of alpha and beta polypeptides form complexes that vary in their ligand-binding specificities. Integrins mediate cell-matrix or cell-cell adhesion, and transduced signals that regulate gene expression and cell growth [3]. This gene encodes the integrin beta 4 subunit, a receptor for the laminins. This subunit tends to associate with alpha 6 subunit and is likely to play a pivotal role in the biology of invasive carcinoma.

Natural medicine in MUC5AC down regulation

Natural medicines use herbs and natural minerals for treating various medical conditions. Mechanisms of action of most of these drugs are still unknown to the modern medicine but they were used effectively for the past centuries. Research on some of these drugs revealed the potential ingredient and their physiological actions on various systems of the body. Some of the herbal medicines have toxic substances in it and may lead to harmful effects. Drug interaction is another important aspect of natural medicines. All these being said, natural medicines have least side effects compared to modern medicine. Let us discuss about some natural medicines that can be useful based on recent researches on lung cancer.

Ginkgo biloba

According to the study by Kwon et al. [4], Ginkgo biloba extract (GBE) suppresses IL-1β-induced MUC5AC gene expression in NCI-H292 cells via the ERK and p38 MAPK pathways. This study sought to identify which ingredients of GBE suppress IL-1β-induced MUC5AC gene expression in NCI-H292 cells and to examine which MAPKs are related to MUC5AC gene suppression for each ingredient. After the cells were pretreated with each ingredient and treated with IL-1β (10 ng/mL), MUC5AC mRNA expression was determined by RT-PCR and real-time PCR. The results showed that kaempferol (KP) and quercetin (QC) suppressed MUC5AC mRNA expression in a dose-dependent manner, both with significant inhibition starting from 40 µM (equal concentration to about a twelfth or thirteenth dose of GBE). MAPK proteins were determined by western blot analysis after pretreatment with KP, QC and GBE. All three suppressed the phosphorylation of ERK and p38 kinases [4]. In conclusion, the data suggested that KP and QC, essential ingredients in GBE, may overcome the dose problem of GBE and play a valuable role, clinically, in controlling mucin hypersecretion in airway inflammation.

Ginger

[6]-Gingerol is a major active component of ginger and a natural polyphenol compound. A study by Kim et al. investigated whether [6]-gingerol suppresses interleukin (IL)-1beta-induced MUC5AC gene expression in human airway epithelial cells and, examined whether the suppression of MUC5AC gene expression is mediated via the mitogen-activated protein kinase (MAPK) signal transduction pathway [5]. MUC5AC mRNA and protein were measured using reverse transcription-polymerase chain reaction (PCR), real-time PCR, and Western blot analysis in cultured NCI-H292 human airway epithelial cells. Extracellular signal-regulated kinase (ERK) and p38 MAPK protein levels were analyzed by Western blot. Expression of MUC5AC mRNA increased in NCI-H292 cells upon treatment with 10 ng/mL of IL-1beta for 24 hours. When the cells were pretreated with 10 microM of [6]-gingerol, expression of IL-1 beta-induced MUC5AC mRNA and protein was significantly suppressed. Suppression of IL-1 beta-induced MUC5AC mRNA was also observed in cells pretreated with ERK- or p38 MAPK-specific inhibitors, suggesting that [6]-gingerol-mediated suppression of IL-1 beta-induced MUC5AC mRNA operated via the ERK- and p38 MAPK-dependent pathways. This study concluded that [6]-Gingerol suppresses IL-1beta-induced MUC5AC gene expression and so it can be used in prevention of lung carcinomas in high risk population and to slow down the disease progress in diagnosed patients [6].

Conclusion

Effectiveness of Ginkgo biloba and Ginger should be studied in
the United States and follow-up with the FDA guideline for the future commercial development of herb based medications to slow down or prevent lung cancer.

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