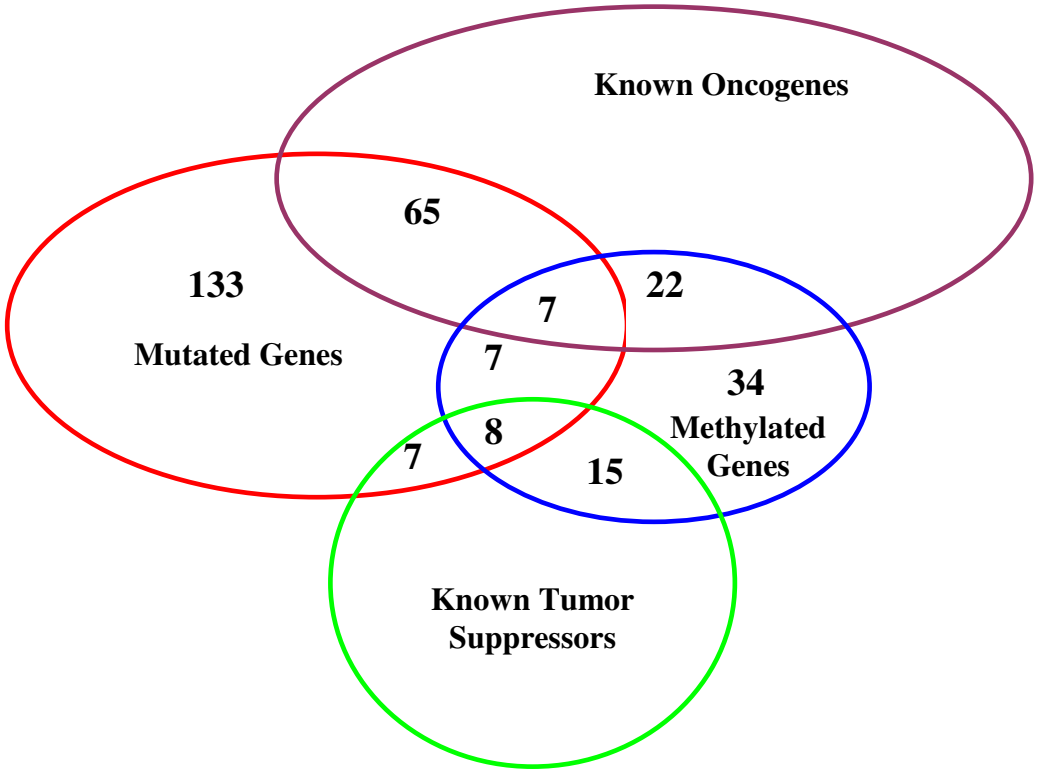
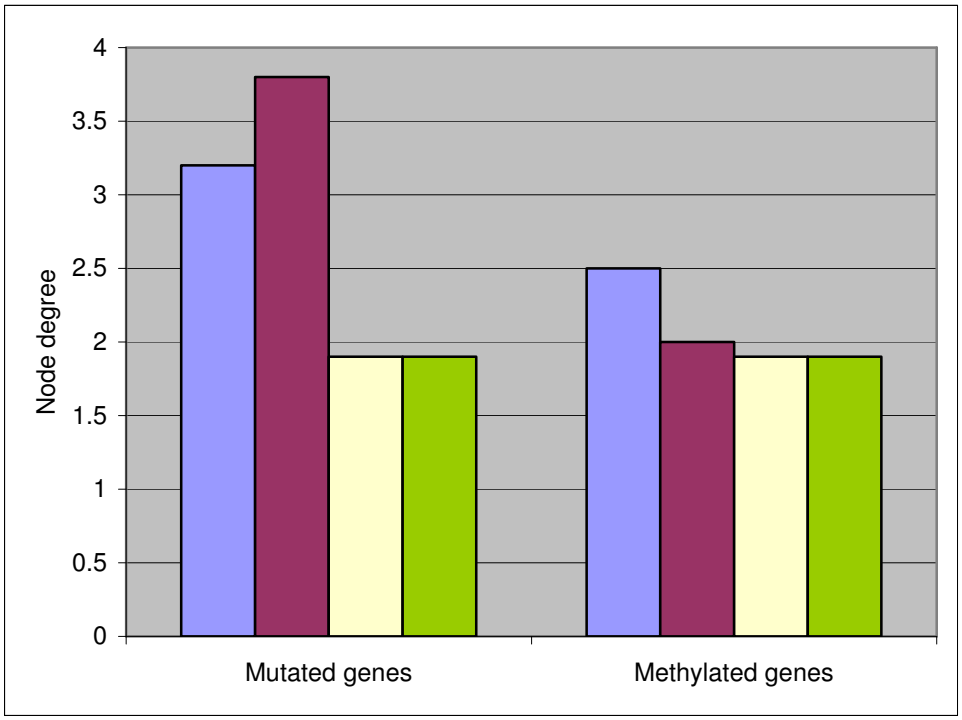
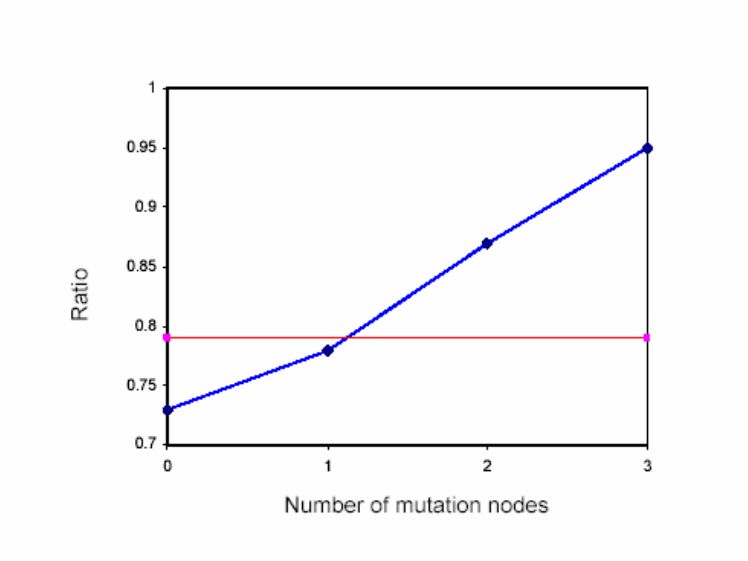


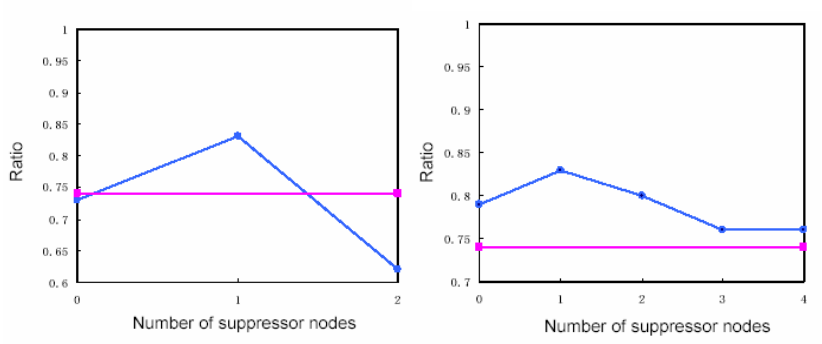
Supplementary Figure 1. Known oncogenes and tumor suppressors in the cancer mutated and methylated network gene sets. 227 cancer mutated genes and 93 cancer methylated genes were mapped onto the signaling network. Certain cancer-associated genes act as either oncogenes or tumor suppressors in different cellular conditions. For example, TGFß pathway genes are oncogenes, but they are also tumor suppressors in the early developmental stages of cancer. Methylated genes in cancer stem cells have been implicated as tumor suppressors. Among the 93 methylated genes, we treated the 13 methylated TGFß pathway genes as known tumor suppressors.



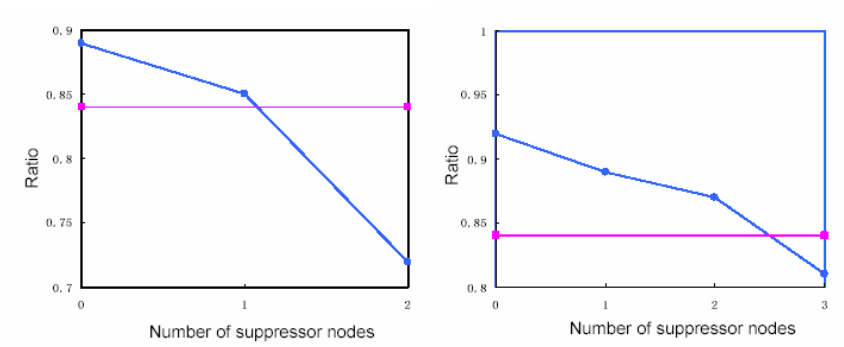
Supplementary Figure 2. Degree of the mutated and methylated genes in the network. The average indegree of the nodes is represented in blue, while the average outdegree of the nodes is represented in purple. The average indegree and outdegree of the whole network nodes are represented in yellow and green, respectively. The average indegree of the mutated nodes is significantly higher than that of the network nodes ($P<1.1\times10^{-6}$, Wilcoxon test), while the average outdegree of the mutated nodes ($P<6.0\times10^{-14}$, Wilcoxon test). Methylated gene nodes do not appear to be differ significantly from the network nodes with regard to their indegree, outdegree and neutral degree, respectively (P=0.32, P=0.16, P=0.09).



Supplementary Figure 3. Relations between the fractions of positive links in the feed-forward loops (FFLs) and the fractions of mutated genes in FFLs. FFLs were classified into several groups based on the number of nodes that are mutated genes. For example, FFLs have no mutated genes (group 0), or have just one mutated gene (group 1), or two (group 2) or all three are mutated genes (group 3). The ratio of positive links to total positive and negative links in each group was plotted. The horizontal lines indicate the ratio of positive links to the total positive and negative links in all FFLs.

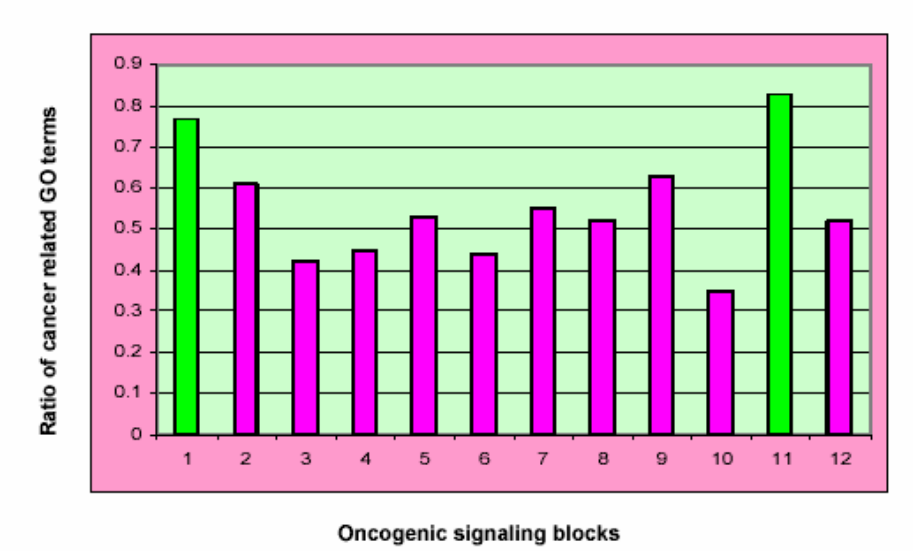


4a **4b**

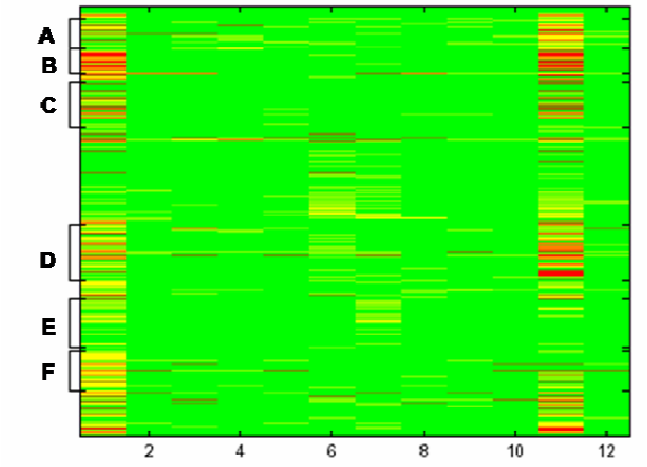


4c **4d**

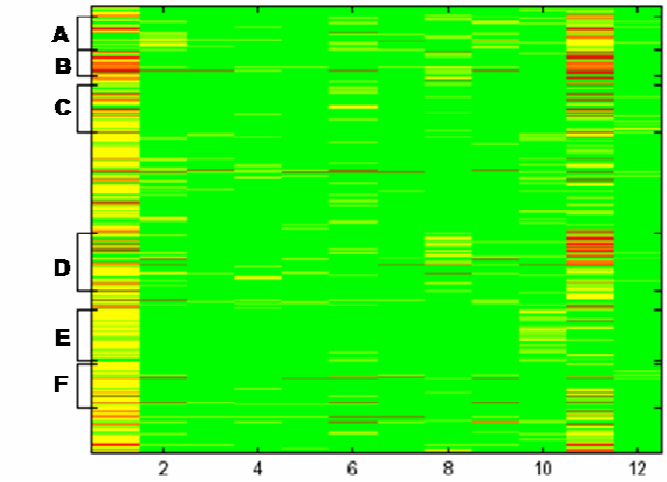
Supplementary Figure 4. Relations between the fractions of positive links in network motifs and the fractions of the 15 known tumor suppressors in network motifs. 3-node (a) and 4-node (b) network motifs in the human signaling network. 3-node (c) and 4-node (d) network motifs in the oncogenic signaling map, which is extracted from the human signaling network by mapping cancer mutated and mythelated genes (see main text). The oncogenic signaling map can be seen as a sub-network containing 'pure cancer signaling events' by removing the 'noisy signals' (i.e., signaling for stress and so on) from the human signaling network. Consistently, the patterns of the 15 tumor suppressors are clearer in the oncogenic signaling map than in the signaling network. Motifs were classified into several groups based on the number of nodes that are tumor suppressors. For example, motifs have no tumor suppressors (group 0), or have just one tumor suppressor (group 1), or two (group 2) or three (group 3) all four are tumor suppressors (group 4). The ratio of positive links to total positive and negative links in each group was plotted. The horizontal lines indicate the ratio of positive links to the total positive and negative links in all motifs.



Supplementary Figure 5. Percentage of cancer-associated Gene Ontology (GO) terms in each oncogenic signaling block. The cancer-associated GO terms are cell adhesion, cell cycle, apoptosis, proliferation, survival and differentiation. We calculated the percentage of these cancer-associated GO terms in total GO terms for each oncogenic signaling block, which were defined in the oncogenic signaling map.



6a



6b

Supplementary Figure 6. Heatmaps of the mutation distributions in oncogenic signaling blocks. (a) the heatmap for the cancer-mutated genes derived from large-scale sequencing of tumors, and (b) the heatmap for the cancer-mutated genes derived from large-scale sequencing of tumors and the literature mining, including 60 literature mined mutated genes that have no further experimental support in the COSMIC database. Rows represent samples, while columns represent oncogenic signaling blocks. The arrangement of the oncogenic signaling blocks in both heatmaps are based on their maximum overleap

with those in the original heatmap shown in Figure 4 of the main text. Samples were organized according to their cancer types. Cancer types which have relatively more samples were marked on the heatmap: (A) breast, (B) central nervous system, (C) blood, (D) lung, (E) pancreas and (F) skin tumors. Blocks with gene mutations are marked in yellow, however, when one sample contains statistically significant co-occurring mutated gene pairs (see Supplementary Table 7), the blocks are marked in red.