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REVIEW

Finding biomarkers for non-small cell lung cancer diagnosis and prognosis

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Abstract **Despite of several decades of efforts, lung cancer remains one of most deadly diseases, with a 5-year survival rate approximately 15% worldwide. In China, the situation is even worse. Although there is no official data released yet, the 5-year survival rate is estimated to be around 10%. In past 30 years, there was a dramatic increase of lung cancer related death about 465% in mainland China. Annually, about 400000 people die of lung cancer and the number is still climbing. At the same time, the number of new lung cancer cases also increase rapidly. The high mortality of lung cancer is mainly ascribed to two factors: the lack of effective ways to identify early diagnostic biomarkers and to treat metastatic cancer. Lung cancer can be pathologically divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), among which NSCLC accounts for about 80% of all cases. In this review, we will focus on the recent efforts and progress in finding biomarkers in NSCLC. Since biomarkers are derived from both invasive and non-invasive ways, we divide them into these two categories and review them separately. We hope the discovery of biomarkers will eventually change the current clinical practice in NSCLC patients and improve their quality of life.**

Keywords non-small cell lung cancer, biomarkers, diagnosis, prognosis

Biomarkers derived from invasive ways

Single gene expression/gene signature

Extensive efforts have been devoted to the mRNA profiling in NSCLC since last decade and have provided novel biological insights into the prognosis of NSCLC (Bhattacharjee et al., 2001; Garber et al., 2001; Beer et al., 2002; Endoh et al., 2004; Petty et al., 2004; Potti et al., 2006; Li et al., 2007; Chen et al., 2007; Newnham et al., 2008; Baty et al., 2010; Sanchez-Palencia et al., 2011). Expression signatures with predictive powers for the prognosis of NSCLC typically included genes involved in cell proliferation and/or immunological functions. Most recently, researchers at National Cancer Institute and University of Michigan conducted a multi-site blinded validation study to evaluate the prognostic expression signatures in lung adenocarcinomas (Shedden et al., 2008). This study included 442 patients with lung adenocarcinomas. The largest cohort to date confirmed that prognostic models utilizing both expression signatures and clinical variables outperformed models utilizing either of them alone. Importantly, several expression signatures identified in previous studies with smaller sample sizes (Potti et al., 2006; Chen et al., 2007) have also been verified to some extent in this study. Promising as this study suggested, future prospective clinical trials are needed to ultimately establish the clinical utility of these prognostic models.

miRNAs

With the identification of hundreds of microRNAs (miRNA), its expression profiling in NSCLC has emerged as an alternative powerful method other than mRNA profiling. Several miRNAs have been implicated in the prognosis of NSCLC in some early studies (Takamizawa et al., 2004; Yanaihara et al., 2006). Perhaps the let-7a and the miR-34 family are the best understood miRNA families with their biological mechanisms underlying the prognostic roles in NSCLC partially uncovered. The let-7a family are tumor suppressors that downregulate the RAS oncogene (Johnson et al., 2005) while the miR-34 family are a component of the p53 network (He et al., 2007). Recently, Yu and coworkers (2008) developed a five-miRNA signature for the prediction

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of treatment outcome of NSCLC. Among the miRNA signature they proposed, miR-221 and let-7a decreased the relapse risks while miR-137, miR-372, and miR-182* did opposite. However, miRNA profiling clearly falls behind the mRNA profiling in NSCLC in terms of both the overall sample size and lack of validation. We anticipate that some well designed miRNA profiling studies with much larger sample size will be carried out in the near future.

Recurrent copy number alterations in lung cancers

The classical approach to identification of tumor suppressor genes (TSG) and oncogenes is to examine the copy number alterations in cancer samples. Genomic deletions that down-regulate the expression of TSG and amplifications that upregulate the expression of oncogenes in lung cancers have long been studied for decades. Recent advances in high-throughput assays like SNP array and array CGH (comparative genomic hybridization) enabled the researchers to conduct such studies in a genome wide unbiased manner and have discovered dozens of lung cancer specific gene deletions and amplifications. The work from Meyerson's group represents one of the most comprehensive copy number alteration studies in lung adenocarcinoma (Weir et al., 2007). Altogether they found 26 large-scale and 31 focal events.

8p has a broad region of single-copy loss in lung adenocarcinoma. Several candidate genes have been identified recently, for example *CSMD1* (Ma et al., 2009), *DUSP4* (Chitale et al., 2009) and *DOK2* (Berger et al., 2010). Loss of *CSMD1* (on 8p23.2) occurred in 46% of lung SCC. Hemizygous loss of *DOK2* (on 8p21.3) occurred in 37% of lung adenocarcinoma. Two other DOK genes, *DOK1* (on 2p13.1) and *DOK3* (on 5q35.3), were also found deleted with a frequency of 1.5% and 7% respectively. Another example of hemizygous loss is *DICER1* (on 14q32.13), which occurred in lung cancer with a frequency of 25% (Kumar et al., 2009). In lung SCCs, 9p24.3 was most frequently deleted (up to 73%) and this deletion event downregulated the expression levels of *DMRT1*, *DMRT3* and *DOCK8* in lung SCCs (Kang et al., 2010). Deletion of *HSP90AA1* (on 14q32.2-33) occurred in 44% of early stage NSCLC (Gallegos Ruiz et al., 2008). However, this deletion was nontypical in the sense that it correlated with good clinical outcome and overall survival, arguing against that the gene was actually a TSG. Finally, metastatic status of lung cancer also correlates to the copy number alterations. For example, 4q12-q32 deletion was associated with the bone marrow-positive status (Wrage et al., 2009).

Recurrent amplification of 14q13.3 was found in 12% of lung adenocarcinoma, which lead to the discovery of a lineage-specific oncogene *NKX2-1* (Weir et al., 2007). Amplification of distal 3q (3q26.33) is one of the most common genomic aberrations in lung SCC, which results in high expression of two oncogenes: *SOX2* and *PIK3CA* (Bass et al., 2009). McCaughan et al. (2010) provided further evidence showing that the disease progression is associated with incremental amplification of *SOX2*. Other members of the SOX family were also found amplified in lung cancer (Medina et al., 2009). Jagadeeswaran et al. (2008) have found that *PXN* (on 12q24.31) amplification occurred in 12% of lung cancer. Some less frequent copy gain events include the 11q12 and 13q34 amplification (Castillo et al., 2010). They occurred in lung cancer with a frequency of 3% and *CTNND1* (for 11q12) and *TFDP1* (for 13q34) were the candidate oncogenes. Finally, *MET* gene amplification occurred in NSCLC with a frequency of 1%–7%. Interestingly, in patients with acquired resistance to EGFR tyrosine kinase inhibitors (TKIs), the frequency of such event went up to 20%, which implied that treatments combining EGFR and MET TKIs could potentially be more effective (Toschi and Cappuzzo, 2010).

Biomarkers from non-invasive ways

Germline DNA variants modifying lung cancer risks

GWAS (genome-wide association studies) have identified a handful of genetic loci that modify the susceptibility of lung cancer occurrence (Chung et al., 2010; Yoon et al., 2010; Galvan et al., 2010; Li et al., 2010; Sato et al., 2011; Wu et al., 2011). Unlike many other diseases where usually dozens of susceptible loci were uncovered by GWAS, only four major loci (chromosomes 5p15.33, 6p21.33, 15q25 and the TP63 locus) were verified in multiple independent studies so far in lung cancer (Table 1). This suggested that the environmental effects (e.g. smoking status) on lung cancer risks could be remarkably important in this case. In addition to the four major loci, in a meta-analysis, the International Lung Cancer Consortium found that variants in four genes (*XRCC3*, *XPD*, *TP53* and *OGG1*) are marginally associated with lung cancer risk (Hung et al., 2008a). For the prognostic angle, five SNPs in genes *STK39*, *PCDH7*, *A2BP1*, and *EYA2* were identified that may affect the overall survival in early-stage NSCLC (Huang et al., 2009).

Serum biomarker

Serum protein

Carcinoembryonic antigen (CEA), tissue polypeptide antigen (TPA), tissue polypeptide-specific antigen (TPS) and cytokeratin 19 fragment (CYFRA 21.1) are well-studied NSCLC serum biomarkers and have been widely used in clinical lung cancer diagnosis and prognosis prediction (Salvati et al., 1985; Pujol et al., 1994; Giovanella et al., 1995; Bates et al., 1997). Since many known cancer biomarkers such as PSA, CA15-3, CA-125 and CEA are glycoproteins, using glycoprotein capture and Label-Free Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS), Zeng et al. (2010,2011) identified 49 candidate serum biomarkers with

Table 1 Genetic loci that modify the susceptibility of lung cancer identified by GWAS

SNP	Locus/Gene	Histology	Population	# cases	# controls	Hazard ratio	Reference
rs2736100	5p15.33	ADC	East Asian	2098	11048	1.27	McKay et al., 2008
rs402710	*TERT*	ADC	East Asian, nonsmoker	1748	2321	1.54	Hsiung et al., 2010
	CLPTM1L	Both	European	6158	9732	1.14	Miki et al., 2010
rs4488809	3q28	ADC	East Asian	2098	11048	1.31	Miki et al., 2010
rs10937405	*TP63*						
rs1051730	15q25.1	Both	European, smoker	3878	4831	1.32	Amos et al., 2008
rs8034191	*CHRNA5*	Both	European	4502	7377	1.30	Hung et al., 2008b
rs3117582	6p21.33	Both	European	9531	9674	1.30	Wang et al., 2008
rs3131379	*BAT3*						
	MSH5						

statistically significant differential abundance across the lung cancer case and control pools. Functional analysis with Ingenuity Pathway Analysis (IPA) tools showed significant enrichment of inflammatory response proteins, key molecules in cell-cell signaling and interaction network, and differential physiologic responses for the adenocarcinoma and squamous cell carcinoma subtypes. Two-dimensional difference gel electrophoresis (2D-DIGE) and enzyme-linked immunosorbent assay (ELISA) are also commonly used for discovering and identifying novel serum biomarkers (Table 2). We have recently identified lysyl oxidase (LOX) as a potential prognostic biomarker for lung cancer using serum enzymatic activity detection (Gao et al., 2010). In NSCLC, the presence of locoregional lymph node metastases remains the most important prognostic factor and significantly guides treatment regimens. Borgia et al. established a multi-analyte serum biomarker panel and identified 15 candidate biomarkers in discerning a patient's preoperative nodal status (Borgia et al., 2009; Patel et al., 2011). Some oncogene and tumor suppressor gene products in serum, such as p53, anti-p53 antibodies, sEGFR or Ras have also been utilized as NSCLC biomarkers (Brandt-Rauf et al., 1992; Angelopoulou et al., 1994; Luo et al., 1994; Baron et al., 2009). However, due to the inconsistent results or low sensitivity, routine use of these proteins for detection of lung cancer is not currently recommended (Helmig and Schneider, 2007).

Serum mRNA/miRNAs profiling

The polymerase chain reaction (PCR)-based technology has allowed us to detect and quantify extremely small amounts of tumor-derived nucleic acids in body fluids. This has led to an increased knowledge of the molecular pathogenesis of lung cancer and a basis for the use of RNA markers in blood for early diagnosis and prognosis prediction (Bremnes et al., 2005). The hnRNP-B1, Her2/neu and 5T4 mRNA were first amplified from the serum of lung cancer patients (Fleischhacker et al., 2001; Kopreski et al., 2001). Besides CEA protein, the mRNA of CEA could also be detected in patients with NSCLC. Patients with CEA mRNA in the preoperative blood samples had a poor survival when compared with those without CEA mRNA. Of these patients, the worst survival was seen in those with CEA mRNA in the postoperative blood samples (Yamashita et al., 2002). Interestingly, the serum mRNA level of some genes which are usually overexpressed in lung cancer tissues and involved in lung tumorigenesis and metastasis was often elevated. Circulating c-Met mRNA was reported to be significantly higher than it was in their normal counterparts, which was significantly correlated with nodal stage and early recurrence in NSCLC (Cheng et al., 2005). EGFR mRNA in serum was correlated with tumor number and clinical stage and the amount of hTERT mRNA in serum was significantly decreased after the surgical treatment. The sensitivity and specificity in lung cancer diagnosis were 89.0% and 72.7% for hTERT mRNA, and 71.3% and 80.0% for EGFR mRNA, respectively (Miura et al., 2006). Moreover, serum COX-2 mRNA expression were significantly lower in healthy donors than in patients, which is independent of gender, age or smoking habits (Ulivi et al., 2008).

Cell-free miRNA content in serum was fist discovered in patients with diffuse large B cell lymphoma in 2008 (Lawrie et al., 2008). These miRNAs are quite stable even under harsh conditions including RNase A digestion, boiling, low/high pH, and multiple freeze-thaw cycles (Chen et al., 2008; Gilad et al., 2008; Mitchell et al., 2008). Thus, the profiling of circulating miRNAs from cancer patients have been explored in a variety of studies aiming to identify novel non-invasive biomarkers. Employing the Solexa sequencing approach, Zhang's group investigated the expression profiles of serum miRNAs in patients with NSCLC. Validation individually by qRT-PCR revealed that serum expression levels of miR-25 and miR-223 are significantly increased in lung cancer sera than normal sera (Chen et al., 2008). Other eight miRNAs were also found to have significantly different expression levels in NSCLC serum samples compared to the control serum samples (Chen et al., 2011). Further studies with larger sample size showed that levels of four miRNAs (miR-486, miR-30d, miR-1 and miR-499) were significantly associated with overall survival (Hu et al., 2010). Besides, serum miR-1254 and miR-574-5p have recently been reported to be significantly increased in the early-stage NSCLC samples than in healthy population (Foss et al., 2011) (Table 3).

Table 2 Serum protein biomarkers for NSCLC identified by 2D-DIGE and ELISA

Protein	Type	Sample size	Study design	Methods	Details	Reference
YKL-40	Glycoprotein	143 men and 46 women	Study on prognosis	ELISA	High serum YKL-40 levels have been associated with a poor prognosis.	Thöm et al., 2010
TRACP5b	Phosphatase	141 newly diagnosed stage IIIA, IIIB or IV NSCLC patients and 41 normal subjects	Bone metastasis or not	In-house immunoassay	TRACP5b activity declined in patients who responded to treatment (P = 0.047), and elevated in patients who developed new BMet (P = 0.05)	Yao et al., 2011
TGF ARG IGF1 IGF binding protein-3	Growth factors	61 patients with advanced NSCLC treated with EGFR-TKIs and 63 matched advanced NSCLC control patients without EGFR-TKIs treatment	Disease specific survival (DSS)	ELISA Chemiluminescent assays	Low concentrations of TGFα and high concentrations of ARG were associated with a better DSS in EGFR TKIs patients compared with control patients. Patients with high concentrations of IGF binding protein-3 had significantly longer DSS, independent of treatment.	Vollebergh et al., 2010
PEDF	Angiogenesis inhibitor	4 patients with NSCLC and 4 with pneumonia	Tumor vs. normal	2D-DIGE mass spectrometry	PEDF was significantly overexpressed both in serum and pleural effusion from NSCLC patients.	Rodríguez-Piñeiro et al., 2010
TTR	Carrier protein	146 lung cancer, 13 pneumonia, 28 tuberculous pleurisy and 40 normal individuals	Tumor vs. normal	SELDI ELISA	Downregulation of TTR was found in both ELISA and SELDI analysis.	Liu et al., 2009
EMAP-II	Proinflammatory cytokine	30 healthy control subjects and 48 patients with untreated NSCLC	Tumor vs. normal	ELISA	The high EMAP-II ($>$100 pg/mL) group had a shorter survival compared with the low EMAP-II ($<$100 pg/mL) group	Sen et al., 2008
CEA RBP AAT SCC		A training set from 100 patients (50 with lung cancer and 50 age- and sex-matched controls). blinded validation set from 97 patients (49 lung cancer patients and 48 matched controls)	Tumor vs. normal	2D-DIGE MALDI-TOF MS	90% of patients who fell into any one of three groupings in the CART analysis had lung cancer.	Patz et al., 2007
Hp SAHp FHp	Preproprotein	10 NSCLC and 10 matched control patients	Tumor vs. normal	2D-DIGE ELISA	Statistically significant differences between lung cancer patients and matched controls were found by ELISA for Hp ($P<0.002$), SAHp ($P<0.001$), and FHp ($P<0.04$)	Hoagland et al., 2007
Serum cyclin B1 antibody	Antibody	291 white subjects	Tumor vs. normal	ELISA	Regression analysis identified gender as well as age in women smokers to be significant determinants of cyclin B1 antibody levels.	Egloff et al., 2005

Table 3 Serum mRNA/miRNAs biomarkers for NSCLC

Type	mRNA/miRNA	Sample size	Methods	Details	Ref.
mRNA	hnRNP-B1 Her2/neu	18 patients with lung cancer before and during chemotherapy	RT-PCR	The hnRNP-B1 mRNA was detectable in 14/18 sera, and Her2/neu-specific mRNA could be amplified from the serum of 7/18 patients.	Rodríguez-Piñeiro et al., 2010
	5T4	5 advanced breast cancer patients, 14 NSCLC patients, and 25 normal control	Heminested RT-PCR	5T4 mRNA was reproducibly detected in 8/19 (42%) cancer patient sera, but in only 3/25 (12%) normal control sera ($P = 0.035$).	Liu et al., 2009
	CEA	103 consecutive patients with NSCLC who underwent a curative lobectomy	RT-PCR	Patients with CEA mRNA in the preoperative blood samples had a poor survival when compared with those without CEA mRNA.	Sen et al., 2008
	c-Met	45 patients with NSCLC, 31 patients with benign lung diseases and 20 normal control	Real-time PCR	67.6% (23 of 34 patients) expressed higher amounts of circulating c-met by 1.4 to 8 times that of the normal control subjects. In addition, overexpression of circulating c-met was significantly correlated with nodal (N) stage ($P = 0.011$) and early recurrence ($P < 0.05$).	Patz et al., 2007
	EGFR hTERT	112 patients with lung tumor and 80 individuals without cancer	Real-time PCR	Serum hTERT mRNA was independently correlated with tumor size, number, presence of metastasis, recurrence, and smoking (all $P < 0.05$). EGFR mRNA correlated with tumor number and clinical stage (both $P < 0.05$).	Hoagland et al., 2007
	COX-2	128 cancer patients and 103 healthy donors	RT-PCR	Serum free COX-2 mRNA expression in peripheral blood were significantly lower in healthy donors than in patients (1.5 vs 2.0, $z = -6.02$, $P < 0.001$) and were not related to sex, age or smoking habits in either group.	Egloff et al., 2005
miRNA	miR-25 miR-223	75 healthy donors and 152 cancer patients	Solexa sequencing Real-time PCR	Serum expression levels of miR-25 and miR-223 are significantly increased in LCS than in NS.	Fleischhacker et al., 2001
	miR-486 miR-30d miR-1 miR-499	Discovery stage: 30 patients with longer survivaland 30 patients with shorter survival; Validation: 243 patients (randomly classified into two subgroups: $n = 120$ for the training set, and $n = 123$ for the testing set).	Solexa sequencing Real-time PCR	Eleven serum miRNAs were found to be altered more than 5-fold by Solexa sequencing between longer-survival and shorter-survival groups, and levels of four miRNAs (ie, miR-486, miR-30d, miR-1 and miR-499) were significantly associated with overall survival.	Cheng et al., 2005
	miR-1254 miR-574-5p	31 controls and 22 patients with early-stage NSCLC	Real-time PCR	The expression of hsa-miR-1254 and hsa-miR-574-5p was significantly increased in the early-stage NSCLC samples with respect to the controls.	Miura et al., 2006

Metabolic biomarkers

Cancer cells have displayed different metabolic activity from their normal counterparts. Hence, investigating the change of metabolites in body fluids of cancer patients may discover some potential biomarkers for cancer diagnosis and prognosis prediction. Back to early 1970s, detection of adrenal cortex steroid hormone metabolites in the urine of patients with lung cancer were first reported (Smirnova and Lazarev, 1970). Subsequently, the levels of sialic acid in serum and urine were found markedly elevated in lung cancer patients, indicating it may be a useful metabolic biomarker for lung cancer diagnosis (Krolikowski et al., 1976; Rokicki et al., 1987). In 1984, Ayesh et al. have identified the debrisoquine 4-hydroxylation phenotypes as a biomarker for susceptibility to lung cancer. However, the follow-up studies failed to reproduce the data (Speirs et al., 1990; Caporaso et al., 1990; Duche et al., 1991; Shaw et al., 1995). Bone metabolic markers, cross-linked telopeptide of type I collagen (ICTP) and bone-specific alkaline phosphatase (BAP) in serum of lung cancer patients with bone metastasis were significantly higher than those without bone metastasis and healthy population, suggesting that they might be good indicators of lung cancer metastasis and helpful for the monitoring of therapy for bone metastasis (Aruga et al., 1997; Chung et al., 2005). Recently, ^{1}H NMR-based metabonomics has been applied to investigate lung cancer metabolic signatures in urine. The main different metabolites which were highlighted by multivariate analysis and confirmed by spectral integration are hippurate and trigonelline (reduced in patients), and β-hydroxyisovalerate, α-hydroxyisobutyrate, N-acetylglutamine, and creatinine (elevated in patients). These results showed the valuable potential of NMR-based metabonomics for finding putative biomarkers of lung cancer in urine through non-invasive way (Carrola et al., 2011).

Perspective

In clinical lung cancer practice, diagnosis at early stage is crucial for effective and favorable treatment. Great efforts have been paid to identifying reliable biomarkers for selective treatments. Thanking to the rapid development of genomic and proteomics technologies, we have seen great advances in the discovery of lung cancer biomarkers in last decades. However, the currently available or potential lung cancer biomarkers are not sensitive or specific enough to be applied in clinical diagnosis and prognosis prediction. To establish promising biomarkers with higher sensitivity and specificity, larger sample sets with long-term follow-up clinical information are urgently required. The application of recently improved genetic tools, e.g. genome-wide deep sequencing, will definitely help discover new genetic biomarker. Understanding the physiological changes and molecular mechanisms underlying these biomarkers is also crucial. Since it is highly unlikely that a universal biomarker with high sensitivity and specificity exists in all cancer types, efforts in finding more specific and low abundant biomarkers within a certain subtype of lung cancer will be greatly appreciated. Moreover, one specific biomarker is usually not enough to predict or monitor lung cancer. Integrative biomarkers or signature is of potential use in the clinical practice. We believe that persistent efforts on discovery of lung cancer biomarkers for early diagnosis and prognosis, the life quality and survival of lung cancer patients will be greatly improved in the future.

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