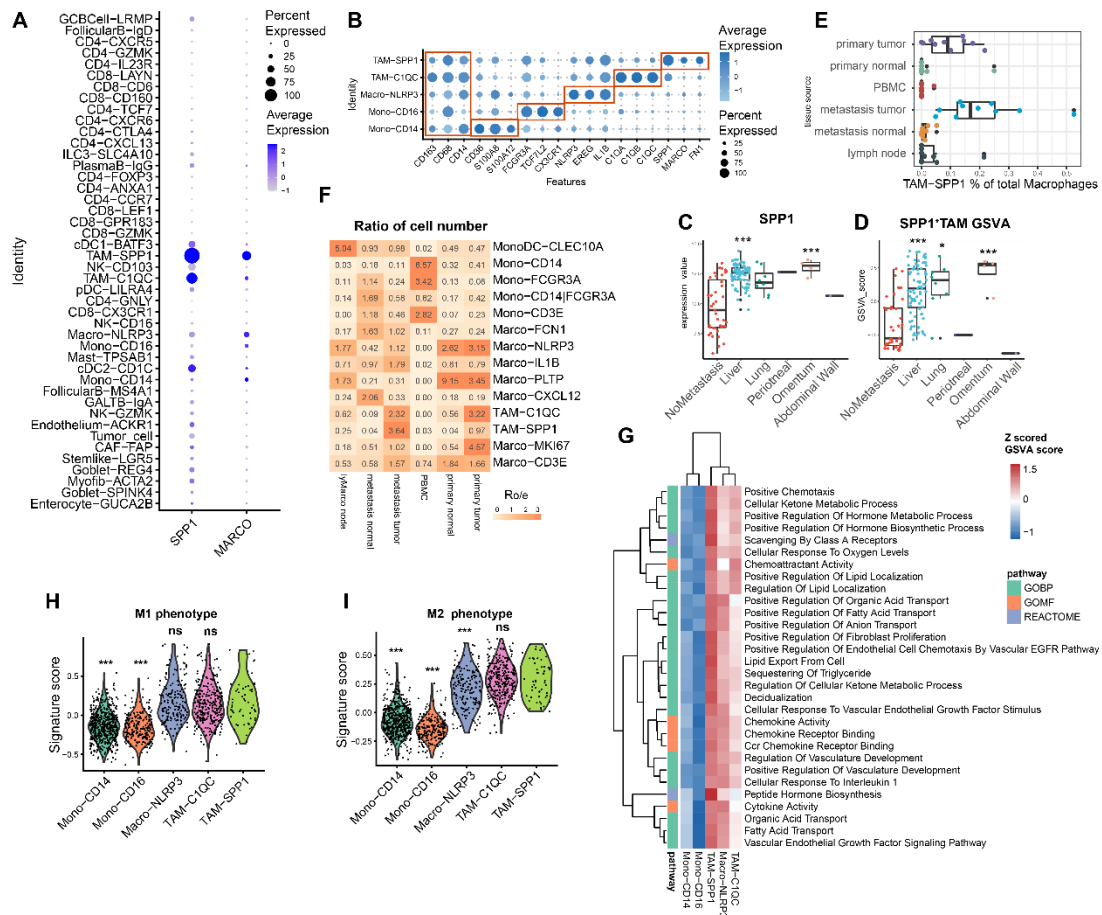
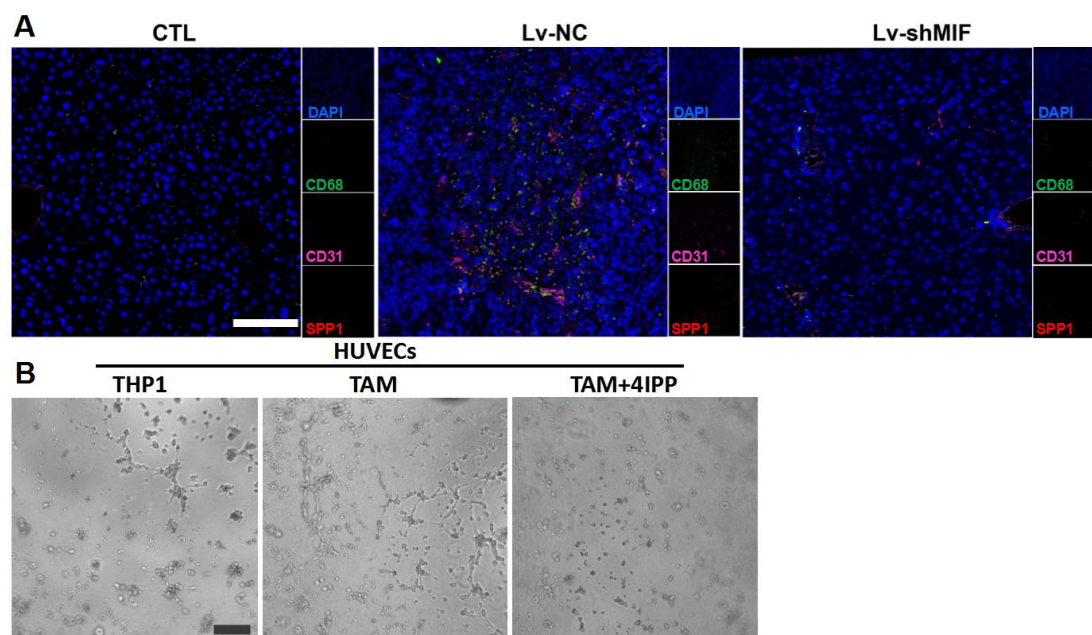


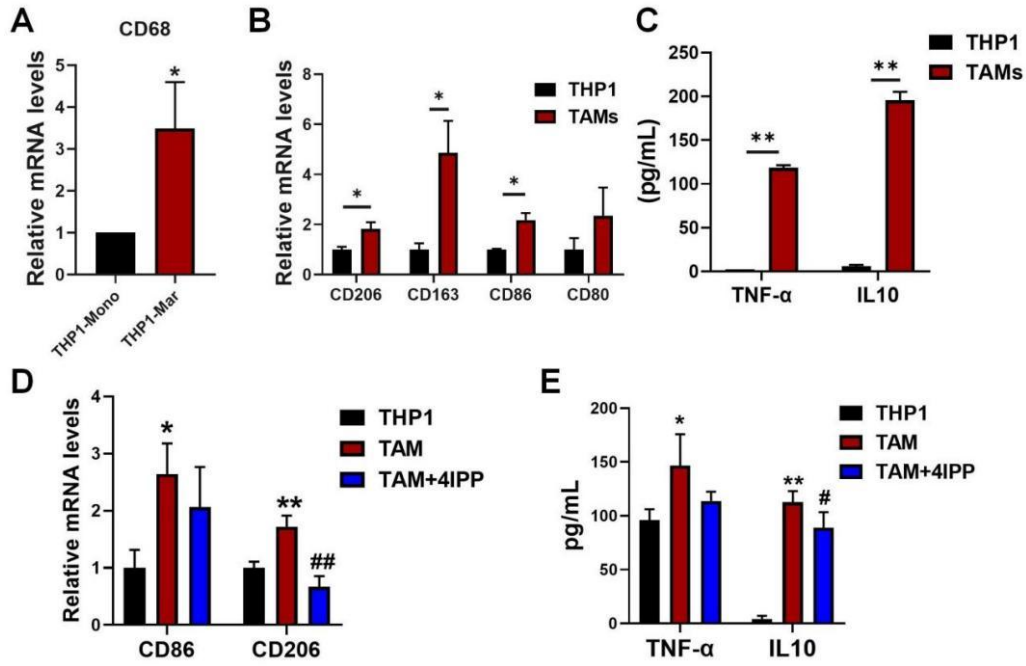


**Supplementary Figure S1. Characteristics of SPP1<sup>+</sup>TAMs identified from the CRC scRNA-seq data.**

(A) SPP1 and MARCO expression value compared across cell type in GSE146771. (B) Dotplot displaying the expression of myeloid marker and monocyte and macrophage sub-clusters marker. (C-D) The boxplot shows the expression of SPP1 (C) and SPP1<sup>+</sup>TAMs GSVA score (D) in non-metastatic CRC and different types of CRC metastasis tissues. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  vs. No metastasis. (E) The percentage of SPP1<sup>+</sup>TAMs among the total macrophages in different tumor tissues based on scRNA-seq data from CRC liver metastatic tissues. (F) The tissue distribution ratio of each monocyte and macrophage cluster estimated by the Ro/e score in CRC liver metastases. (G) Heatmap showing the results of the GSVA enrichment analysis of monocyte and macrophage population subsets, highlighting the pathways that were significantly upregulated in the SPP1<sup>+</sup>TAMs. (H-I) M1 and M2 signature were compared across multiple monocyte and macrophage clusters. *ns*, not significant; \*\*\* $P < 0.001$  vs. TAM-SPP1.

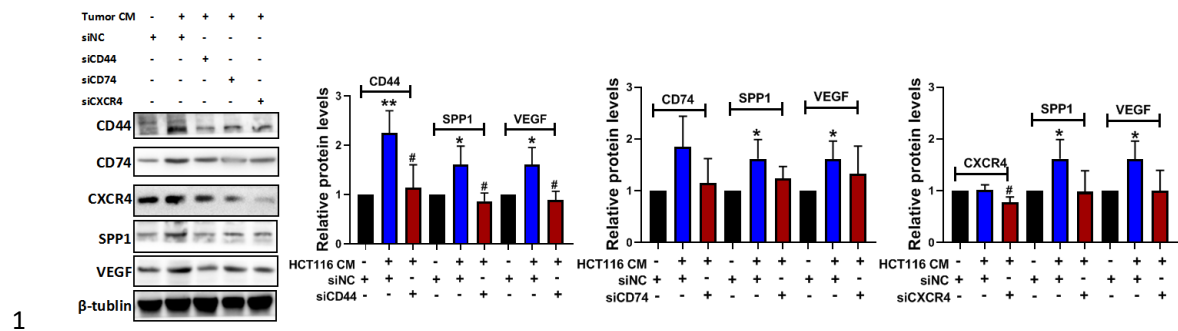


**Supplementary Figure S2. MIF is essential for the activation of SPP1<sup>+</sup>TAM-mediated angiogenesis.** (A) Representative immunofluorescence images of CRC liver metastasis model showing the abundance of SPP1<sup>+</sup>TAMs and its co-localization of the microvessels (scale bar=100  $\mu$ m). CTL: control mice; Lv-NC: CT26 liver metastasis model mice; Lv-shMIF: CT26 liver metastasis model with MIF knockdown. (B) Effect of the condition median from THP1, TAM and 4-IPP treated TAMs on tube formation ability of HUVECs by tube formation assay (scale bar=100  $\mu$ m).

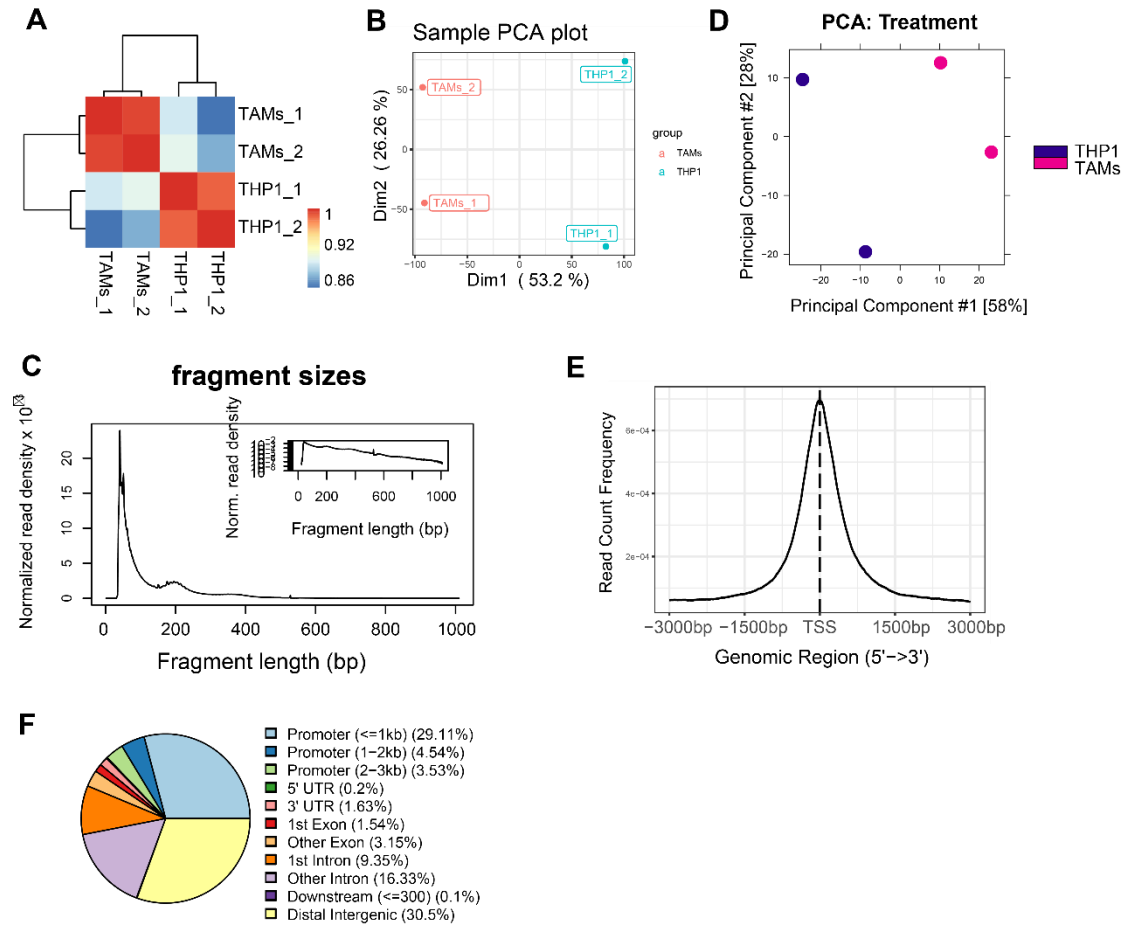


**Supplementary Figure S3. Characterization of PMA-induced THP-1 macrophages and their M1/M2 polarization phenotype in co-culture model.**

(A) The mRNA levels of CD68 were determined using the RT-qPCR. PMA was used to induce the differentiation of THP-1 cells into macrophages for 24 h. Data are shown as Mean  $\pm$  SD. \* $P$  < 0.05, vs. THP-1-Mono group (n=3). (B) The mRNA levels of the M1 macrophage markers (CD86, CD80), and the M2 macrophage markers (CD206 and CD163) in PMA-induced THP-1 macrophages or TAMs were determined by using the RT-qPCR assay (n=3). (C) The levels of TNF- $\alpha$  and IL10 in PMA-induced THP-1 macrophages or TAM were determined using the ELISA assay. Data are shown as Mean  $\pm$  SD. \*\* $P$  < 0.01 vs. THP-1 group (n=3). (D) The mRNA levels of the M1 macrophage markers (CD86) and the M2 macrophage markers (CD206) in PMA-induced THP-1 macrophages, TAMs or 4-IPP treated TAMs were measured by RT-qPCR (n=3). (E) The levels of TNF- $\alpha$  and IL10 in PMA-induced THP-1 macrophages, TAMs or 4-IPP treated TAMs were measured by ELISA assay. \* $P$  < 0.05, \*\* $P$  < 0.01, vs. THP-1; # $P$  < 0.05, ## $P$  < 0.01, vs. TAMs (n=3).



1  
2 **Supplementary Figure S4. Effects of the three receptors on the activation of SPP1<sup>+</sup> TAMs**  
3 **determined by siRNA knockdown assays.** The protein expression levels of SPP1<sup>+</sup>TAM markers  
4 in TAM cells after siRNA-mediated knockdown of MIF receptors (CD44, CD74 and CXCR4)  
5 were determined by Western blotting (left panel), and quantified data were shown using Image J  
6 software (right panel). Data are shown as Mean  $\pm$  SD (n=3). \* $P < 0.05$ , vs. the corresponding  
7 control; # $P < 0.05$  vs. si-NC.



## Supplementary Figure S5. Quality control for the TAMs RNA-seq and ATAC-seq data.

(A-B) Cluster heatmap (A) and PCA plot (B) showing the correlation of RNA-seq data between two group samples. (C) Fragment size distribution of ATAC-seq reads. (D) PCA plot showing the correlation of ATAC-seq data between two groups of samples. (E) Average ATAC-seq peak intensity near the transcription start site (TSS). (F) The pie plot displays the genomic annotation of ATAC-seq peak locations.

1 **Supplementary Table S1. The signaling pathways involved in the interaction between tumor cells and the SPP1<sup>+</sup>TAMs.**

| source     | target       | ligand     | receptor    | prob         | pval | interaction_name  | interaction_name_2     | pathway_name  | annotation            | evidence                          |
|------------|--------------|------------|-------------|--------------|------|-------------------|------------------------|---------------|-----------------------|-----------------------------------|
| Tumor_cell | TAM-S<br>PP1 | MIF        | CD74_CD44   | 0.353<br>098 | 0    | MIF_CD74_CD44     | MIF<br>(CD74+CD44)     | -<br>MIF      | Secreted<br>Signaling | PMID: 29637711;<br>PMID: 26175090 |
| Tumor_cell | TAM-S<br>PP1 | MIF        | CD74_CXCR4  | 0.304<br>816 | 0    | MIF_CD74_CXCR4    | MIF<br>(CD74+CXCR4)    | -<br>MIF      | Secreted<br>Signaling | PMID: 29637711;<br>PMID: 24760155 |
| Tumor_cell | TAM-S<br>PP1 | LAMB3      | CD44        | 0.237<br>938 | 0    | LAMB3_CD44        | LAMB3 - CD44           | LAMININ       | ECM-Receptor          | KEGG: hsa04512                    |
| Tumor_cell | TAM-S<br>PP1 | MDK        | NCL         | 0.216<br>687 | 0    | MDK_NCL           | MDK - NCL              | MK            | Secreted<br>Signaling | PMID: 28356350                    |
| Tumor_cell | TAM-S<br>PP1 | APP        | CD74        | 0.209<br>625 | 0    | APP_CD74          | APP - CD74             | APP           | Cell-Cell<br>Contact  | PMID: 19849849                    |
| Tumor_cell | TAM-S<br>PP1 | LAMC2      | CD44        | 0.202<br>936 | 0    | LAMC2_CD44        | LAMC2 - CD44           | LAMININ       | ECM-Receptor          | KEGG: hsa04512                    |
| Tumor_cell | TAM-S<br>PP1 | LAMB1      | CD44        | 0.152<br>977 | 0    | LAMB1_CD44        | LAMB1 - CD44           | LAMININ       | ECM-Receptor          | KEGG: hsa04512                    |
| Tumor_cell | TAM-S<br>PP1 | MDK        | SDC4        | 0.132<br>88  | 0    | MDK_SDC4          | MDK - SDC4             | MK            | Secreted<br>Signaling | PMID: 28356350                    |
| Tumor_cell | TAM-S<br>PP1 | LAMA3      | CD44        | 0.129<br>044 | 0    | LAMA3_CD44        | LAMA3 - CD44           | LAMININ       | ECM-Receptor          | KEGG: hsa04512                    |
| Tumor_cell | TAM-S<br>PP1 | LAMA5      | CD44        | 0.108<br>809 | 0    | LAMA5_CD44        | LAMA5 - CD44           | LAMININ       | ECM-Receptor          | KEGG: hsa04512                    |
| Tumor_cell | TAM-S<br>PP1 | NAMPT<br>T | ITGA5_ITGB1 | 0.106<br>967 | 0.02 | NAMPT_ITGA5_ITGB1 | NAMPT<br>(ITGA5+ITGB1) | -<br>VISFATIN | Secreted<br>Signaling | PMID: 28490838                    |

|                |              |           |                 |              |          |                       |                        |                  |                       |                                   |
|----------------|--------------|-----------|-----------------|--------------|----------|-----------------------|------------------------|------------------|-----------------------|-----------------------------------|
| Tumor_<br>cell | TAM-S<br>PP1 | LAMC<br>1 | CD44            | 0.105<br>072 | 0        | LAMC1_CD44            | LAMC1 - CD44           | LAMINI<br>N      | ECM-Recep<br>tor      | KEGG: hsa04512                    |
| Tumor_<br>cell | TAM-S<br>PP1 | MDK       | LRP1            | 0.090<br>575 | 0        | MDK_LRP1              | MDK - LRP1             | MK               | Secreted<br>Signaling | PMID: 28356350                    |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMB<br>2 | CD44            | 0.079<br>177 | 0        | LAMB2_CD44            | LAMB2 - CD44           | LAMINI<br>N      | ECM-Recep<br>tor      | KEGG: hsa04512                    |
| Tumor_<br>cell | TAM-S<br>PP1 | F11R      | ITGAL_IT<br>GB2 | 0.068<br>683 | 0        | JAM1_ITGAL_IT<br>GB2  | JAM1<br>(ITGAL+ITGB2)  | -<br>JAM         | Cell-Cell<br>Contact  | PMID: 11812992                    |
| Tumor_<br>cell | TAM-S<br>PP1 | MDK       | SDC2            | 0.053<br>338 | 0        | MDK_SDC2              | MDK - SDC2             | MK               | Secreted<br>Signaling | PMID: 28356350                    |
| Tumor_<br>cell | TAM-S<br>PP1 | MDK       | ITGA4_IT<br>GB1 | 0.050<br>509 | 0        | MDK_ITGA4_IT<br>GB1   | MDK<br>(ITGA4+ITGB1)   | -<br>MK          | Secreted<br>Signaling | PMID: 28356350                    |
| Tumor_<br>cell | TAM-S<br>PP1 | PTPR<br>C | MRC1            | 0.041<br>412 | 0.<br>01 | PTPRC_MRC1            | PTPRC - MRC1           | CD45             | Cell-Cell<br>Contact  | PMID: 27601670;<br>PMID: 10575006 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMB<br>3 | ITGA3_IT<br>GB1 | 0.036<br>748 | 0        | LAMB3_ITGA3_I<br>TGB1 | LAMB3<br>(ITGA3+ITGB1) | -<br>LAMINI<br>N | ECM-Recep<br>tor      | KEGG: hsa04512                    |
| Tumor_<br>cell | TAM-S<br>PP1 | VEGF<br>A | FLT1            | 0.032<br>212 | 0        | VEGFA_VEGFR1          | VEGFA - VEGFR1         | VEGF             | Secreted<br>Signaling | KEGG: hsa04370;<br>PMID: 16633338 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMB<br>3 | ITGA1_IT<br>GB1 | 0.031<br>835 | 0        | LAMB3_ITGA1_I<br>TGB1 | LAMB3<br>(ITGA1+ITGB1) | -<br>LAMINI<br>N | ECM-Recep<br>tor      | KEGG: hsa04512                    |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMC<br>2 | ITGA3_IT<br>GB1 | 0.030<br>17  | 0        | LAMC2_ITGA3_I<br>TGB1 | LAMC2<br>(ITGA3+ITGB1) | -<br>LAMINI<br>N | ECM-Recep<br>tor      | KEGG: hsa04512                    |
| Tumor_<br>cell | TAM-S<br>PP1 | THBS<br>1 | SDC4            | 0.029<br>995 | 0        | THBS1_SDC4            | THBS1 - SDC4           | THBS             | ECM-Recep<br>tor      | KEGG: hsa04512                    |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMC<br>2 | ITGA1_IT<br>GB1 | 0.026<br>113 | 0        | LAMC2_ITGA1_I<br>TGB1 | LAMC2<br>(ITGA1+ITGB1) | -<br>LAMINI<br>N | ECM-Recep<br>tor      | KEGG: hsa04512                    |

|                |              |             |                 |              |   |                       |                        |               |                       |                |
|----------------|--------------|-------------|-----------------|--------------|---|-----------------------|------------------------|---------------|-----------------------|----------------|
| Tumor_<br>cell | TAM-S<br>PP1 | FN1         | CD44            | 0.025<br>021 | 0 | FN1_CD44              | FN1 - CD44             | FN1           | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | COL9<br>A3  | CD44            | 0.023<br>365 | 0 | COL9A3_CD44           | COL9A3 - CD44          | COLLAG<br>EN  | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | EFNA<br>1   | EPHA1           | 0.021<br>593 | 0 | EFNA1_EPHA1           | EFNA1 - EPHA1          | EPHA          | Cell-Cell<br>Contact  | PMID: 15114347 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMB<br>1   | ITGA3_IT<br>GB1 | 0.021<br>591 | 0 | LAMB1_ITGA3_I<br>TGB1 | LAMB1<br>(ITGA3+ITGB1) | - LAMINI<br>N | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | IL7         | IL7R_IL2<br>RG  | 0.019<br>014 | 0 | IL7_IL7R_IL2RG        | IL7 - (IL7R+IL2RG)     | IL2           | Secreted<br>Signaling | KEGG: hsa04060 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMB<br>1   | ITGA1_IT<br>GB1 | 0.018<br>665 | 0 | LAMB1_ITGA1_I<br>TGB1 | LAMB1<br>(ITGA1+ITGB1) | - LAMINI<br>N | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | SCGB<br>3A2 | MARCO           | 0.018<br>417 | 0 | SCGB3A2_MAR<br>CO     | SCGB3A2<br>MARCO       | - UGRP1       | Secreted<br>Signaling | PMID: 12847263 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMA<br>3   | ITGA3_IT<br>GB1 | 0.017<br>782 | 0 | LAMA3_ITGA3_I<br>TGB1 | LAMA3<br>(ITGA3+ITGB1) | - LAMINI<br>N | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | CDH1        | CDH1            | 0.015<br>384 | 0 | CDH1_CDH1             | CDH1 - CDH1            | CDH           | Cell-Cell<br>Contact  | KEGG: hsa04514 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMA<br>3   | ITGA1_IT<br>GB1 | 0.015<br>364 | 0 | LAMA3_ITGA1_I<br>TGB1 | LAMA3<br>(ITGA1+ITGB1) | - LAMINI<br>N | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | F11R        | F11R            | 0.015<br>24  | 0 | F11R_F11R             | F11R - F11R            | JAM           | Cell-Cell<br>Contact  | KEGG: hsa04514 |
| Tumor_<br>cell | TAM-S<br>PP1 | SEMA<br>3C  | NRP1_NR<br>P2   | 0.014<br>757 | 0 | SEMA3C_NRP1_<br>NRP2  | SEMA3C<br>(NRP1+NRP2)  | - SEMA3       | Secreted<br>Signaling | PMID: 27533782 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMA<br>5   | ITGA3_IT<br>GB1 | 0.014<br>699 | 0 | LAMA5_ITGA3_I<br>TGB1 | LAMA5<br>(ITGA3+ITGB1) | - LAMINI<br>N | ECM-Recep<br>tor      | KEGG: hsa04512 |

|                |              |            |                 |              |          |                        |                         |   |              |                       |                |
|----------------|--------------|------------|-----------------|--------------|----------|------------------------|-------------------------|---|--------------|-----------------------|----------------|
| Tumor_<br>cell | TAM-S<br>PP1 | LAMC<br>1  | ITGA3_IT<br>GB1 | 0.014<br>143 | 0        | LAMC1_ITGA3_I<br>TGB1  | LAMC1<br>(ITGA3+ITGB1)  | - | LAMINI<br>N  | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | COL4<br>A2 | CD44            | 0.013<br>765 | 0        | COL4A2_CD44            | COL4A2 - CD44           |   | COLLAG<br>EN | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | ANXA<br>1  | FPR2_LX<br>A4   | 0.013<br>005 | 0.<br>03 | ANXA1_FPR2_L<br>XA4    | ANXA1<br>(FPR2+LXA4)    | - | ANXA1        | Cell-Cell<br>Contact  | PMID: 22610094 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMA<br>5  | ITGA1_IT<br>GB1 | 0.012<br>695 | 0        | LAMA5_ITGA1_I<br>TGB1  | LAMA5<br>(ITGA1+ITGB1)  | - | LAMINI<br>N  | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMB<br>3  | ITGAV_IT<br>GB8 | 0.012<br>608 | 0        | LAMB3_ITGAV_I<br>TGB8  | LAMB3<br>(ITGAV+ITGB8)  | - | LAMINI<br>N  | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | SEMA<br>3C | NRP1_PL<br>XNA3 | 0.012<br>23  | 0        | SEMA3C_NRP1_<br>PLXNA3 | SEMA3C<br>(NRP1+PLXNA3) | - | SEMA3        | Secreted<br>Signaling | PMID: 27533782 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMC<br>1  | ITGA1_IT<br>GB1 | 0.012<br>214 | 0        | LAMC1_ITGA1_I<br>TGB1  | LAMC1<br>(ITGA1+ITGB1)  | - | LAMINI<br>N  | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | COL1<br>A1 | CD44            | 0.012<br>179 | 0        | COL1A1_CD44            | COL1A1 - CD44           |   | COLLAG<br>EN | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | THBS<br>1  | ITGA3_IT<br>GB1 | 0.011<br>853 | 0.<br>04 | THBS1_ITGA3_I<br>TGB1  | THBS1<br>(ITGA3+ITGB1)  | - | THBS         | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | CCL15      | CCR1            | 0.011<br>573 | 0        | CCL15_CCR1             | CCL15 - CCR1            |   | CCL          | Secreted<br>Signaling | KEGG: hsa04060 |
| Tumor_<br>cell | TAM-S<br>PP1 | SEMA<br>3C | PLXND1          | 0.010<br>489 | 0        | SEMA3C_PLXN<br>D1      | SEMA3C<br>PLXND1        | - | SEMA3        | Secreted<br>Signaling | PMID: 27533782 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMB<br>2  | ITGA3_IT<br>GB1 | 0.010<br>397 | 0        | LAMB2_ITGA3_I<br>TGB1  | LAMB2<br>(ITGA3+ITGB1)  | - | LAMINI<br>N  | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMC<br>2  | ITGAV_IT<br>GB8 | 0.010<br>305 | 0        | LAMC2_ITGAV_I<br>TGB8  | LAMC2<br>(ITGAV+ITGB8)  | - | LAMINI<br>N  | ECM-Recep<br>tor      | KEGG: hsa04512 |

|        |       |      |          |       |   |               |               |   |        |           |                |
|--------|-------|------|----------|-------|---|---------------|---------------|---|--------|-----------|----------------|
| Tumor_ | TAM-S | SEMA | NRP2_PL  | 0.009 | 0 | SEMA3C_NRP2_  | SEMA3C        | - | SEMA3  | Secreted  | PMID: 27533782 |
| cell   | PP1   | 3C   | XNA3     | 159   |   | PLXNA3        | (NRP2+PLXNA3) |   |        | Signaling |                |
| Tumor_ | TAM-S | LAMB | ITGA1_IT | 0.008 | 0 | LAMB2_ITGA1_I | LAMB2         | - | LAMINI | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | 2    | GB1      | 974   |   | TGB1          | (ITGA1+ITGB1) |   | N      | tor       |                |
| Tumor_ | TAM-S | SEMA | NRP1_PL  | 0.008 | 0 | SEMA3B_NRP1_  | SEMA3B        | - | SEMA3  | Secreted  | PMID: 27533782 |
| cell   | PP1   | 3B   | XNA3     | 735   |   | PLXNA3        | (NRP1+PLXNA3) |   |        | Signaling |                |
| Tumor_ | TAM-S | FN1  | ITGA5_IT | 0.008 | 0 | FN1_ITGA5_ITG | FN1           | - | FN1    | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   |      | GB1      | 627   |   | B1            | (ITGA5+ITGB1) |   |        | tor       |                |
| Tumor_ | TAM-S | COL1 |          | 0.008 | 0 | COL1A2_CD44   | COL1A2 - CD44 |   | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A2   | CD44     | 216   |   |               |               |   | EN     | tor       |                |
| Tumor_ | TAM-S | FN1  | SDC4     | 0.008 | 0 | FN1_SDC4      | FN1 - SDC4    |   | FN1    | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   |      |          | 019   |   |               |               |   |        | tor       |                |
| Tumor_ | TAM-S | COL9 | SDC4     | 0.007 | 0 | COL9A3_SDC4   | COL9A3 - SDC4 |   | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A3   |          | 479   |   |               |               |   | EN     | tor       |                |
| Tumor_ | TAM-S | LAMB | ITGAV_IT | 0.007 | 0 | LAMB1_ITGAV_I | LAMB1         | - | LAMINI | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | 1    | GB8      | 332   |   | TGB8          | (ITGAV+ITGB8) |   | N      | tor       |                |
| Tumor_ | TAM-S | COL4 |          | 0.007 | 0 | COL4A1_CD44   | COL4A1 - CD44 |   | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A1   | CD44     | 068   |   |               |               |   | EN     | tor       |                |
| Tumor_ | TAM-S | SEMA | NRP2_PL  | 0.006 | 0 | SEMA3B_NRP2_  | SEMA3B        | - | SEMA3  | Secreted  | PMID: 27533782 |
| cell   | PP1   | 3B   | XNA3     | 536   |   | PLXNA3        | (NRP2+PLXNA3) |   |        | Signaling |                |
| Tumor_ | TAM-S | EFNB | EPHB4    | 0.006 | 0 | EFNB2_EPHB4   | EFNB2 - EPHB4 |   | EPHB   | Cell-Cell | PMID: 15114347 |
| cell   | PP1   | 2    |          | 111   |   |               |               |   |        | Contact   |                |
| Tumor_ | TAM-S | LAMA | ITGAV_IT | 0.006 | 0 | LAMA3_ITGAV_  | LAMA3         | - | LAMINI | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | 3    | GB8      | 023   |   | ITGB8         | (ITGAV+ITGB8) |   | N      | tor       |                |
| Tumor_ | TAM-S | EFNB | EPHB4    | 0.005 | 0 | EFNB1_EPHB4   | EFNB1 - EPHB4 |   | EPHB   | Cell-Cell | PMID: 15114347 |
| cell   | PP1   | 1    |          | 925   |   |               |               |   |        | Contact   |                |

|                |              |            |                 |              |          |                       |                        |               |                       |                |
|----------------|--------------|------------|-----------------|--------------|----------|-----------------------|------------------------|---------------|-----------------------|----------------|
| Tumor_<br>cell | TAM-S<br>PP1 | HBEG<br>F  | EGFR            | 0.005<br>906 | 0        | HBEGF_EGFR            | HBEGF - EGFR           | EGF           | Secreted<br>Signaling | KEGG: hsa04012 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMA<br>5  | ITGAV_IT<br>GB8 | 0.004<br>968 | 0        | LAMA5_ITGAV_<br>ITGB8 | LAMA5<br>(ITGAV+ITGB8) | - LAMINI<br>N | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | AREG       | EGFR            | 0.004<br>856 | 0        | AREG_EGFR             | AREG - EGFR            | EGF           | Secreted<br>Signaling | KEGG: hsa04012 |
| Tumor_<br>cell | TAM-S<br>PP1 | JAG1       | NOTCH2          | 0.004<br>809 | 0        | JAG1_NOTCH2           | JAG1 - NOTCH2          | NOTCH         | Cell-Cell<br>Contact  | PMID: 22353464 |
| Tumor_<br>cell | TAM-S<br>PP1 | LAMC<br>1  | ITGAV_IT<br>GB8 | 0.004<br>779 | 0        | LAMC1_ITGAV_I<br>TGB8 | LAMC1<br>(ITGAV+ITGB8) | - LAMINI<br>N | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | GAS6       | TYRO3           | 0.004<br>775 | 0        | GAS6_TYRO3            | GAS6 - TYRO3           | GAS           | Secreted<br>Signaling | PMID: 27801848 |
| Tumor_<br>cell | TAM-S<br>PP1 | ULBP<br>1  | KLRK1_H<br>CST  | 0.004<br>555 | 0        | ULBP1_KLRK1_<br>HCST  | ULBP1<br>(KLRK1+HCST)  | - NKG2D       | Cell-Cell<br>Contact  | PMID: 24223577 |
| Tumor_<br>cell | TAM-S<br>PP1 | CD6        | ALCAM           | 0.004<br>517 | 0.<br>03 | CD6_ALCAM             | CD6 - ALCAM            | CD6           | Cell-Cell<br>Contact  | PMID: 23602662 |
| Tumor_<br>cell | TAM-S<br>PP1 | COL4<br>A2 | SDC4            | 0.004<br>377 | 0        | COL4A2_SDC4           | COL4A2 - SDC4          | COLLAG<br>EN  | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | FN1        | ITGAV_IT<br>GB1 | 0.004<br>256 | 0.<br>01 | FN1_ITGAV_ITG<br>B1   | FN1<br>(ITGAV+ITGB1)   | - FN1         | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | EFNA<br>4  | EPHA1           | 0.003<br>966 | 0        | EFNA4_EPHA1           | EFNA4 - EPHA1          | EPHA          | Cell-Cell<br>Contact  | PMID: 15114347 |
| Tumor_<br>cell | TAM-S<br>PP1 | COL1<br>A1 | SDC4            | 0.003<br>868 | 0        | COL1A1_SDC4           | COL1A1 - SDC4          | COLLAG<br>EN  | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | DLL4       | NOTCH2          | 0.003<br>585 | 0        | DLL4_NOTCH2           | DLL4 - NOTCH2          | NOTCH         | Cell-Cell<br>Contact  | PMID: 22353464 |

|        |       |      |          |       |    |               |                |   |        |           |                 |
|--------|-------|------|----------|-------|----|---------------|----------------|---|--------|-----------|-----------------|
| Tumor_ | TAM-S | LAMB | ITGAV_IT | 0.003 | 0  | LAMB2_ITGAV_I | LAMB2          | - | LAMINI | ECM-Recep | KEGG: hsa04512  |
| cell   | PP1   | 2    | GB8      | 504   |    | TGB8          | (ITGAV+ITGB8)  |   | N      | tor       |                 |
| Tumor_ | TAM-S | AREG | EGFR_ER  | 0.003 | 0. | AREG_EGFR_ER  | AREG           | - | EGF    | Secreted  | KEGG: hsa04012  |
| cell   | PP1   |      | BB2      | 448   | 01 | BB2           | (EGFR+ERBB2)   |   |        | Signaling |                 |
| Tumor_ | TAM-S | GAS6 | AXL      | 0.003 | 0. | GAS6_AXL      | GAS6 - AXL     |   | GAS    | Secreted  | PMID: 27801848  |
| cell   | PP1   |      |          | 199   | 01 |               |                |   |        | Signaling |                 |
| Tumor_ | TAM-S | FN1  | ITGA3_IT | 0.003 | 0. | FN1_ITGA3_ITG | FN1            | - | FN1    | ECM-Recep | KEGG: hsa04512  |
| cell   | PP1   |      | GB1      | 126   | 01 | B1            | (ITGA3+ITGB1)  |   |        | tor       |                 |
| Tumor_ | TAM-S | KITL | KIT      | 0.002 | 0  | KITL_KIT      | KITL - KIT     |   | KIT    | Secreted  | KEGG: hsa04080  |
| cell   | PP1   | G    |          | 978   |    |               |                |   |        | Signaling |                 |
| Tumor_ | TAM-S | COL9 | ITGA3_IT | 0.002 | 0  | COL9A3_ITGA3_ | COL9A3         | - | COLLAG | ECM-Recep | KEGG: hsa04512  |
| cell   | PP1   | A3   | GB1      | 915   |    | ITGB1         | (ITGA3+ITGB1)  |   | EN     | tor       |                 |
| Tumor_ | TAM-S | PGF  | FLT1     | 0.002 | 0  | PGF_VEGFR1    | PGF - VEGFR1   |   | VEGF   | Secreted  | KEGG: hsa04370; |
| cell   | PP1   |      |          | 859   |    |               |                |   |        | Signaling | PMID: 16633338  |
| Tumor_ | TAM-S | TNC  | SDC4     | 0.002 | 0  | TNC_SDC4      | TNC - SDC4     |   | TENASC | ECM-Recep | KEGG: hsa04512  |
| cell   | PP1   |      |          | 799   |    |               |                |   | IN     | tor       |                 |
| Tumor_ | TAM-S | SEMA | PLXNB2   | 0.002 | 0  | SEMA4G_PLXN   | SEMA4G         | - | SEMA4  | Cell-Cell | PMID: 27533782  |
| cell   | PP1   | 4G   |          | 666   |    | B2            | PLXNB2         |   |        | Contact   |                 |
| Tumor_ | TAM-S | COL1 | SDC4     | 0.002 | 0  | COL1A2_SDC4   | COL1A2 - SDC4  |   | COLLAG | ECM-Recep | KEGG: hsa04512  |
| cell   | PP1   | A2   |          | 603   |    |               |                |   | EN     | tor       |                 |
| Tumor_ | TAM-S | EFNA | EPHA1    | 0.002 | 0  | EFNA3_EPHA1   | EFNA3 - EPHA1  |   | EPHA   | Cell-Cell | PMID: 15114347  |
| cell   | PP1   | 3    |          | 57    |    |               |                |   |        | Contact   |                 |
| Tumor_ | TAM-S | VEGF | FLT1     | 0.002 | 0  | VEGFB_VEGFR1  | VEGFB - VEGFR1 |   | VEGF   | Secreted  | KEGG: hsa04370; |
| cell   | PP1   | B    |          | 543   |    |               |                |   |        | Signaling | PMID: 16633338  |
| Tumor_ | TAM-S | COL9 | ITGA1_IT | 0.002 | 0  | COL9A3_ITGA1_ | COL9A3         | - | COLLAG | ECM-Recep | KEGG: hsa04512  |
| cell   | PP1   | A3   | GB1      | 513   |    | ITGB1         | (ITGA1+ITGB1)  |   | EN     | tor       |                 |

|                |              |            |                 |              |          |                        |                         |                |                       |                |
|----------------|--------------|------------|-----------------|--------------|----------|------------------------|-------------------------|----------------|-----------------------|----------------|
| Tumor_<br>cell | TAM-S<br>PP1 | COL4<br>A1 | SDC4            | 0.002<br>237 | 0        | COL4A1_SDC4            | COL4A1 - SDC4           | COLLAG<br>EN   | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | COL4<br>A2 | ITGA3_IT<br>GB1 | 0.001<br>703 | 0        | COL4A2_ITGA3_<br>ITGB1 | COL4A2<br>(ITGA3+ITGB1) | - COLLAG<br>EN | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | PROS<br>1  | TYRO3           | 0.001<br>689 | 0        | PROS1_TYRO3            | PROS1 - TYRO3           | PROS           | Secreted<br>Signaling | PMID: 30501104 |
| Tumor_<br>cell | TAM-S<br>PP1 | COL1<br>A1 | ITGA3_IT<br>GB1 | 0.001<br>504 | 0        | COL1A1_ITGA3_<br>ITGB1 | COL1A1<br>(ITGA3+ITGB1) | - COLLAG<br>EN | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | ULBP<br>1  | KLRK1           | 0.001<br>49  | 0        | ULBP1_KLRK1            | ULBP1 - KLRK1           | MHC-I          | Cell-Cell<br>Contact  | PMID: 24223577 |
| Tumor_<br>cell | TAM-S<br>PP1 | COL4<br>A2 | ITGA1_IT<br>GB1 | 0.001<br>468 | 0        | COL4A2_ITGA1_<br>ITGB1 | COL4A2<br>(ITGA1+ITGB1) | - COLLAG<br>EN | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | COL1<br>A1 | ITGA1_IT<br>GB1 | 0.001<br>297 | 0        | COL1A1_ITGA1_<br>ITGB1 | COL1A1<br>(ITGA1+ITGB1) | - COLLAG<br>EN | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | SEMA<br>5A | PLXNA3          | 0.001<br>233 | 0        | SEMA5A_PLXN<br>A3      | SEMA5A<br>PLXNA3        | - SEMA5        | Cell-Cell<br>Contact  | PMID: 27533782 |
| Tumor_<br>cell | TAM-S<br>PP1 | PROS<br>1  | AXL             | 0.001<br>13  | 0        | PROS1_AXL              | PROS1 - AXL             | PROS           | Secreted<br>Signaling | PMID: 29531161 |
| Tumor_<br>cell | TAM-S<br>PP1 | FN1        | ITGAV_IT<br>GB8 | 0.001<br>048 | 0.<br>04 | FN1_ITGAV_ITG<br>B8    | FN1<br>(ITGAV+ITGB8)    | - FN1          | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | COL1<br>A2 | ITGA3_IT<br>GB1 | 0.001<br>011 | 0.<br>01 | COL1A2_ITGA3_<br>ITGB1 | COL1A2<br>(ITGA3+ITGB1) | - COLLAG<br>EN | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | COL9<br>A3 | ITGAV_IT<br>GB8 | 0.000<br>977 | 0        | COL9A3_ITGAV_<br>ITGB8 | COL9A3<br>(ITGAV+ITGB8) | - COLLAG<br>EN | ECM-Recep<br>tor      | KEGG: hsa04512 |
| Tumor_<br>cell | TAM-S<br>PP1 | COL1<br>A2 | ITGA1_IT<br>GB1 | 0.000<br>872 | 0.<br>01 | COL1A2_ITGA1_<br>ITGB1 | COL1A2<br>(ITGA1+ITGB1) | - COLLAG<br>EN | ECM-Recep<br>tor      | KEGG: hsa04512 |

|        |       |       |          |       |    |               |                |   |        |           |                |
|--------|-------|-------|----------|-------|----|---------------|----------------|---|--------|-----------|----------------|
| Tumor_ | TAM-S | COL4  | ITGA3_IT | 0.000 | 0  | COL4A1_ITGA3_ | COL4A1         | - | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A1    | GB1      | 869   |    | ITGB1         | (ITGA3+ITGB1)  |   | EN     | tor       |                |
| Tumor_ | TAM-S | COL9  | ITGA11_I | 0.000 | 0  | COL9A3_ITGA11 | COL9A3         | - | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A3    | TGB1     | 793   |    | _ITGB1        | (ITGA11+ITGB1) |   | EN     | tor       |                |
| Tumor_ | TAM-S | COL4  | ITGA1_IT | 0.000 | 0  | COL4A1_ITGA1_ | COL4A1         | - | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A1    | GB1      | 749   |    | ITGB1         | (ITGA1+ITGB1)  |   | EN     | tor       |                |
| Tumor_ | TAM-S | COL4  | ITGAV_IT | 0.000 | 0  | COL4A2_ITGAV_ | COL4A2         | - | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A2    | GB8      | 57    |    | ITGB8         | (ITGAV+ITGB8)  |   | EN     | tor       |                |
| Tumor_ | TAM-S | ENTP  | ADORA2   | 0.000 | 0  | ENTPD1_ADOR   | ENTPD1         | - | CD39   | Cell-Cell | PMID: 21677139 |
| cell   | PP1   | D1    | A        | 529   |    | A2A           | ADORA2A        |   |        | Contact   |                |
| Tumor_ | TAM-S | COL1  | ITGAV_IT | 0.000 | 0  | COL1A1_ITGAV_ | COL1A1         | - | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A1    | GB8      | 504   |    | ITGB8         | (ITGAV+ITGB8)  |   | EN     | tor       |                |
| Tumor_ | TAM-S | CAD   | CADM1    | 0.000 | 0. | CADM1_CADM1   | CADM1 - CADM1  |   | CADM   | Cell-Cell | PMID: 24503895 |
| cell   | PP1   | M1    |          | 463   | 03 |               |                |   |        | Contact   |                |
| Tumor_ | TAM-S | COL4  | ITGA11_I | 0.000 | 0  | COL4A2_ITGA11 | COL4A2         | - | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A2    | TGB1     | 463   |    | _ITGB1        | (ITGA11+ITGB1) |   | EN     | tor       |                |
| Tumor_ | TAM-S | COL1  | ITGA11_I | 0.000 | 0  | COL1A1_ITGA11 | COL1A1         | - | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A1    | TGB1     | 409   |    | _ITGB1        | (ITGA11+ITGB1) |   | EN     | tor       |                |
| Tumor_ | TAM-S | COL1  | ITGAV_IT | 0.000 | 0. | COL1A2_ITGAV_ | COL1A2         | - | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A2    | GB8      | 339   | 01 | ITGB8         | (ITGAV+ITGB8)  |   | EN     | tor       |                |
| Tumor_ | TAM-S | NECTI | CD96     | 0.000 | 0  | NECTIN1_CD96  | NECTIN1 - CD96 |   | NECTIN | Cell-Cell | PMID: 23027581 |
| cell   | PP1   | N1    |          | 332   |    |               |                |   |        | Contact   |                |
| Tumor_ | TAM-S | COL4  | ITGAV_IT | 0.000 | 0  | COL4A1_ITGAV_ | COL4A1         | - | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A1    | GB8      | 291   |    | ITGB8         | (ITGAV+ITGB8)  |   | EN     | tor       |                |
| Tumor_ | TAM-S | COL1  | ITGA11_I | 0.000 | 0. | COL1A2_ITGA11 | COL1A2         | - | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A2    | TGB1     | 275   | 04 | _ITGB1        | (ITGA11+ITGB1) |   | EN     | tor       |                |

|        |       |      |          |       |   |               |                |   |        |           |                |
|--------|-------|------|----------|-------|---|---------------|----------------|---|--------|-----------|----------------|
| Tumor_ | TAM-S | COL4 | ITGA11_I | 0.000 | 0 | COL4A1_ITGA11 | COL4A1         | - | COLLAG | ECM-Recep | KEGG: hsa04512 |
| cell   | PP1   | A1   | TGB1     | 236   |   | _ITGB1        | (ITGA11+ITGB1) |   | EN     | tor       |                |

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1 **Supplementary Table S2. Information of the clinical tissue microarray sample (n=42).**

| <b>Characteristic</b>                                | <b>CRC, N = 38<sup>1</sup></b> | <b>Control, N = 4<sup>1</sup></b> |
|------------------------------------------------------|--------------------------------|-----------------------------------|
| Age                                                  | 54 (50, 68)                    | NA                                |
| Unknown                                              | 5                              | 4                                 |
| Gender                                               |                                |                                   |
| female                                               | 17 (46%)                       | 0 (0%)                            |
| male                                                 | 20 (54%)                       | 4 (100%)                          |
| Unknown                                              | 1                              | 0                                 |
| Tissue source                                        |                                |                                   |
| colon                                                | 32 (84%)                       | 4 (100%)                          |
| Metastasis-liver                                     | 3 (7.9%)                       | 0 (0%)                            |
| Metastasis-lung                                      | 1 (2.6%)                       | 0 (0%)                            |
| Metastasis-ovarian                                   | 2 (5.3%)                       | 0 (0%)                            |
| Tissue Type                                          |                                |                                   |
| normal tissue                                        | 0 (0%)                         | 4 (100%)                          |
| adenocarcinoma                                       | 26 (68%)                       | 0 (0%)                            |
| tubular adenomas                                     | 3 (7.9%)                       | 0 (0%)                            |
| tubulovillous adenoma with intraepithelial neoplasia | 3 (7.9%)                       | 0 (0%)                            |
| metastatic adenocarcinoma                            | 6 (16%)                        | 0 (0%)                            |
| Pathological_staging                                 |                                |                                   |
| II grade                                             | 11 (61%)                       |                                   |
| II-III grade                                         | 2 (11%)                        |                                   |
| low grade                                            | 5 (28%)                        |                                   |
| Unknown                                              | 20                             |                                   |
| Metastasis                                           |                                |                                   |
| No                                                   | 27 (71%)                       |                                   |

| Characteristic   | CRC, N = 38 <sup>1</sup> | Control, N = 4 <sup>1</sup> |
|------------------|--------------------------|-----------------------------|
| Liver            | 8 (21%)                  |                             |
| Lung             | 1 (2.6%)                 |                             |
| ovarian          | 2 (5.3%)                 |                             |
| Unknown          | 0                        |                             |
| T                |                          |                             |
| not applicable   | 0 (0%)                   |                             |
| T2               | 2 (20%)                  |                             |
| T3               | 8 (80%)                  |                             |
| Unknown          | 28                       |                             |
| N                |                          |                             |
| N0               | 9 (35%)                  |                             |
| N1a              | 7 (27%)                  |                             |
| N1b              | 3 (12%)                  |                             |
| N2a              | 3 (12%)                  |                             |
| N2b              | 4 (15%)                  |                             |
| not applicable   | 0 (0%)                   |                             |
| Unknown          | 12                       |                             |
| M                |                          |                             |
| M0               | 21 (66%)                 |                             |
| M1               | 6 (19%)                  |                             |
| M1a              | 5 (16%)                  |                             |
| not applicable   | 0 (0%)                   |                             |
| Unknown          | 6                        |                             |
| AJCC-7th-staging |                          |                             |
| 1                | 2 (6.3%)                 |                             |
| 2                | 5 (16%)                  |                             |

| Characteristic | CRC, N = 38 <sup>1</sup>    | Control, N = 4 <sup>1</sup> |
|----------------|-----------------------------|-----------------------------|
| 2A             | 2 (6.3%)                    |                             |
| 3              | 8 (25%)                     |                             |
| 3B             | 4 (13%)                     |                             |
| 4              | 6 (19%)                     |                             |
| 4A             | 5 (16%)                     |                             |
| Unknown        | 6                           |                             |
| Tumor_volumns  | 50 (25, 116)cm <sup>3</sup> |                             |
| Unknown        | 6                           |                             |

<sup>1</sup>Median (Interquartile range); n (%)

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