**Fig. S1 Cell composition and cell cycling analysis.** (A) Quality control of scRNA-seq analysis. (B-D) u-MAP plot showing original clusters (B), clusters from PDAC and normal pancreatic specimens (C), clusters from various specimens (D). (E-G) The proportion of cell populations for PDAC vs normal pancreatic specimens (E), normal specimens (F), PDAC specimens (G). (H-J) The proportion of cell cycling state of cell populations for PDAC vs normal pancreatic specimens (H), normal specimens (I), PDAC specimens (J). (K) The proportion of cell cycling state of endothelial cells in PDAC and normal pancreatic specimens. (L) The proportion of cell cycling state of cell
Fig.S2 Endothelial cells in PDAC were related angiogenesis and hypoxia. (A-C) Gene ontology analysis showing molecular function (A), KEGG pathway (B), disease (C) terms of upregulated genes in Endothelial 1, colorful dots represented the level of statistical significance. (D) The top hallmark terms in GSEA analysis. (E) Hypoxic incubator chamber. (F) Multilayer culture flask was used to expand cells in a large-scale.
**Fig. S3** Exosomal small RNA-seq and conventional RNA-seq of HUVEC after exosomes treatment. (A) HUVEC permeability was tested using FITC-dextran with 70000 MW. (B) The transendothelial cells ability of tumor cells labeled with Hoechst33342 was tested. Blue dot represented the nucle of tumor cells. (C) The basic results of exosomal small RNA-seq. (D–E) Volcano plot showing differential expression miRNAs between No_HPNE_Exos and No_BxPC-3_Exos (D), No_HPNE_Exos and Hp_BxPC-3_Exos (E). (F) Dot plot showing differential expression miRNAs between No_BxPC-3_Exos and Hp_BxPC-3_Exos. (G) The basic results of RNA-seq of HUVEC.

### Table 1: Exosomal small RNA-seq Results

| Samples           | Total Reads | Mapped Reads | Q30(%) | Known miRNAs | Novel miRNAs | Total miRNAs |
|-------------------|-------------|--------------|--------|--------------|--------------|--------------|
| HPNE exo          | 27495472    | 674811       | 96.79  | 815          | 25           | 840          |
| Normoxic BxPC-3 exo | 15023843    | 2005010      | 96.58  | 797          | 22           | 819          |
| Hypoxic BxPC-3 exo | 8208967     | 829732       | 97.27  | 643          | 18           | 661          |

### Table 2: RNA-seq Results

| Samples           | Total Clean Reads (M) | Mapped Reads (%) | Q30(%) | Clean Reads Ratio (%) |
|-------------------|-----------------------|------------------|--------|-----------------------|
| WT                | 45.19                 | 75.7             | 91.9   | 95.49                 |
| HPNE exo          | 45.5                  | 74.96            | 92.16  | 96.14                 |
| Normoxic BxPC-3 exo | 45.17                 | 76.75            | 91.97  | 95.59                 |
| Hypoxic BxPC-3 exo | 45.31                 | 75.54            | 91.72  | 95.73                 |
Table S1. Clinicopathologic characteristics of specimens by scRNA-seq analysis.

| D | Diagnosis                        | Sex | Age (Y) | CA199 (U/ml) | Diabetes | Procedure | Location            | Diameter (mm) | TNM   | AJCC stage |
|---|----------------------------------|-----|---------|--------------|----------|-----------|---------------------|---------------|-------|------------|
| T1| moderately-poorly differentiated PDAC | M   | 64      | 86.0         | N        | LDP       | body                | 26            | T4N2M0 | II         |
| T2| well differentiated PDAC          | M   | 52      | 46.3         | N        | PD        | head                | 20            | T1cN1M0 | II         |
| T3| moderately-poorly differentiated PDAC | F   | 58      | 49.2         | Y        | PD        | uncinate process    | 22            | T2N0M0 | IB         |
| T4| moderately differentiated PDAC    | F   | 72      | 40.4         | Y        | LDP       | body                | 14            | T1cN1M0 | II         |
| T5| well-moderately differentiated PDAC | F   | 65      | 37.0         | Y        | PD        | uncinate process    | 29            | T2N0M0 | IB         |
| T6| moderately-poorly differentiated PDAC | M   | 64      | 155.1        | N        | ODP       | tail                | 91            | T3N0M0 | IIA        |
| T7| moderately differentiated PDAC    | M   | 70      | <0.6         | Y        | ODP       | body                | 80            | T3N1M0 | II         |
| T8| moderately-poorly differentiated PDAC | F   | 66      | 82.5         | N        | PD        | uncinate process    | 17            | T1cN2M0 | III        |
| T9| moderately-poorly differentiated PDAC | M   | 36      | 11.2         | N        | PD        | head                | 26            | T2N0M0 | IIA        |
| T10| poorly differentiated PDAC       | M   | 61      | 972.8        | Y        | PD        | uncinate process    | 40            | T2N1M0 | II         |
| T11| moderately-poorly differentiated PDAC | M   | 51      | 211.1        | N        | ODP       | body and tail       | 76            | T3N1M0 | II         |
| T12| poorly differentiated PDAC       | M   | 54      | 146.1        | N        | PD        | uncinate process    | 50            | T3N2M0 | III        |
| T13| moderately-poorly differentiated PDAC | F   | 58      | 21.9         | Y        | PD        | head                | 30            | T2N1M0 | II         |
| T14| well differentiated PDAC          | F   | 67      | 77           | Y        | PD        | head                | 33            | T2N1M0 | II         |
| T15| well differentiated PDAC          | F   | 54      | 18.4         | N        | LDP       | head                | 23            | T2N1M0 | II         |
| T16| poorly differentiated PDAC       | F   | 56      | 42.9         | N        | LDP       | body                | 30            | T2N1M0 | II         |
| T17| moderately differentiated PDAC    | F   | 71      | 209.3        | N        | LDP       | body and tail       | 30            | T2N0M0 | IB         |
| Case | Tumor Type                  | Gender | Age | Differentiation | Procedure  | Site    | Stage | Location        | Margin | T Status | N Status | Stage  |
|------|----------------------------|--------|-----|----------------|------------|---------|-------|-----------------|--------|----------|----------|--------|
| T18  | moderately-poorly differentiated PDAC | F      | 68  | Y              | ODP        | body    | 28    | T2N0M0          | IB     |          |          |        |
| T19  | moderately-poorly differentiated PDAC | F      | 59  | Y              | LPD        | head    | 35    | T2N0M0          | IB     |          |          |        |
| T20  | moderately differentiated PDAC      | M      | 59  | N              | PD         | head    | 43    | T3N1M0          | IIB    |          |          |        |
| T21  | moderately-poorly differentiated PDAC | M      | 59  | N              | LPD        | head    | 35    | T2N0M0          | IB     |          |          |        |
| T22  | moderately differentiated PDAC      | F      | 67  | N              | ODP        | body    | 27    | T2N0M0          | IB     |          |          |        |
| T23  | moderately-poorly differentiated PDAC | M      | 54  | N              | PD         | head    | 27    | T2N1M0          | IIB    |          |          |        |
| T24  | moderately differentiated PDAC      | F      | 44  | N              | PD         | head    | 20    | T1eN0M0         | IB     |          |          |        |
| N1   | normal pancreas/mucinous cystic neoplasia | F      | 64  | N              | ODP        | tail    | 50    | NA             | NA     |          |          |        |
| N2   | normal pancreas/small intestine papillary adenocarcinoma | M      | 55  | N              | PPPD       | descending duodenum | 11 | NA | NA |        |
| N3   | normal pancreas/duodenal intraepithelial neoplasia | M      | 50  | N              | PD         | descending duodenum | 20 | NA | NA |        |
| N4   | normal pancreas/pancreatic neuroendocrine tumor | M      | 53  | N              | LDP        | body and tail | 40 | NA | NA |        |
| N5   | normal pancreas/serous cystic neoplasia | F      | 52  | N              | LDP        | body and tail | 24 | NA | NA |        |
| N6   | normal pancreas/solid pseudopapillary tumor | F      | 31  | N              | ODP        | body    | 22    | NA             | NA     |          |          |        |
| N7   | normal pancreas/mucinous cystic neoplasia | F      | 42  | N              | LDP        | tail    | 94    | NA             | NA     |          |          |        |
| N8   | normal pancreas/solid pseudopapillary tumor | M      | 41  | N              | LDP        | body and tail | 76 | NA | NA |        |
| N9   | normal pancreas/pancreatic neuroendocrine tumor | M      | 34  | N              | LDP        | tail    | 22    | NA             | NA     |          |          |        |
| N10  | normal pancreas/choledochal neuroendocrine tumors | F      | 65  | N              | PD         | common bile duct | NA | T3N0M0 | IIA |        |
| N11  | normal pancreas/solid pseudopapillary tumor | F      | 30  | N              | LDP        | body    | 33    | NA             | NA     |          |          |        |

ODP, Open distal pancreatectomy; LPD, Laparoscopic distal pancreatectomy; PD, Pancreatoduodenectomy; LPD, Laparoscopic pancreatoduodenectomy; PPPD, Pylorus preserved pancreatoduodenectomy.
Table S2. Signature genes for clusters identification.

| Subpopulations   | Signature genes                                      |
|------------------|------------------------------------------------------|
| Ductal Cell      | AMBP, CFTR, MMP7, SOX9, LCN2, KRT18, KRT8, TFF2, FXYD2, TSPAN8 |
| Macrophage       | AIF1, CD68                                            |
| B Cell           | MS4A1, VPREB3, CD79A, CD79B                          |
| Endothelial Cell | CDH5, RAMP2, PLVAP, VWF                             |
| Stellate Cell    | RGS5, NDUFA4L2                                       |
| T Cell           | CD3D, CD3E, CD2                                      |
| Fibroblast       | LUM, COL1A1, SFRP2, COL3A1, DCN                       |
| Acinar           | PRSS1, CTRB2, REG1A, REG1B                           |
| Endocrine        | CHGB, CHGA, PCSK1N, INS                              |

Table S3. Clinicopathologic characteristics of specimens for miR-30b-5p detection.

| ID      | Diagnosis                   | Sex | Age (Y) | BMI  | CA199 (U/ml) | TNM | AJCC stage | Diabetes |
|---------|-----------------------------|-----|---------|------|--------------|-----|------------|----------|
| PKUFH-1 | well differentiated PDAC    | F   | 61      | 23.69| 411.2        | T2N2M0 | III        | N        |
| PKUFH-2 | moderately-poorly differentiated PDAC | M   | 63      | 22.83| >1000        | T2N2M1 | IV         | N        |
| PKUFH-3 | moderately differentiated PDAC | F   | 65      | 18.38| 302.1        | T2N1M0 | III        | N        |
| PKUFH-4 | moderately-poorly differentiated PDAC | M   | 65      | 23.7 | >1000        | T1N2M0 | III        | N        |
| PKUFH-5 | moderately-poorly differentiated PDAC | M   | 54      | 29   | 277.3        | T3N2M0 | III        | N        |
| PKUFH-6 | moderately differentiated PDAC | F   | 70      | 24.89| >1000        | T2N0M0 | IB         | N        |
| PKUFH-7 | poorly differentiated PDAC  | F   | 84      | 27.3 | 249.2        | T2N1M0 | IB         | N        |
| PKUFH-8 | moderately differentiated PDAC | M   | 60      | 25.73| 472.2        | T2N1M0 | IB         | N        |
| PKUFH-9 | moderately differentiated PDAC | F   | 67      | 27.16| 108.4        | T2N2M0 | III        | Y        |
| PKUFH-10| poorly differentiated PDAC  | M   | 61      | 24.5 | 203.5        | T3N1M0 | III        | Y        |
| PKUFH-11| moderately-poorly differentiated PDAC | M   | 59      | 24.9 | 28.38        | T4N2M0 | III        | N        |
| PKUFH-12| moderately differentiated PDAC | M   | 70      | 23.16| 432.4        | T2N0M0 | IB         | Y        |
| PKUFH-13| poorly differentiated PDAC  | F   | 89      | 21.27| 213.9        | T2N0M0 | IB         | Y        |
| PKUFH-14| moderately-poorly differentiated PDAC | F   | 62      | 25.17| >1000        | T3N1M0 | IIIB       | Y        |
| PKUFH-15| moderately-poorly differentiated PDAC | M   | 76      | 22.49| 51.43        | T1N2M0 | III        | N        |
| PKUFH-16| moderately differentiated PDAC | M   | 73      | 24.78| 372.4        | T2N1M0 | IB         | N        |
| PKUFH-17| moderately differentiated PDAC | F   | 59      | 24.78| 115.4        | T2N2M0 | III        | Y        |
| PKUFH-18| poorly differentiated PDAC  | M   | 66      | 19.98| 347.5        | T3N1M0 | III        | Y        |
| PKUFH-19| well differentiated PDAC    | F   | 68      | 20.14| 58.78        | T3N2M0 | III        | N        |
| PKUFH-20| moderately differentiated PDAC | F   | 75      | 22.14| >1000        | T2N1M0 | III        | N        |
| PKUFH-21| poorly differentiated PDAC  | F   | 81      | 26.45| 347.9        | T2N1M0 | III        | Y        |
| PKUFH-22| poorly differentiated PDAC  | F   | 62      | 23.67| >1000        | T1N2M0 | III        | Y        |
| PKUFH-23| moderately-poorly differentiated PDAC | M   | 76      | 24.44| 179.3        | T2N1M0 | III        | Y        |
| PKUFH-24| moderately differentiated PDAC | M   | 71      | 27.69| 679.3        | T1N2M0 | III        | N        |