Supplementary Table 1. Correlation between expression, relative copy number and methylation of selected genes

| Gene    | Correlation between expression and relative copy number (Spearman coefficient ) | Correlation between expression and methylation (Spearman coefficient ) |
|---------|---------------------------------------------------------------------------------|---------------------------------------------------------------------|
| B4GALT4 | 0.42                                                                            | -0.28                                                               |
| BCL2L1  | 0.17                                                                            | -0.18                                                               |
| CDH2    | 0.25                                                                            | -0.37                                                               |
| COPG1   | 0.51                                                                            | NA                                                                  |
| CRB3    | 0.13                                                                            | -0.47                                                               |
| FERMT2  | 0.42                                                                            | -0.38                                                               |
| GET4    | 0.34                                                                            | NA                                                                  |
| GPX4    | 0.24                                                                            | -0.28                                                               |
| HNF1B   | 0.15                                                                            | -0.16                                                               |
| ITGAV   | 0.14                                                                            | -0.27                                                               |
| MDM2    | 0.14                                                                            | -0.13                                                               |
| NFE2L2  | 0.19                                                                            | -0.09                                                               |
| PAX8    | 0.14                                                                            | -0.27                                                               |
| RUVBL1  | 0.39                                                                            | -0.34                                                               |
| TFRC    | 0.21                                                                            | -0.01                                                               |
| TNFSF10 | 0.10                                                                            | -0.43                                                               |

NA, not available
Supplementary Figure 1 Flow diagram of data acquisition and analysis

- Screen top 10 preferentially essential genes of 8 ccRCC cell lines in Depmap.
  - 106 candidate genes
  - A gene that could be found in both RNAi and CRISPR-Cas9 methods or more than one ccRCC cell line was selected.
    - 16-Gene set
      - Gene effect scores
      - Expression profiles in normal tissues
      - PCA reveals the potential tissue or tumor specificity.
      - Correlations between expression, methylation, and copy numbers
    - Genetic alteration of these genes in KIRC cohort
    - Expressions of patient-matched tumor and normal tissue in KIRC
    - Network of co-expression, physical and genetic interaction
      - GO and KEGG enrichment analysis
      - Regulatory correlations between genes and several critical pathways
    - Tumor-infiltrating immune cells
      - Correlations between its expression level and immunotherapy responses
    - Univariable and multivariable COX regression
      - KM curves of OS and DFS
      - ROC curves
    - Functional analysis
    - Immune-associated analysis
      - RNA-seq level in tumor and normal tissue
      - Protein level in tumor tissue
      - qPCR in RCC cell lines
    - Prognostic value
      - Validation of CRB3 and GET4
Supplementary Figure 2. Expression of genes in tumor and unpaired adjacent normal tissue in the KIRC cohort
**Supplementary Figure 3. Functional analysis**

**Networks**
- Co-expression
- Physical Interactions
- Genetic Interactions

**Functions**
- regulation of apoptotic signaling pathway
- signal transduction in absence of ligand
- extrinsic apoptotic signaling pathway in absence of ligand
- nephron tubule development
- apoptotic mitochondrial changes
- cell junction organization

**Supplementary Figure 4. Differential expression between responders and non-responders from two datasets**
Supplementary Figure 5. ROC curves

Supplementary Figure 6. Gene effect scores of GET4 and CRB3 between different lineages, microsatellite status, and tumor types of cell lines

Supplementary Figure 7. Expression levels of CRB3 and GET4 in cell lines (qPCR)