Detecting Lung Cancer Earlier – New Bio-Marker May Supplement Current Tests

By Vijay Shankar Balakrishnan, Ph.D.

After prostate and breast cancers, lung cancer is the second most common cancer in men and women [1]. In addition to genetic factors, different environmental and lifestyle factors, such as pollution, smoking, or living with a smoker for a long time, can drive lung cancers. There are two types of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC being the more common (85-90%) of the two [2]. The malignant cells of SCLC are small and seem to have no room for a cell nucleus, whereas NSCLC cells are of any size, but are not smaller than the normal (non-cancerous) cell in the lungs [3]. There are three types of NSCLC [4] including adenocarcinomas, which frequently affect the cells in outer regions of the lung [5]. Several lab tests can diagnose different types of lung cancers, but unfortunately treatments are frequently not initiated early enough, as a major driver of lung cancer mortality is late diagnosis [6].

One recent study published in *Clinical Cancer Research* now gives hope for early detection of adenocarcinomas. Led by Dr. Jie He at the Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China [7], the study reports that levels of the enzyme isocitrate dehydrogenase 1 (IDH1) are dramatically elevated in the blood of lung cancer patients, indicating that IDH1 may function as a diagnostic biomarker. According to Dr. He, "This study is the first to report IDH1 as a novel biomarker for the diagnosis of [NSCLC] using a large number of clinical samples" [8].

"With an increase in [the] aging population, we are likely to see an increase in lung cancer incidence and a need for better biomarkers for early diagnosis", added Jie He [8]. Moreover, He claims that, "IDH1 [is] an effective plasma biomarker with high sensitivity and specificity in the diagnosis of NSCLC, especially lung adenocarcinoma".

Usually, diagnosis involves a parade of time-consuming, non-invasive means like chest X-ray and Computed Tomography (CT), as well as more painful, invasive approaches such as bronchoscopy and needle biopsies. In their article, He and colleagues point out problems with the accuracy, sensitivity, and specificity of current techniques, which limit their effectiveness. This is compounded by the side effects of the current tests (such as the effect of radiation during a CT scan) as well as, according to the authors, the potential for false-positives from CT scans that could culminate in over-diagnosis.

These shortcomings highlight the potential benefits of blood-based tests. Cancer cells or their surroundings produce biomarkers that can be found in plasma, and these tumor-specific circulating proteins are useful in identifying other cancers. Previously identified biomarkers include Carcino-Embryonic Antigen (CEA) for colon cancer [11] and Cancer Antigen 125 (CA125) [12] for ovarian cancer. CEA and another protein, Cyfra21-1, have been found to be useful in identifying lung cancer [9]. However, these are of "low [sensitivity] (50-60%) and are specific only up to 90%", write the authors [7]. Therefore, a major issue is not the lack of tests, but a lack of efficiency in available tests.

IDH1 is an oxidizing enzyme that has its role in the second part of glucose breakdown in a process known as the Krebs cycle [13]. The authors found in an earlier study [10] that IDH1 is produced to a greater extent in lung cancer patients, indicating that it could be a potential bi-

omarker to diagnose the disease. IDH1's function is associated with redox processes, and redox reactions have been linked to carcinogenesis and cancer treatment. Using a technique called RNA interference, the authors silenced the gene that produces IDH1 in cells and also in tumors in mice (xenograft tumors). "We have found that knocking down IDH1 by siRNA [small interfering RNA] suppressed the proliferation of NSCLC cells and decreased the growth of xenograft tumors", recalls He, in an email. Thus, the bait fell in their hands to further test the diagnostic value of IDH1. He and colleagues are, in fact, intrigued by the IDH1 levels in blood. They explain it as either due to an exceptional cellular event or as a result of cell damage and cell death. However, it is not clear which cells are potentially damaged or dead.

In this first-ever large study on 1,422 participants, He and colleagues measured the levels of the known biomarkers CA125, Cyfra21-1, and CEA, along with IDH1, in the plasma. Mathematical analysis of the results revealed that IDH1 performs well in accordance with other tested markers, and hence is not the only marker that may be useful for the early diagnosis of adenocarcinoma. Additionally, He mentions that, "based on the present data, IDH1 can be used to detect stage 1 lung cancer. However, it is also possible that IDH1 could be used to detect pre-cancer; but further studies are required to address that possibility" [8].

The outstanding question is, is He's group investigating the detailed mechanism of IDH1 further? He answers: "We are not planning to explore the detailed mechanism of IDH1, because our interest is on identifying and validating the biomarkers for clinical use". However, when asked whether IDH1 could be used to diagnose other types of cancer, He says, "It is necessary to determine whether plasma IDH1 can be used as a specific biomarker for NSCLCs against other cancers [and] we are planning to test IDH1 on other cancers, such as breast cancer, colon cancer, gastric cancer and liver cancer".

It should also be noted that a diagnostic marker may function as a therapeutic target. He, commenting on that possibility, states that, "I can't give you a definite answer now, [and] the finding of IDH1 knockdown leading to suppression of cell proliferation could not provide sufficient evidence to make a conclusion [either]". However, He reveals that in one of their projects, the group is assessing whether small molecule inhibitors of IDH1 may have any effect on the viability of NSCLC cells. He and colleagues are also planning to conduct a multi-center clinical trial for further validation of IDH1.

However, an important question still remains: what about a treatment-responsive change in IDH1 levels in the blood? He states that, "we did not analyze the association between IDH1 level and treatment information of NSCLC patients". As a result, we may have to wait for answers on IDH1's versatility. The arrival of an IDH1-based blood test in clinical labs for enhanced detection of adenocarcinoma is hopefully coming soon!

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