C1qTNF2 is differentially expressed in non-small cell lung adenocarcinomas.

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Non-small cell lung adenocarcinoma (NSCLC) is a leading cause of death in the United States and worldwide^{1,2}. We mined published microarray data^{3,4} to discover genes associated with NSCLC. We identified significant differential expression of the complement component C1qTNF2⁵ in tumors from patients with NSCLC. C1qTNF2 may be of relevance to the initiation, progression or maintenance of non-small cell lung cancers.

Keywords: non-small cell lung adenocarcinoma, non-small cell lung cancer, NSCLC, C1qTNF2, systems biology of NSCLC, targeted therapeutics in NSCLC.

Over 80% of patients diagnosed with non-small cell lung cancer (NSCLC) will expire within 5 years⁶. Improved understanding of the fundamental transcriptional biology of NSCLC tumors is important for discovery of novel therapeutic targets. We performed a systems-level, unbiased transcriptome analysis of human NSCLC tumors to identify genes whose expression was most different as compared to the lung by mining independent published microarray datasets^{3,4}. We observed significant differential expression of C1qTNF2 in NSCLC tumors, suggesting C1qTNF2 may be important to the biology of non-small cell lung adenocarcinomas.

Methods

We utilized microarray datasets GSE74706³ and GSE33532⁴ for this differential gene expression analysis of NSCLC tumors in conjunction with GEO2R. GSE74706 was generated using Agilent-026652 Whole Human Genome Microarray 4x44K v2 technology (platform: GPL13497) with $n=18$ control lung tissue and $n=10$ NSCLC tumors. GSE33532 was generated using Affymetrix Human Genome U133 Plus 2.0 Array technology (platform: GPL570) with $n=20$ control lung tissue and $n=10$ NSCLC tumors.

The Benjamini and Hochberg method of p-value adjustment was used for ranking of differential expression but raw p-values were used for assessment of statistical significance of global differential expression. Log-transformation of data was auto-detected, and the NCBI generated category of platform annotation was used. A statistical test was performed to evaluate whether C1qTNF2 expression was significantly different when comparing normal lung tissue from control subjects to tumor tissue from NSCLC patients, using a two-tailed, unpaired t-test with Welch's correction. We used PRISM for all statistical analyses (Version 8.4.0)(455).

Results

We interrogated two independently published microarray datasets^{3,4} to determine in a blind fashion and at the transcriptome-level genes whose expression was most significantly perturbed in NSCLC tumors.

C1qTNF2 is differentially expressed in NSCLC.

We observed significant differential expression of C1q and tumor necrosis factor related protein 2, C1qTNF2, in human NSCLC tumors when compared to the lung³. When sorting each gene by significance of difference in expression between NSCLC tumor and the normal lung, C1qTNF2 ranked 174 out of 34183 total transcripts. Differential expression of C1qTNF2 was statistically significant (Table 1; $p=1.14E-11$).

We queried a second dataset⁴ to determine if we could validate C1qTNF2 differential expression in independent microarray data. We again observed significant differential expression of C1qTNF2 in human NSCLC tumors when compared to the lung. When sorting each gene by significance of difference in expression between NSCLC tumor and the normal lung, C1qTNF2 ranked 148 out of 25906 total transcripts. Differential expression of C1qTNF2 in this second dataset was also statistically significant (Table 2; $p=5.3E-14$).

C1qTNF2 expression is significantly decreased in NSCLC tumors.

We obtained exact mRNA expression levels for the differentially expressed C1qTNF2 transcript in both datasets queried, in normal lung tissue and in primary NSCLC tumors. We also

performed a statistical test to determine whether the difference in expression of C1qTNF2 was statistically significant when comparing NSCLC tumors to the normal lung. C1qTNF2 was expressed at lower levels across each dataset (Figures 1-2); decreased expression of C1qTNF2 was statistically significant in each case (Figure 1: $p < 0.0001$; Figure 2: $p < 0.0001$). We calculated a mean fold change in C1qTNF2 expression of 0.7413 ± 0.0375 (Table 2) when comparing NSCLC tumor to normal lung in one dataset.

Thus, we identified C1qTNF2 as a differentially expressed gene in human non-small cell lung adenocarcinoma and found that C1qTNF2 was expressed at significantly lower levels in NSCLC tumors as compared to the normal lung.

Discussion

Complement protein C1qTNF2 is a member of the C1qDC-A subfamily of the C1q subcomplex of complement component C1. C1qTNF2 protein contains a signal peptide, C1q domain, and in between a collagen-like region with 34 GXY repeats⁵. We could not identify literature describing a role for C1qTNF2 in NSCLC.

In summary, we probed multiple independent published microarray datasets to search for differentially expressed genes in patients with non-small cell lung adenocarcinoma and discovered significantly decreased expression of the complement molecule C1qTNF2 in tumors from patients with NSCLC. C1qTNF2 may be relevant to the biology of NSCLC.

References

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Rank	ID	p-value	t	B	Gene
174	A_33_P3403153	1.14E-11	-1.08E+01	16.7096789	C1QTNF2

Table 1: C1qTNF2 is differentially expressed in non-small cell lung adenocarcinomas.

The rank of differential expression, probe ID, p-value of global differential expression, t, a t-statistic, B, the log-odds of differential expression when comparing tumor to lung and gene name are listed in this chart.

Rank	ID	p-value	t	B	FC	Gene	Gene name
148	223749_at	5.3E-14	-12.881024	21.9598726	0.7413 ± 0.0375	C1QTNF2	C1q and tumor necrosis factor related protein 2

Table 2: C1qTNF2 is differentially expressed in non-small cell lung adenocarcinomas.

The rank of differential expression, probe ID, p-value of global differential expression, t, a t-statistic, B, the log-odds of differential expression when comparing tumor to lung, the fold change in C1qTNF2 expression when comparing tumor to lung, and gene name are listed in this chart.

Figure 1: C1qTNF2 expression is significantly decreased in NSCLC tumors.

Expression of C1qTNF2 is graphically represented in control, normal lung tissue (left) and in primary tumors from patients with non-small cell adenocarcinoma (right); mean mRNA expression level is marked in each group and the result of a statistical test evaluating significance of difference in C1qTNF2 expression between the groups, a *p*-value, is listed above.

Figure 2: C1qTNF2 expression is significantly decreased in NSCLC tumors.

Expression of C1qTNF2 is graphically represented in control, normal lung tissue (left) and in primary tumors from patients with non-small cell adenocarcinoma (right); mean mRNA expression level is marked in each group and the result of a statistical test evaluating significance of difference in C1qTNF2 expression between the groups, a *p*-value, is listed above.