Fig. 4. The effect of SP and/or NK-1R antagonists on cancer cell invasive ability. (A) SP promotes the invasion of pancreatic cancer cells which can be inhibited by NK-1R antagonists: L733, 060 and L-732,138. *P < 0.05 as compared with control group, #P < 0.05 as compared with SP group. SP increases the expression of MMP-2 at mRNA level (B) and protein level (C) that can be counterbalanced by the NK-1R antagonists. *P < 0.05 as compared with control group, #P < 0.05 as compared with SP group.

Fig. 5. **SP promotes neurotropism in BxPC-3 cells.** In the co-culture model, pancreatic cancer cell clusters gradually migrated to the DRG and the neurite outgrowth extended to the clusters from the DRGs that provided an invasive pathway for the clusters (A, original magnification ×40). This trend was enhanced by adding 100 nM SP significantly (B). L-733,060 and L-732,138 could impaire the promoting effect of SP on cancer cell clusters migration and neurite outgrowth (D, F). Adding NK-1R antagonists alone in the co-culture system could also reduce the number of migrated pancreatic cancer cell clusters to the DRG and the length and dencity of neurite outgrowth (C, E). Arrows indicate the outgrowth of neurites. *P < 0.05 as compared with control group, #P < 0.05 as compared with SP group.

Supplementary Fig 1. **The effects of SP on neurites and BxPC-3cells.** SP promotes neurite outgrowth from newborn DRGs in a dose-dependent manner (A: control, B: 5

nM, C: 10 nM, D: 50 nM, E: 100 nM) in co-culture experiments (F). *P < 0.05 as compared with control group. Pancreatic cancer cells gradually migrated to the DRG and formed spike-like structures (G-I, in 0, 5 nM, 10 nM, 50 nM, and 100 nM, respectively). The neurite outgrowth (J, arrow, original magnification ×200) extended to the clusters from the DRGs and provided an invasive path for the clusters (K, arrow, original magnification ×200); pancreatic cancer cell clusters and neurite contact gradually.

Supplementary Figure 1