

Supplementary Table 1 | Characteristics of patients for RCC-PDC1 and RCC-PDC2.

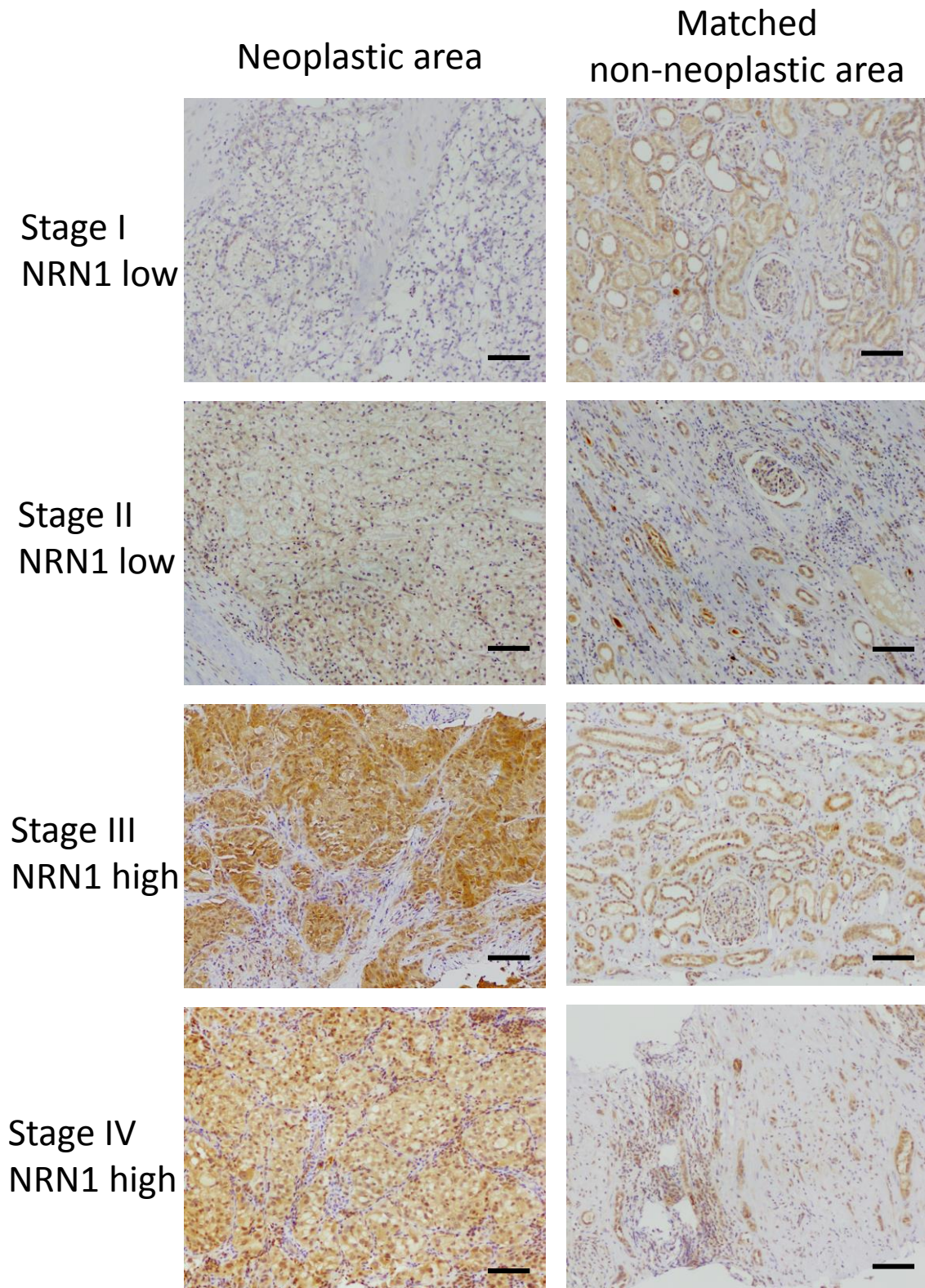
| Cancer cells | Age | Gender | Stage | Pathological findings | Grade | Infiltration | Surgical procedure |
|--------------|-----|--------|---------------------|---------------------------------|-------|--------------|---------------------|
| RCC-PDC1 | 46 | M | T3bN0M1 Stage IV | Clear cell renal cell carcinoma | 3 | b | Radical nephrectomy |
| RCC-PDC2 | 80 | M | T1bN0M0 Stage I | Clear cell renal cell carcinoma | 2 | b | Radical nephrectomy |

Supplementary Table 2 | Sequences of primers for quantitative reverse transcription polymerase chain reaction (qRT-PCR).

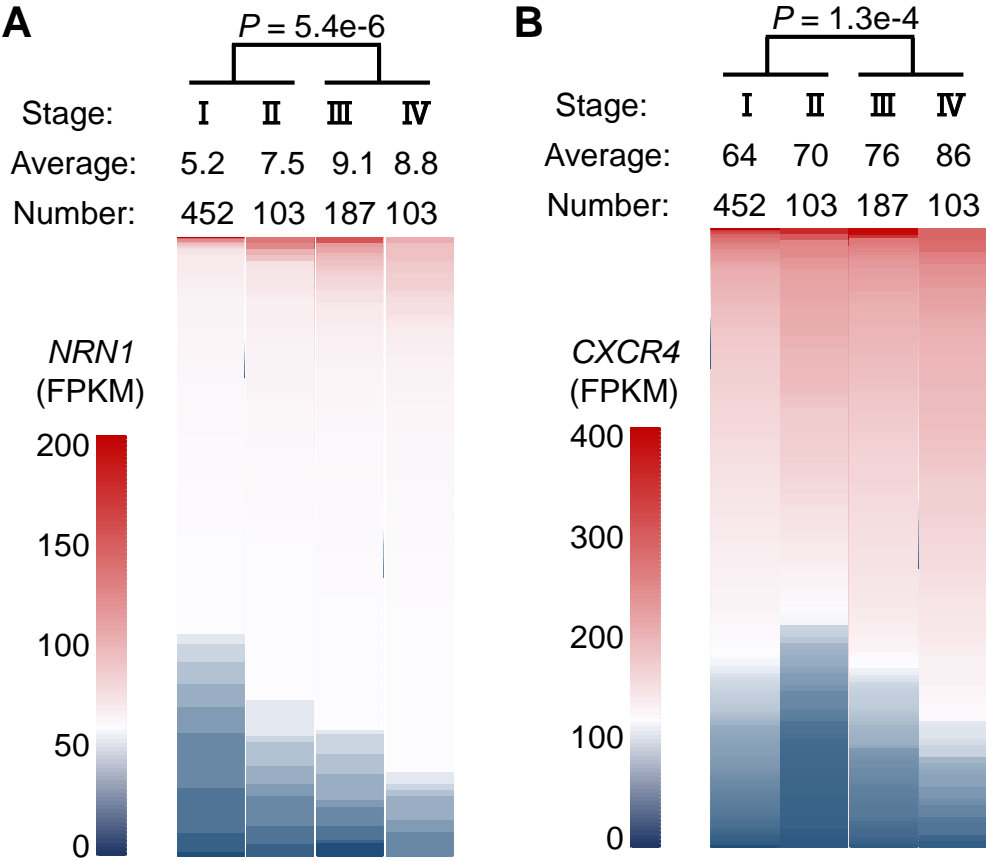
| Primer name | Sequence (5' to 3') |
|------------------|-------------------------|
| <i>NRN1_Fw</i> | GGGCGACAGCATGGCCAACT |
| <i>NRN1_Rv</i> | CCGCTGCCGCAGAGTTCGAA |
| <i>CXCR4_Fw</i> | GCATGACGGACAAGTACAGGCT |
| <i>CXCR4_Rv</i> | AAAGTACCAGTTTGCCACGGC |
| <i>ACTB_Fw</i> | CCTGGCACCCAGCACAA |
| <i>ACTB_Rv</i> | AGCGAGGCCAGGATGGA |
| <i>NFATC4_Fw</i> | CCGTATCACAGGCAAGATGGT |
| <i>NFATC4_Rv</i> | AGCAGAGTCATCTCCAACACCTT |

Supplementary Table 3 | Sequences of short interfering RNAs (siRNAs).

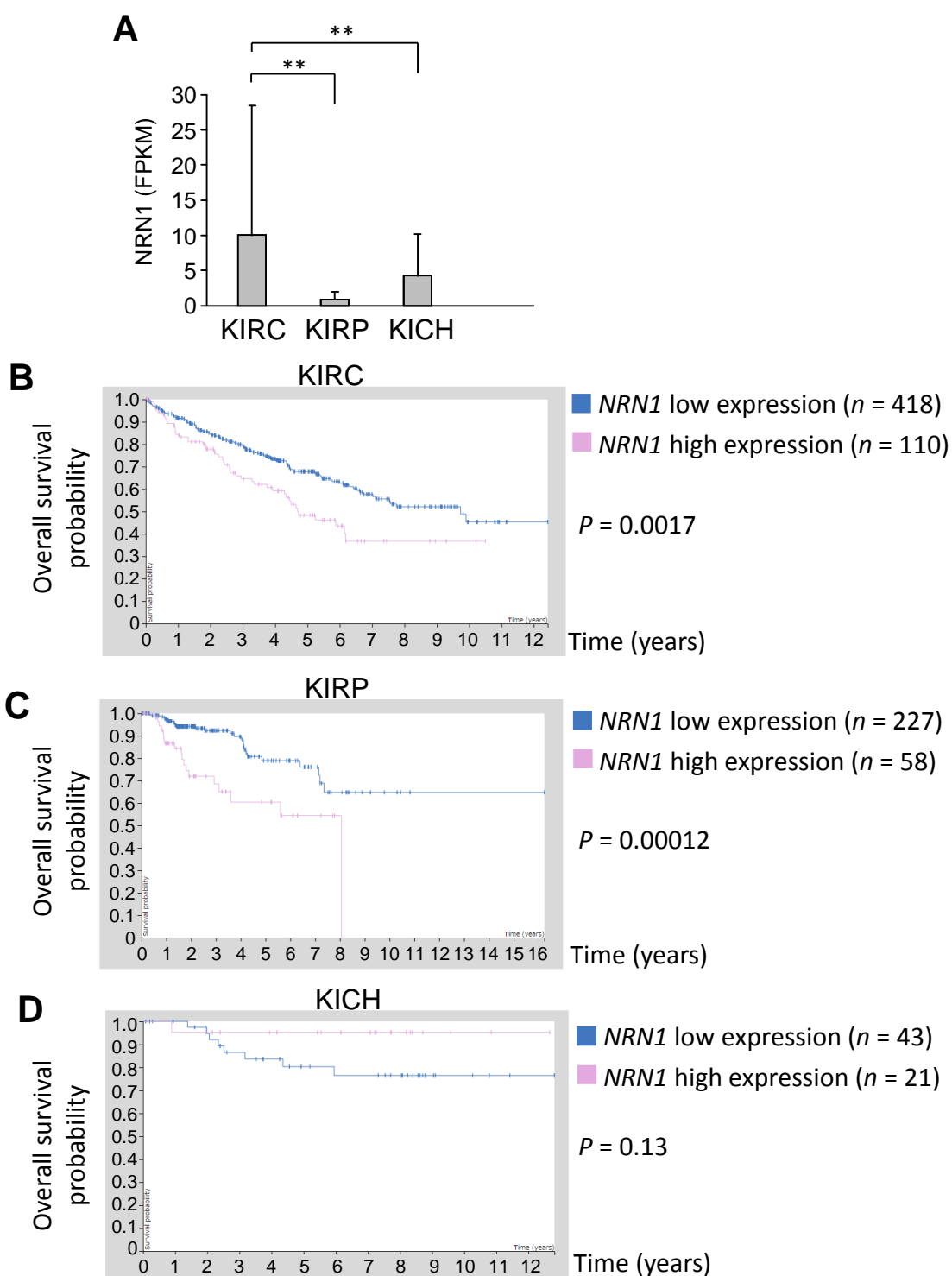
| siRNA | | Sequence (5' to 3') |
|------------|------------------|-----------------------|
| siNRN1 #1 | Sense strand | AUUCUUUUCUCAGUUUAUCCC |
| | Antisense strand | GAUAAACUGAGAAAAGAAUCC |
| siNRN1 #2 | Sense strand | AAAUAAAACACAAGAAAUCAA |
| | Antisense strand | GAUUUCUUGUGUUUUAUUUGC |
| siCXCR4 #1 | Sense strand | UGAAAUUAGCAUUUUCUUCAC |
| | Antisense strand | GAAGAAAUGCUAAUUUCAAU |
| siCXCR4 #2 | Sense strand | CCGACCUCUUCUUUGUCAUCA |
| | Antisense strand | AUGACAAAGAGGAGGUCGGCC |
| siControl | Sense strand | GUACCGCACGUCAUUCGUAUC |
| | Antisense strand | UACGAAUGACGUGCGGUACGU |



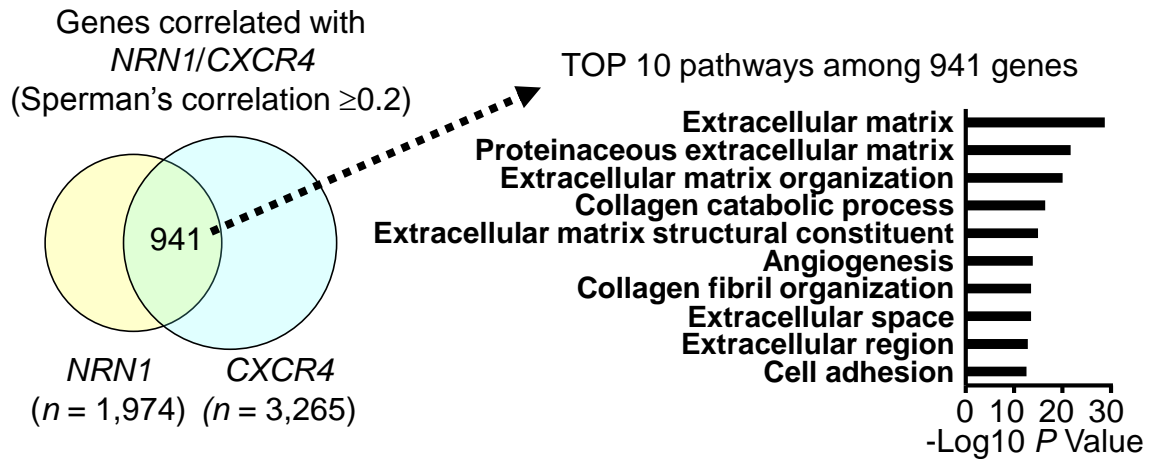
Supplementary Figure 1 | Representative NRN1 immunohistochemistry staining of neoplastic area (left panel) and its paired corresponding non-neoplastic area (right panel) with each stage in ccRCC tissue sections. Scale bars, 100 μ m.



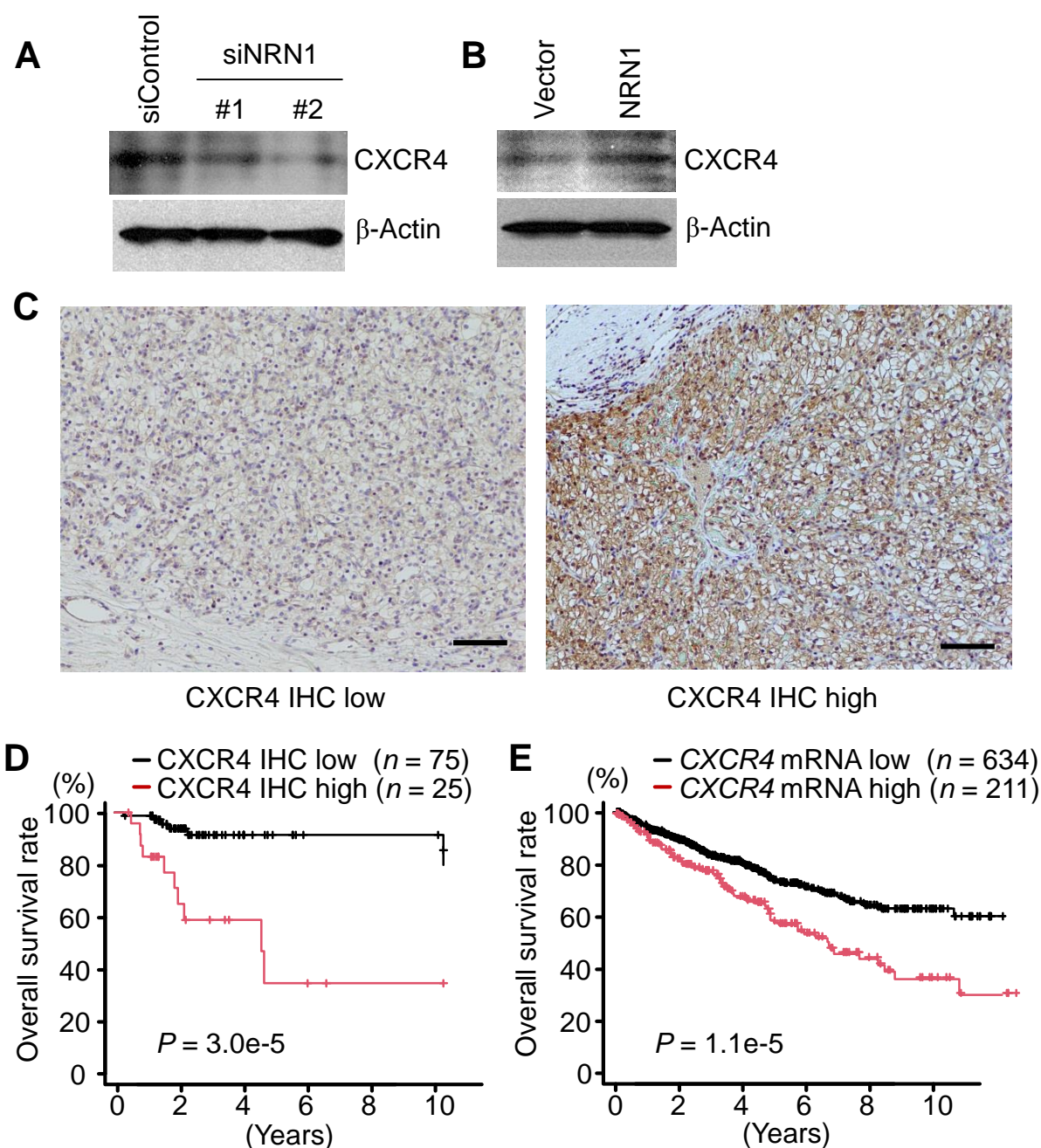
Supplementary Figure 2 | Expression levels of *NRN1* and *CXCR4* associated with clinical tumor stages in RCC. **(A, B)** Association of *NRN1* (A) and *CXCR4* (B) mRNA expression levels and clinical tumor stages in RCC. Expression levels are shown in Fragments Per Kilobase of exon per Million mapped reads (FPKM). Data are retrieved from The Human Protein Atlas (<https://www.proteinatlas.org/>).



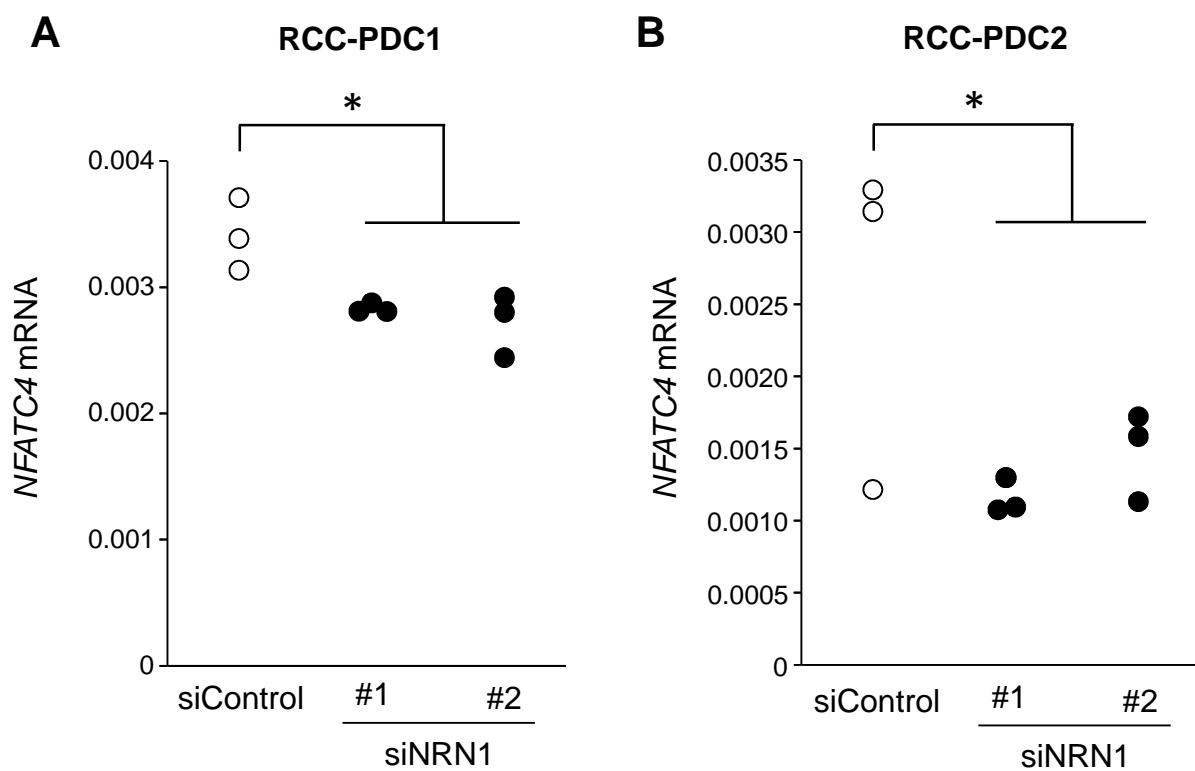
Supplementary Figure 3 | *NRN1* is associated with prognosis in patients with KIRC and KIRP. **(A-D)** Data of *NRN1* expression and patient overall survival were retrieved from TCGA dataset (ccRCC [KIRC], papillary RCC [KIRP], and chromophobe RCC [KICH]) in The Human Protein Atlas. *NRN1* expression levels are shown in FPKM (A). Overall survival of patients with KIRC (B), KIRP (C), and KICH (D) were analyzed using Kaplan-Meier method with stratification by *NRN1* expression levels. Statistical significance was evaluated by log-rank test.



Supplementary Figure 4 | Gene ontology analysis of co-expressed genes with both *NRN1* and *CXCR4*. Expression data retrieved from cBioPortal (<https://www.cbioportal.org>) were analyzed for mRNA co-expression and the selected 941 common genes were further analyzed with gene ontology using the Database for Annotation, Visualization and Integrated Discovery (DAVID) (<https://david.ncifcrf.gov/tools.jsp>).



Supplementary Figure 5 | CXCR4 is associated with poor prognosis in RCC patients. (A, B) RCC-PDC1 cells were transfected with siRNAs (A) or expression vectors (B) indicated, and then subjected to Western blot analysis using CXCR4 or β -actin antibodies. (C) Representative immunohistochemistry (IHC) staining of low (left panel) and high (right panel) expression of CXCR4 in RCC tissue sections. Scale bars, 100 μ m. (D) Overall survival of 100 clear cell RCC (ccRCC) patients with low or high CXCR4 IHC staining was analyzed by Kaplan-Meier method. Statistical significance was evaluated by log-rank test. (E) CXCR4 expression data in TCGA RCC dataset were retrieved from The Human Protein Atlas ($n = 845$). Overall survival of RCC patients with low or high CXCR4 expression levels were analyzed by Kaplan-Meier method. High and low CXCR4 expressions were determined at an expression cut off level as 99.5 FPKM (expression level range: 2.1-372.0, expression median level: 61.8 FPKM, $P = 1.1e-5$). Statistical significance was evaluated by log-rank test.



Supplementary Figure 6 | NRN1 silencing represses *NFATC4* mRNA in RCC-PDCs. (**A**, **B**) RCC-PDC1 (**A**) and 2 (**B**) spheroid cultures were transfected with NRN1 (siNRN1 #1 and #2) or control (siControl) siRNAs. *NFATC4* mRNA levels were analyzed by qRT-PCR ($n = 3$). Data are shown as means \pm SD. * $P < 0.05$ by two-way ANOVA test.