Comprehensive Expression Analysis Suggests Functional Overlapping of Human FOX Transcription Factors in Cancer

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Abstract

Forkhead-box (FOX) transcription factors comprise a large gene family that contains more than 50 members in man. Extensive studies have revealed that they not only have functions in control of growth and development, but also play important roles in different diseases, especially in cancer. However, biological functions for most of the members in the FOX family remain unknown. In the present study, the expression of 39 FOX genes in 48 kinds of cancer was mined from the Gene Expression Atlas database of European Bioinformatics Institute. The analysis results showed that some FOX genes demonstrate overlapping expression in various cancers, which suggests particular biological functions. The pleiotropic features of the FOX genes make them excellent candidates in efforts aimed to give medical treatment for cancers at the genetic level. The results also indicated that different FOX genes may have the synergy or antagonistic effects in the same cancers. The study provides clues for further functional analysis of FOX genes, especially for the pleiotropic biological functions and crosstalk of FOX genes in human cancers.

Keywords: FOX transcription factors - overlapping expression - cancer diseases - gene expression atlas

Introduction

The FOX transcription factors (Forkhead box, FOX), as one of the largest gene families, are characterized by the highly conserved 110 amino acids DNA-binding domain (Wijchers et al., 2006). The FOX domain is also known as winged-helix domain with two wing-like loops and three α-helices structure (Kaestner et al., 2000). Genome-based bioinformatics analyses have showed that FOX proteins comprise a large family members identified in species ranging from yeasts to humans, and have been classified into different subfamilies (Kaestner et al., 2000; Mazet et al., 2003; Wotton et al., 2006; Tu et al., 2006; Benayoun et al., 2011). Animals appeared to have more FOX genes than fungi, for example, with 4 genes identified in Saccharomyces and Schizosaccharomyces, and over 50 members in the human (Wotton et al., 2006; Benayoun et al., 2011). Up to date, the members of the FOX gene family have been demonstrated to play important roles in diverse biological processes, including cell differentiation, embryonic development, morphogenesis, metabolism, and effectors of signal transduction (Kaestner et al., 2000; Carlsson et al., 2002; Pohl et al., 2005).

The FOX transcription factors also play key roles in the health and disease (Hannenhalli et al., 2009; Benayoun et al., 2011; Katoh et al., 2013). Mutations in eight different FOX genes including FOXC1, FOXC2, FOXE1, FOXE3, FOXL2, FOXL1, FOXP2, and FOXP3 have been associated with human congenital disorders or hereditary diseases (Carlsson et al., 2002). For example, FOXC1 has been identified in patients with defects in development of the anterior chamber of the eye (Lehmann et al., 2000). Mutations in FOXC2 lead to distichiasis, or double rows of eyelashes, together with lymphedema (Bell et al., 2001). Mutations in FOXL2 cause variable eyelid defects and also associated with ovarian failure (Crisponi et al., 2001; De et al., 2001). FOX family genes are also involved in carcinogenesis (Katoh et al., 2013). Several FOX genes such as FOXA1, FOXM1, FOXO1, FOXO2 (FOXO6), FOXO3, FOXO4, FOXP1, FOXR1 have been reported to play important roles in carcinogenesis as oncogenes and/or tumor suppressor genes (Katoh et al., 2013).

Although several FOX genes of human have been characterized functionally in the cancer diseases, the biological functions for the most members in this family remain unknown. To extend our understanding the biological function of the human FOX genes, we analyzed expression of human FOX genes in different cancer diseases from the European Bioinformatics Institute (EBI) (http://www-test.ebi.ac.uk/gxa/). The results suggested that most of human FOX family genes are different expression in cancer diseases. The results also provide...
Materials and Methods

The sequence analysis of human FOX transcription factors

Using “forkhead human” to search the human FOX family genes in the gene mode of National Center of Biotechnology Information (http://www.ncbi.nlm.nih.gov/gene), the FOX genes were obtained. The protein sequences of human FOX transcription factors were obtained from National Center of Biotechnology Information. In addition, the chromosome, site, location, and protein length of human FOX genes were obtained.

Protein domain architectures of the FOX transcription factors were analyzed in SMART database (http://smart.embl-heidelberg.de/). The physics and chemistry features of FOX protein including molecular weight and isoelectric point, instability index, aliphatic index, and grand average hydropathicity were obtained from protParam (http://web.expasy.org/protparam/). The subcellular localization was predicted by Protcomp 9.0 (http://linux1.softberry.com/berry.phtml?).

Multiple sequence alignment of full-length protein sequences of human FOX transcription factors was performed using ClustalW2 program with default parameters. Phylogenetic tree was plotted using MEGA5.05 software by the Neighbor-joining method with 1000 bootstrap replicates. The conserved motifs in full length human FOX proteins were identified using Multiple Expectation Maximization for Motif Elicitation (MEME) program version 4.6.1 (http://meme.nbcr.net/meme/) with default parameters.

Expression profiling analysis in cancer diseases

The differential expression of human FOX genes in different cancer diseases was mined from Gene Expression Atlas database of European Bioinformatics Institute (http://www-test.ebi.ac.uk/gxa/). The Gene Expression Atlas is an added-value database providing information about gene expression in different cell types, organism parts, developmental stages, disease states, sample treatments and other biological/experimental conditions. The content of this database derives from re-annotation and statistical analysis of selected data from the arrayExpress archive of functional genomics data. The query results are ranked using various statistical measures and many independent studies in the database to show the particular gene-condition association. An interface allows us to query for differential gene expression (i) by FOX gene names; (ii) by cancer diseases. By the condition of P-value <0.05 of the automated screening, we have obtained the differential expression of 39 FOX genes in different cancer diseases. Moreover, P-value of up-regulated FOX genes was set as positive number, while the down-regulated genes as negative number. In order to illustrate the expression of FOX genes in the same cancer diseases, P-value was taken to the base 10 of a negative logarithm. Then invert P-value of up-regulated genes was set as positive number and down-regulated genes as negative number. The histograms were plotted with invert P-value and its corresponding FOX genes.

Results and Discussion

Identification of human FOX genes

Using “forkhead human” to search the human FOX family genes in the gene mode of National Center of Biotechnology Information, the 50 FOX genes of human were obtained (Table 1). The FOX transcription factors of human have been named by a capital letter, and a number is used to distinguish members in the same subclass. The method of definition is similar with previous report (Kaestner et al., 2000). The 50 protein sequences of human FOX genes were obtained from National Center of Biotechnology Information. Protein domain architectures of the FOX transcription factors were analyzed in SMART database. The physics and chemistry features of FOX protein are analyzed by protparam (Table 1). The amino acid number of FOX protein is from 292 to 748 with average 473. The weight of protein is from 33 to 82.7 kDa with average 50.5 kDa. There is positive correlation between protein molecular weight and the number of amino acid. The isoelectric point of protein is from 4.92 to 9.82 with average 7.95. The instability index of protein is from 49.44 to 86.35. The aliphatic index of protein is from 50 to 75.37 with average 64.67. The grand average hydropathicity of protein is from -0.887 to -0.163 with average -0.496. The subcellular localization was predicted by Protcomp 9.0. The results showed that almost of predicted nuclear location scores are above 9.9, which indicated that most of FOX transcription factors can locate in nuclear.

Chromosomal location and Phylogenetic analysis of human FOX genes

50 FOX genes distribute on 19 chromosomes of human (Table 1). Among them, 8 FOX genes locate on the Chromosome 9. Chromosome 1 and 6 contains 5 FOX genes, Chromosome 2, 12, 14, 16, 17 and X contains 3 FOX genes, Chromosome 3, 5, 7, and 20 contains 2 FOX genes, Chromosome 8, 10, 11, 13, 15, 19 contains 1 FOX genes, respectively. The phylogenetic analysis suggested that human FOX transcription factors can be divided into A to S 19 subgroups (Figure 1). According to the phylogenetic tree and gene location analysis, it was found that there are fragments replication and string copying phenomenon of FOX transcription factors. For example, FOXA1/FOXA2, FOXC1/FOX2, FOXD1/FOXD2, FOXK1/FOXK2, FOXP1/FOXP2, FOXN1/FOXN4, and FOXN2/FOXN3 are fragments replication. Several genes FOXD4L2, FOXD4L3, FOXD4L4, FOXD4L5, and FOXD4L6 are string copying. In order to analyze the diversity of human FOX proteins, the conserved motifs were identified. There were 2 or 3 conservative FOX motifs in the structure of human FOX domain. Among them, FOXH1, FOXJ2, FOXP1, FOXP2, FOXP3, FOXP4, FOXR1, and FOXR2 only have 2 motifs (motif 1 and motif 2). For the motif 1, the possible match is “CGWKNSIRHNLSDLDFVKVPRE”. For the motif 2, the possible match is
Expression profiling analysis of FOX genes in cancer diseases

To study the possible involvement of FOX genes in different cancer diseases, we mined expression of human FOX genes in different cancer diseases from the European Bioinformatics Institute (EBI) (http://www-test.ebi.ac.uk/gxa/). The results showed that the differential expression of 39 FOX genes in various diseases, including 48 kind of cancer diseases.

Overlapping expression patterns of the FOX genes in response to different cancer diseases were analyzed. The results showed that FOX genes exhibited overlapping expression patterns in response to different diseases. It is noteworthy that FOX genes exhibited overlapping expression patterns in response to brain tumor, adenoma, metastatic prostate cancer, renal cell carcinoma, acute myeloid leukemia, myeloma, B-cell lymphoma, papillary thyroid carcinoma, breast cancer, leiomyoma, oral squamous cell carcinoma, invasive ductal carcinoma (Table 1). For example, FOXE1 was overlapping expression in eight cancer diseases. FOXA2, FOXC1, FOXD3, FOXG1, FOXJ1 and FOXM1, were overlapping expression in seven cancer diseases.

Table 1. The Distribution of FOX Transcription Factor Family on the Scaffolds of Genome and Physico-chemical analysis in Human

| Gene     | Chromosome | Site Location | Length/aa | Molecular Weight/Kda | Isoelectric point | Instability index | Aliphatic index | Grand average hydrophobicity | Nuclear location score |
|----------|------------|---------------|-----------|----------------------|------------------|------------------|----------------|-----------------------------|-----------------------|
| FOXA1    | 14         | NC_000014.9   | 37589552..37595120 | 472           | 49.1             | 8.93             | 55.56           | 50.61                      | -0.483                | 10                   |
| FOXA2    | 20         | NC_000020.11  | 22581004..22585463 | 463           | 48.9             | 8.82             | 65.48           | 49.96                      | -0.532                | 9.9                  |
| FOXA3    | 10         | NC_000010.10  | 45795710..45926064 | 350           | 37.1             | 7.01             | 59.93           | 60.57                      | -0.447                | 10                   |
| FOXA15   | 15         | NC_000015.10  | 59871343..60397986 | 325           | 35               | 9.66             | 65.89           | 71.32                      | -0.270                | 9.9                  |
| FOXB2    | 9          | NC_000019.12  | 71019657..72009953 | 432           | 45.6             | 9.55             | 61.54           | 65                         | -0.372                | 9.9                  |
| FOXC1    | 6          | NC_000006.12  | 1525864..2245564 | 553           | 56.8             | 8.7              | 65.39           | 54.72                      | -0.534                | 9.9                  |
| FOXC2    | 6          | NC_000006.12  | 1525864..2245564 | 553           | 56.8             | 8.7              | 65.39           | 54.72                      | -0.534                | 9.9                  |
| FOXE1    | 13         | NC_000013.11  | 47416672..47505750 | 495           | 48.7             | 6.76             | 55.24           | 63.84                      | -0.163                | 9.9                  |
| FOXE11   | 13         | NC_000013.11  | 53240348..53330394 | 500           | 54.8             | 6.74             | 55.24           | 63.84                      | -0.163                | 9.9                  |
| FOXE3    | 1          | NC_000001.11  | 44428780..44507172 | 365           | 39.3             | 9.6              | 65.23           | 71.67                      | -0.416                | 10                   |
| FOXE9    | 8          | NC_000008.11  | 14442870..14450712 | 365           | 39.3             | 9.6              | 65.23           | 71.67                      | -0.416                | 10                   |
| FOXH1    | 8          | NC_000008.11  | 16953697..170199141 | 378           | 41               | 5.91             | 51.19           | 53.95                      | -0.749                | 9.9                  |
| FOXJ2    | 12         | NC_000012.11  | 68302667..68305084 | 417           | 45.9             | 8.82             | 72.74           | 68.28                      | -0.579                | 9.9                  |
| FOXK1    | 7          | NC_000014.9   | 28593773..285332960 | 489           | 52.4             | 8.99             | 51.19           | 53.95                      | -0.749                | 9.9                  |
| FOXL1    | 17         | NC_000017.11  | 76809993..76240367 | 421           | 45.2             | 5.04             | 56.8            | 71.54                      | -0.439                | 9.9                  |
| FOXL1    | 17         | NC_000017.11  | 76809993..76240367 | 421           | 45.2             | 5.04             | 56.8            | 71.54                      | -0.439                | 9.9                  |
| FOXL1    | 17         | NC_000017.11  | 76809993..76240367 | 421           | 45.2             | 5.04             | 56.8            | 71.54                      | -0.439                | 9.9                  |
| FOXL1    | 17         | NC_000017.11  | 76809993..76240367 | 421           | 45.2             | 5.04             | 56.8            | 71.54                      | -0.439                | 9.9                  |
| FOXL1    | 17         | NC_000017.11  | 76809993..76240367 | 421           | 45.2             | 5.04             | 56.8            | 71.54                      | -0.439                | 9.9                  |

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FOXH1, FOXJ3, FOXN2, FOXP1, and FOXP3 were overlapping expression in six cancer diseases. FOXF2, FOXJ2, FOXK2, FOXO1, and FOXP2 were overlapping expression in five cancer diseases. FOXB1, FOXC2, FOXD2, FOXI1, FOXL2 and FOXO4 were overlapping expression in four cancer diseases. FOXA1, FOXD4, FOXE3, FOXF1, FOXL1, FOXN1, and FOXQ1 were overlapping expression in three cancer diseases. Several FOX genes in this study showed the similar expression pattern with previous reported and these genes have been proved to play important roles in cancer diseases (Katoh et al., 2013). Among them, FOXA1 is upregulated in estrogen receptor (ER)-positive breast cancer (Schneider et al., 2006) and FOXA1 point mutations also occur in prostate cancer (Grasso et al., 2012). Overexpression of FOXA1 is associated with estrogen receptor (ER)-positive breast cancer (Hu et al., 2009), lung cancer, esophageal...
Table 2. Differential Expression of FOX Genes in Response to Cancer Diseases

| Gene   | brain tumor | adenoma | metastatic prostate cancer | renal cell carcinoma | breast cancer | oral squamous cell carcinoma | acute myeloid leukemia | B-cell lymphoma | papillary thyroid carcinoma | invasive ductal carcinoma |
|--------|-------------|---------|-----------------------------|----------------------|---------------|------------------------------|------------------------|----------------|----------------------------|--------------------------|
| FOX1   | -           | -0.004  | -0.00034                    | -                    | -0.006E-05    | -                            | -                      | -              | -                          | -                        |
| FOX2   | -1.00E-10   | -0.009  | 0.026                       | -                    | -0.0000413    | -0.007                       | -0.004                 | -0.002         | -                          | -                        |
| FOX3   | -           | -0.01   | -                            | -                    | -0.002        | -                            | -                      | -              | -                          | -                        |
| FOX81  | 2.15E-08    | 0.028   | -1.00E-10                   | -                    | -2.11E-08     | -                            | -                      | -              | -                          | -                        |
| FOXC1  | -0.011      | -0.028  | -0.033                      | -                    | -0.007        | -                            | -0.011                 | -0.0008        | -0.01                       | -                        |
| FOXC2  | -0.000001   | 0.003   | -1.00E-10                   | -                    | -0.000023     | -                            | -                      | -              | -                          | -                        |
| FOXD1  | -           | -0.003  | -                            | -                    | -            | -                            | -                      | -              | -                          | -                        |
| FOXD2  | 0.029       | -0.035  | -                            | -                    | 1.00E-10      | -                            | 0.011                  | -              | -                          | -                        |
| FOXD3  | -0.00E-06   | 0.037   | -0.011                      | -                    | -0.00875      | 1.00E-10                     | 2.40E-10               | 0.017          | -                          | -                        |
| FOXD4  | -1.00E-10   | -0.048  | -0.011                      | -                    | -3.00E-04     | -1.00E-10                    | -                      | -              | -                          | -                        |
| FOXD4L1| 0.005       | -0.005  | -                            | 1.00E-10             | -            | -0.06                        | -0.02                  | 0.012          | -                          | -                        |
| FOXE1  | 1.00E-10    | 0.005   | -0.000516                   | 1.00E-10             | -0.000082     | 1.00E-10                     | -1.76E-09              | 0.004          | -                          | -                        |
| FOXE1H | 0.019       | 0.006   | -0.00000374                 | 1.00E-10             | -            | 1.00E-10                     | 0.002                  | 0.001          | -                          | -                        |
| FOXE1I | -1.00E-04   | 0.003   | 1.00E-10                   | -0.018               | -0.004        | -0.0004                      | 0.014                  | -              | -                          | -                        |
| FOXE1J | 1.00E-06    | 0.007   | 0.00025                     | -0.00016             | -0.004        | -0.0004                      | 1.00E-10               | -0.049         | -                          | -                        |
| FOXF1  | 0.000058    | -0.001  | -0.039                      | -                    | -0.000135     | 0.00056                      | -0.015                 | -              | -                          | -                        |
| FOXF2  | 0.019       | 0.004   | -                            | 1.00E-10             | -            | -0.06                        | -0.02                  | 0.012          | -                          | -                        |
| FOXG1  | 0.00E-09    | 0.0000124 | -                            | -                    | -0.00000374   | 1.00E-10                     | 0.002                  | 0.001          | -                          | -                        |
| FOXG1H| -1.00E-10   | 0.00013 | -0.000017                   | -0.018               | -0.004        | -0.0004                      | 0.014                  | -              | -                          | -                        |
| FOXH1  | 1.00E-06    | 0.007   | 0.00025                     | -0.00016             | -0.004        | -0.0004                      | 1.00E-10               | -0.049         | -                          | -                        |
| FOXI2  | 0.000058    | -0.001  | -0.039                      | -                    | -0.000135     | 0.00056                      | -0.015                 | -              | -                          | -                        |
| FOXN2  | 0.019       | 0.004   | -                            | 1.00E-10             | -            | -0.06                        | -0.02                  | 0.025          | 0.024                      | -                        |
| FOXN3  | -1.00E-10   | -0.00028 | -                            | -                    | -0.000017     | 1.00E-10                     | 0.002                  | 0.001          | -                          | -                        |
| FOXN4  | 0.019       | 0.004   | -                            | 1.00E-10             | -            | -0.06                        | -0.02                  | 0.018          | -                          | -                        |
| FOXN5  | -0.006      | -1.69E-08 | 0.016                      | -                    | -0.001        | -0.012                       | 1.00E-06               | -              | -                          | -                        |
| FOXN6  | 0.0000124   | -0.0003 | -0.028                      | -                    | 0.009         | -0.0001                      | 4.00E-06               | -              | -                          | -                        |
| FOXP1  | -0.006      | -1.69E-08 | 0.016                      | -                    | -0.001        | -0.012                       | 1.00E-06               | -              | -                          | -                        |
| FOXP3  | -0.006      | -0.057  | -0.028                      | -                    | -0.009        | -0.0001                      | 4.00E-06               | -              | -                          | -                        |
| FOXO1  | 0.000002    | 0.00025 | -                            | -                    | 0.00013       | -                            | 0.013                  | -              | -                          | -                        |
| FOXO1R | 0.023       | -0.0000124 | -0.0003 | 0.000714 | -0.0009       | -                            | 0.013                  | -              | -                          | -                        |

*The P-value of differential expressions of FOX genes in response to cancer diseases. The up-regulated genes as positive number and the down-regulated genes as negative number.

cancer (Lin et al., 2002), and anaplastic thyroid cancer (Nucera et al., 2009). FOXM1 is overexpressed in basal-type breast cancer (Curtis et al., 2012), non-Hodgkins lymphoma (Green et al., 2011), and malignant peripheral nerve sheath tumors (Yu et al., 2011). Down-regulation of FOXM1 in laryngeal squamous carcinoma cells resulted in an inhibition of cell proliferation, migration, and invasion, which indicated that inhibition of FOXM1 represents an attractive target for cancer therapy (Chen et al., 2011). Xu et al. (2012) indicated that FOXM1 expression in tumor tissue had clinical significance for predicting recurrence in patients with non-small cell lung cancer after tumor surgery. FOXO1 gene is located within the commonly deleted region in prostate cancer and the expression FOXO1 is frequently down regulated in prostate cancer (Dong et al., 2006). FOXO4 is fused to the MLL gene as a result of chromosomal translocation in acute lymphoblastic leukemia (ALL) (Dansen et al., 2008). FOXC2 acts as regulators of Lymphangiogenesis and Angiogenesis in Oral Squamous Cell Carcinoma (Sasahira et al., 2014). The expression of FOXC2 gene also increases with malignancy of Cervical Cancer, especially with blood vessel hyperplasia and invasion degree (Zheng et al., 2014). FOXL1 plays an inhibitory role in renal tumor progression and over-expression of FOXL1 can inhibit tumor cell growth, migration and invasion in renal cancer cells (Yang et al., 2013). The responsiveness of these cancer-responsive FOX genes with overlapping expression patterns might imply that they have pleiotropic biological functions in cancer diseases, therefore, the detailed functional analysis using mutants and/or overexpression transgenic lines is required. Taken together, the pleiotropic feature of the biological functions of the FOX genes make them become excellent candidates in efforts aimed to give medical treatment for cancer diseases at genetic.

The expression characteristics of FOX genes in the same kind of cancer disease were also analyzed (Figure 2, and Figure 3). Twenty-three FOX genes (4 up-regulated and 19 down-regulated) were differentially expressed in brain tumor. It is noted that most of them were down-regulated expression in the brain tumor indicated that the FOX family genes may play important roles in brain tumor. The study suggested that FOX2 and FOX3 maybe play suppressor roles in the meningioma tumor, which is a kind of brain tumor (Sulman et al., 2004). Twenty-three FOX genes (13 up-regulated and 10 down-regulated) were differentially expressed in adenoma. Seventeen FOX genes (9 up-regulated and 8 down-regulated) were found.
to be differentially expressed in metastatic prostate cancer. Among them, FOXA1 (Grasso et al., 2012), FOXM1 (Lokody, 2014), and FOXL1 (Dong et al., 2006) have been reported to play key roles in prostate cancer. Ten FOX genes (3 up-regulated and 7 down-regulated) were found to be differentially expressed in renal cell carcinoma. Nine FOX genes (2 up-regulated and 7 down-regulated) were differentially expressed in breast cancer. For example, FOXA1 (Schneider et al., 2006; Hu et al., 2009), and FOXM1 (Curtis et al., 2012) were upregulated expression in breast cancer, which play an important roles in breast cancer. In addition, eighteen FOX genes (5 up-regulated and 13 down-regulated) were found to be differentially expressed in oral squamous cell carcinoma. Twelve FOX genes (2 up-regulated and 10 down-regulated) were found to be differentially expressed in acute myeloid leukemia. Fourteen FOX genes (4 up-regulated and 10 down-regulated) were found to be differentially expressed in myeloma. Thirteen FOX genes (5 up-regulated and 8 down-regulated) were found to be differentially expressed in B-cell lymphoma. Twelve FOX genes (4 up-regulated and 8 down-regulated) were found to be differentially expressed in papillary thyroid carcinoma. Eight FOX genes (3 up-regulated and 5 down-regulated) were found to be differentially expressed in leiomyoma. Nine FOX genes (4 up-regulated and 5 down-regulated) were found to be differentially expressed in invasive ductal carcinoma. All of these results showed that multiple genes may have the synergy or antagonism effects in the same kind of cancer disease, which suggested that the FOX genes involved redundant function in the cancer disease.

In conclusions, the present study, we analyzed the expression of FOX genes in different cancer diseases. The cancer-responsive FOX genes with overlapping expression patterns might imply that they have pleiotropic biological functions in cancer diseases. The pleiotropic feature of the biological functions of the FOX genes make them become excellent candidates in efforts aimed to give medical treatment for cancer diseases at genetic. The cancer-responsive FOX genes are also different expression in the same disease, which indicated that they may have the synergy or antagonism effects in the same kind of cancer disease. In all, the results of this study provide clues for further functional analysis of FOX genes, especially for the pleiotropic biological functions and the crosstalk of FOX genes in cancer diseases of human

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Comprehensive Expression Analysis Suggests Functional Overlapping of the Human FOX Transcription Factors in Cancers

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