Despite decades of extensive research into cancer and well-established knowledge of the crucial role of the tumor microenvironment, this disease still remains a leading cause of death worldwide. Recently, cancer-nerve crosstalk in non-neural solid tumor progression has increasingly gained attention as an emerging evidence of cancer aggravation. Current understanding of cancer-nerve crosstalk includes 1) tumor innervation, in which nerve fibers infiltrate solid tumors, and 2) perineural invasion, in which cancer cells invade adjacent nerves and use them as an additional route to metastasis. While numerous studies have shown the evidence of cancer-nerve crosstalk in patient samples and some understanding of potential mechanisms at molecular, cellular and tissue-levels are beginning to emerge, much remains unknown about this under-appreciated yet potentially critical feature of cancer progression. My lab, named Therapeutic Tissue Engineering, in the Department of Biomedical Engineering at the University of Arkansas uses tissue engineering approaches, in particular tissue decellularization techniques, to build in vitro mimics of cancer-nerve crosstalk. This talk will highlight our recent efforts in understanding breast tumor innervation and pancreatic cancer perineural invasion, with a particular focus on metabolism and tumor-glial paracrine signaling via tumor-derived extracellular vesicles (EVs). Our results so far hint that metabolic rewiring of breast cancer cells may regulate neurotrophin secretion, which subsequently drives neurite infiltration, while interleukin-8 in pancreatic cancer-secreted EVs may activate Schwann cells to promote pancreatic cancer cell invasion into the nerves. Continued investigation into cancer-nerve crosstalk may contribute to the development of novel therapeutic strategies to curb metastatic aggravation.