Interaction of cancer cells with diverse cell types in the tumor stroma is today recognized to have a fate-determining role for the progression and outcome of human cancers. Despite the well-described interactions of cancer cells with several stromal components, i.e., inflammatory cells, cancer-associated fibroblasts, endothelial cells, and pericytes, the investigation of their peculiar relationship with neural cells is still at its first footsteps. Pancreatic cancer (PCa) with its abundant stroma represents one of the best-studied examples of a malignant tumor with a mutually trophic interaction between cancer cells and the intratumoral nerves embedded in the desmoplastic stroma. Nerves in PCa are a rich source of neurotrophic factors like nerve growth factor (NGF), glial-cell-derived neurotrophic factor (GDNF), artemin; of neuronal chemokines like fractalkine; and of autonomic neurotransmitters like norepinephrine which can all enhance the invasiveness of PCa cells via matrix-metalloproteinase (MMP) upregulation, trigger neural invasion (NI), and activate pro-survival signaling pathways. Similarly, PCa cells themselves provide intrapancreatic nerves with abundant trophic agents which entail a remarkable neuroplasticity, leading to emergence of more routes for NI and cancer spread, to augmented local neuro-surveillance, neural sensitization, and neuropathic pain. The strong correlation of NI with PCa-associated desmoplasia suggests the potential presence of a
triangular relationship between nerves, PCa cells, and other stromal partners like myofibroblasts and pancreatic stellate cells which generate tumor desmoplasia. Hence, although not a classical hallmark of human cancers, nerve-cancer interactions can be considered as an indispensable sub-class of cancer-stroma interactions in PCa. The present article provides an overview of the so far known nerve-cancer interactions in PCa and illustrates their ominous role in the stromal biology of human PCa.