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Generation and Impact of Neural Invasion in Pancreatic Cancer

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1. Introduction

Pancreatic cancer (PCa) as one of the most aggressive malignancies of mankind has an unparalleled propensity to invade intrapancreatic nerves. This “neural invasion” is therefore one of the most frequent routes of spread in PCa in addition to lymphatic and vascular paths. The major clinical relevance of neural invasion (NI) has triggered intense research efforts to understand its pathomechanisms, and the findings derived from all these studies show how multi-faceted this peculiar route of cancer invasion in PCa is. This chapter is devoted to a thorough description of the characteristics, the pathomechanism and the clinical impact of NI in PCa, with the discussion of the most important pathways which may be future targets for therapeutic intervention.

2. What is “neural invasion” in pancreatic cancer?

NI is a relatively new and more comprehensive term for the traditionally used description “perineural invasion”. In several malignancies, e.g. in the prostate, head and neck, but also several gastrointestinal malignancies, cancer cells are commonly encountered around nerves (Liebig et al., 2009). The frequent presence of cancer cells along the perineurium, the protective sheet around neural fascicles, has hence made pathologists adopt the term “perineural invasion”. Classically, cancer cells which penetrate through the epineurium come to lie between the epineurium and the underlying perineurium and “push” on the nerve fascicles within the constrained intraneural area. The earliest report on perineural invasion stems from Cruveilhier in 1835 where he noticed that cancer cells can actually extend along the invaded nerves (Demir et al., 2010). Interestingly, although pathologists frequently observed perineural invasion in several types of tumors, its role except for serving as an additional path of cancer spread has not been genuinely investigated and understood until 1990s. In his pioneering article on the ultrastructural features of perineural invasion in PCa, Dale Bockman from Augusta, Georgia, USA performed an electron microscopic analysis of invaded nerves in PCa (Bockman et al., 1994). There, he noted that, in contrast with the traditional assumption, PCa cells penetrate through the perineurium and become intimately associated with the interior of nerve fascicles, i.e. axons and Schwann cells (Bockman et al., 1994). These observations made by Bockman during mid-1990s laid the foundation for our understanding and the subsequent research on NI in PCa into the present time.

It should be noted that NI is often used to denote invasion of intrapancreatic nerves (Liu&Lu, 2002). However, it is at the same time a more comprehensive term for intra- as well as extrapancreatic nerve invasion (Bockman et al., 1994; Takahashi et al., 1997; Takahashi et al., 2001; Mitsunaga et al., 2007). In contrast with their European counterparts, several studies from the Far East were devoted to the study of extrapancreatic nerve invasion through collection of specimens from retro- and peripancreatic nerves during autopsy (Nakao et al., 1996; Takahashi et al., 1997; Hirai et al., 2002; Liu&Lu, 2002; Mitsunaga et al., 2007). In those studies, “extrapancreatic nerve invasion” is often used synonymously with NI (Nakao et al., 1996; Takahashi et al., 1997; Hirai et al., 2002; Liu&Lu, 2002; Mitsunaga et al., 2007).

3. What are the specific histological characteristics of NI in PCa?

A review of scientific literature on NI in PCa reveals that NI has mostly been perceived as the presence of PCa on and along the perineurium (Kayahara et al., 2007; Liebig et al., 2009). Recent studies, however, revealed that PCa cells are readily encountered in the endoneural area, i.e. between nerve fascicles, as originally observed by Bockman (Ceyhan et al., 2009). Consequently, subsequent studies applied a scoring system to describe the degree of penetration of PCa cells into intrapancreatic nerves, classifying NI into “no invasion” (score of 0/zero), “perineural invasion” (score of I/one) and “endoneural invasion” (score of II/two) (Ceyhan et al., 2006; Ceyhan et al., 2009; Ceyhan et al., 2011). Importantly, the presence of PCa cells in the interior of nerves should not necessarily be perceived as the invasion of the “endoneurium” which is the connective tissue within nerve fascicles of a nerve. Similarly, invasion around nerves does not directly imply invasion of the “perineurium” as the connective tissue layer encircling nerve fascicles. Rather, “endo-” and “perineural” stand for “between” or “around” nerve fascicles (Figure 1) (Ceyhan et al., 2009; Ceyhan et al., 2011).

Careful examination of PCa tissue specimens also reveals that the presence of NI is not independent of the localization of the nerves within the pancreatic tissue. Particularly, we could demonstrate that NI in ductal adenocarcinoma of the pancreas is detected more frequently in areas with severe desmoplasia (Ceyhan et al., 2009). The reasons for this association between desmoplasia and NI are so far not known. However, it is assumed that the extracellular matrix is a rich source of growth factors which may be trophic upon nerves (Zhu et al., 1999; Demir et al., 2010). Still, NI should not be assumed to be limited to desmoplastic areas. In a histopathological study on the normal pancreatic regions of PCa patients who underwent pancreatic resection, NI was also encountered in normal pancreatic areas which are distant from the actual tumor (Takahashi et al., 1997). In the original study, this type of NI termed “nex” was found in more than 50% of resected pancreatic specimens and correlated to the grade of intrapancreatic neural invasion or the presence of extrapancreatic neural plexus invasion (Takahashi et al., 1997). Moreover, its presence was also found to correlate to worse survival after removal of the tumor (Takahashi et al., 1997). Therefore, the presence of NI in the supposedly normal regions of the pancreas implies that NI is a rapidly progressive process where PCa cells grow very early along intrapancreatic nerves.

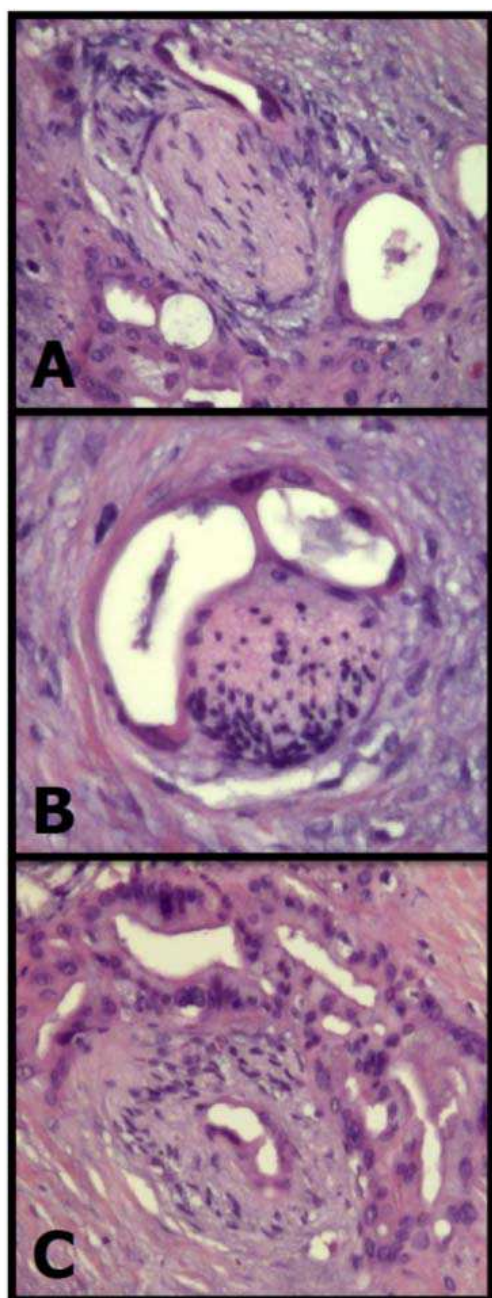
The different histological appearances of NI in PCa have also been employed to understand its pathomechanism and spread pattern. In a study by Kayahara et al. (Kayahara et al.,

2007), the investigators analyzed consecutive sections of surgically resected PCa specimens in order to elucidate the main patterns of cancer cell growth along nerves: (1) direct invasion of the nerves, (2) continuous tumor cells growth in the perineural space, (3) branching of the growing tumor mass along neural branches, (4) formation of a foremost growth cone of tumor cells, and (5) direct invasion of contiguous lymph nodes (Kayahara et al., 2007). Hence, the authors could provide an anatomical mechanism for the manifestation of NI and particularly extrapancreatic neural plexus invasion. Importantly, their study proved the continuous growth of PCa cells along intrapancreatic nerves towards the extrapancreatic neural plexus (Kayahara et al., 2007).

4. Why is neural invasion so deciding in the course of PCa?

There are several factors which make NI a crucial aspect of PCa and an attractive field of research. First, NI has an utmost high prevalence in PCa, varying between 88% to 100% (Takahashi et al., 2001; Liu&Lu, 2002). Interestingly, according to a study by Kayahara et al., NI in PCa is significantly more common than in cancers which originate from direct anatomical neighbours of the pancreas, e.g. cancers of the distal bile duct or carcinoma of the papilla of Vater (Kayahara et al., 1991; Kayahara et al., 1993; Kayahara et al., 1994; Kayahara et al., 1995; Kayahara et al., 1996). Unfortunately, intrapancreatic NI is nearly always accompanied by invasion to the extrapancreatic neural plexus: In their series, Nakao et al detected intrapancreatic NI in 116 out of 129 (90%) patients, of whom 80 (69%) showed extrapancreatic nerve plexus involvement (Nakao et al., 1996). Based on these findings, it seems that clinicians should assume the presence of NI in every patient with PCa even if the pathology report does not include a statement regarding this histopathological feature.

In the face of such a high prevalence, NI is at the same time one of the foremost reasons for local tumor recurrence after curative tumor resection (Kayahara et al., 1991; Nagakawa et al., 1991; Kayahara et al., 1995; Kayahara et al., 1996; Nagakawa et al., 1996; Ozaki et al., 1999). In a study by Kayahara et al., the investigators analyzed the mode of recurrence in 30 patients who had originally undergone macroscopically curative resection (Kayahara et al., 1993; Liu&Lu, 2002). They showed that the rate of local retroperitoneal recurrence, i.e. the prevalence of extrapancreatic NI was 80%, of hepatic metastasis 66%, of peritoneal dissemination 53%, and of lymph node recurrence 47%, an observation which was confirmed by further antemortem studies (Kayahara et al., 1993; Kayahara et al., 1995; Liu&Lu, 2002). Among the several parts of the extrapancreatic neural plexus which demonstrate local tumor recurrence, pancreatic head plexus and splenic plexus are the most common sites of tumor recurrence (Liu&Lu, 2002). Based on the frequency of NI towards retropancreatic neural plexus, several surgeons advocated routine extended resections (including celiac plexus) or at least more aggressive surgery in the surgical treatment of PCa (Hiraoka et al., 1986; Nagakawa et al., 1991; Nagakawa et al., 1996; Imamura et al., 1999). However, subsequent clinical studies confirmed that, while extended resection - even in combination with radiotherapy- can contribute to local tumor control, there is no survival benefit for patients due to the early spread pattern of PCa (Bachmann et al., 2006; Takamori et al., 2008; Yokoyama&Nagino, 2011). However, these studies mostly concentrated on more extensive lymphadenectomy rather than plexus resection as the actual measure to reduce NI. In further newer studies (Hirano et al., ; Sperti et al., ; Kondo et al., 2001; Hirano et al., 2007; Chakravarty et al., 2011), the feasibility and safety of an en bloc resection including celiac artery, plexus and ganglia was demonstrated, but the actual survival benefit from this



No neural invasion (score 0)

- ✓ Intact epineurium
- ✓ Cancer cells are often attached to the epineurium.
- ✓ In several cases merely an „epineural association“

Perineural invasion (score I)

- ✓ Epineural barrier not visible
- ✓ Cancer cells are attached to the perineurium.
- ✓ No contact of cancer cells with the endoneurium

Endoneural invasion (score II)

- ✓ Cancer cells are encountered in the interior of the nerve, between nerve fascicles.
- ✓ Neural integrity distorted

Fig. 1. Severity of neural invasion (NI) in pancreatic cancer (PCa). Examination of intrapancreatic nerves with NI reveals that PCa cells demonstrate varying degrees of interaction with the nerves. In many cases, PCa cells surround intrapancreatic nerves without breaching the epineural barrier (A, also termed epineural association). On the other hand, several nerves demonstrate a lack of the epineural barrier where pancreatic cancer cells surround the fascicles along their perineurium (B, perineural invasion). In most severe cases, PCa cells are encountered between nerve fascicles, along their endoneurium (C, endoneural invasion). There is a significant association between the severity of NI and the degree of pain sensation among PCa patients (please refer to the main text for the respective references). All images at 200x magnification.

radical operation remains to be demonstrated. Importantly, a common denominator of these studies on “en bloc” resection of retropancreatic neural plexus is the pronounced pain relief as a result of the resection of celiac plexus (Kondo et al., 2001; Hirano et al., 2007). This deciding association between extrapancreatic neural plexus and pain sensation builds up the link to the concept of “pancreatic neuropathy” in PCa which encompasses NI and several other neural alterations in PCa (Ceyhan et al., 2009), as explained in the following section.

5. Neural invasion as part of “pancreatic neuropathy” in PCa

The pancreas is one of the most densely innervated visceral organs (Bradley & Bem, 2003). The extrinsic component of its innervation is composed of nerve fibers running within the vagal and splanchnic nerves which originate from vagal nuclei or DRGs, respectively. Like the intestine, it also has an intrinsic innervation which is represented by intrapancreatic neurons. Importantly, enteric and intrapancreatic neurons are embryologically closely related: intrapancreatic neurons develop from a subgroup of neural crest-derived enteric nervous system (ENS) precursors and thus belong to the ENS (Kirchgessner & Gershon, 1990; Kirchgessner & Gershon, 1991). Moreover, there exists a direct innervation of the pancreas from the duodenum termed “entero-pancreatic innervations”, as evidenced by the entrance of nerve fibers directly from the duodenal ENS into intrapancreatic ganglia (Kirchgessner & Gershon, 1990; Kirchgessner & Gershon, 1991).

In the currently most comprehensive systematic analysis of NI in PCa, our group aimed at the study of nerve morphology in 546 patients with different pancreatic tumors, including ductal adenocarcinoma, neuroendocrine tumors, intraductal papillary mucinous neoplasms (IPMN), serous and mucinous cystadenoma and other neoplasms of the pancreas (Ceyhan et al., 2009). In the mentioned study, we could demonstrate that ductal adenocarcinoma of the pancreas exhibits the highest degree of NI in comparison to all other pancreatic tumors (Ceyhan et al., 2009). Interestingly, ductal adenocarcinoma (PCa) also harbored an unparalleled degree of nerve alterations among all these tumors (Ceyhan et al., 2009). In particular, PCa was characterized by a prominently increased neural density, a pronounced neural hypertrophy and neural inflammatory cell infiltration (“pancreatic neuritis”) (Ceyhan et al., 2006; Ceyhan et al., 2009). Moreover, we could also detect a key link between the severity of NI in PCa and the extent of intrapancreatic neuroplastic alterations: The more nerves and neural hypertrophy were present, the higher was the extent/severity of NI in PCa (Ceyhan et al., 2009).

This association between pancreatic neuroplasticity and NI gained a further dimension in a subsequent study where the pancreatic “innervation quality” in PCa was studied and compared to normal human pancreas (NP) (Ceyhan et al., 2009). Interestingly, not only had nerves in PCa tissue fewer sympathetic nerve fibers than in NP, but nerves with NI had at the same time reduced amounts of both sympathetic and cholinergic nerve fibers (Ceyhan et al., 2009). This “neural remodeling” in PCa implies that PCa cells may not be arbitrarily invading intrapancreatic nerves but also aiming at specific fiber qualities for so far unknown reasons. Overall, these neural alterations which seem to be specific for PCa, i.e. pancreatic neuroplasticity, neural remodeling and the high degree of NI, are the three hallmarks of so-called “pancreatic neuropathy” in PCa (Ceyhan et al., 2009).

While the mechanisms of these neuroplastic alterations are not completely understood, there is increasing evidence that these neuropathic alterations in PCa can in part be attributed to the neurotrophic character of the tumor microenvironment in PCa (Demir et al., 2010). In a novel *in vitro* neuroplasticity assay, we could demonstrate that tissue extracts of PCa, PCa cell supernatants and supernatants of human pancreatic stellate cells as main generators of desmoplasia can all induce axonal sprouting, increased neurite density and perikaryonal hypertrophy of neurons isolated from dorsal root ganglia or myenteric plexus under *in vitro* conditions (Demir et al., 2010). In a very recent study, Li et al. added a novel dimension to our understanding of neural alterations in PCa: In accordance with their former hypothesis (Li&Ma, 2008), patients with hyperglycemia demonstrate more pronounced neural hypertrophy and increased neural density than normoglycemic patients (Li et al., 2011). Hence, it is to be expected that research on pancreatic neuroplasticity and especially NI in PCa may take a direction towards increased investigation of the impact of impaired glucose metabolism upon pancreatic neuropathy in PCa.

6. The role of neural invasion in the pain due to PCa

Decreased survival and local tumor recurrence are undoubtedly among the leading factors which make NI into a highly relevant clinical subject. However, within the true clinical impact of NI, its role in *pain* sensation occupies a special place. It has long been accepted that the extension of PCa along the intrapancreatic nerves towards extrapancreatic neural plexus may be a causal factor in the generation of pain in advanced Pca (Kayahara et al., 1991; Nakao et al., 1996; Kayahara et al., 2007). Bockman also postulated a significant role for NI in pain generation in PCa (Bockman et al., 1994), but the actual pioneering study in this context came from Zhu et al. who for the first time demonstrated the correlation between the intrapancreatic expression of the nerve growth factor (NGF) (Zhu et al., 1999), the frequency of perineural invasion and the degree of pain sensation in PCa patients, an observation which was later also discovered for the expression of NGF receptor TrkA (Zhang et al., 2005; Dang et al., 2006). Owing to this study and its successors, it became increasingly clear that the extent of NI in the pancreas affects pain sensation, where nerve-derived molecules like NGF play a key role in both pain sensation and potentially in the attraction of PCa cell to nerves (Demir et al., 2010). The resulting interest in such nerve-derived mediators, especially in neurotrophic factors, have inaugurated the era of research on the molecular biological mechanisms of NI which last until the present time (Demir et al., 2010). Moreover, the identified cross-link between NI, pancreatic neuroplastic alterations and pain sensation by PCa patients revealed the potential involvement of “neuropathic” pain mechanisms in PCa (Ceyhan et al., 2009; Demir et al., 2010). Hence, researchers and clinicians have recently and increasingly understood that damage to nerves within the pancreas may be the actual pain-triggering mechanism in PCa (Ceyhan et al., 2009; Demir et al., 2010).

One can assume that the blockade of pain transmission via the damaged nerves from the pancreas may be of major benefit to treat pain due to PCa. As the celiac plexus contains a large portion of the afferent nerve fibers from the pancreas, several studies have tested the efficiency of celiac plexus blockade/neurolysis in the treatment of pain due to PCa. In all these studies, patients had significant pain relief (Wong et al., 2004; Stefaniak et al., 2005; Yan&Myers, 2007) following this intervention. While the efficiency of this “denervation”

technique does not necessarily prove the neuropathic character of pain in PCa, it underlines the deciding contribution of nerves and the transmitted signals in the generation of the pain syndrome in PCa (Ceyhan et al., 2008). Considering the neuropathic character of pain in PCa, one can assume that neuropathic analgesics may be of benefit to treat PCa-associated pain. As of today, the impact of neuropathic analgesic regimens to treat of patients with advanced PCa has not yet been systematically investigated.

7. Why are pancreatic cancer cells attracted to nerves? Molecular mechanisms of neural invasion in PCa

7.1 In vitro models

Researchers and clinicians have long puzzled about why PCa cells are frequently encountered around intrapancreatic nerves. Early reports had claimed that PCa cells enter nerves through the perineurium at its weakest points, i.e. along neural lymph vessels (di Mola & di Sebastiano, 2008), which, however, could not be confirmed in later studies. In later studies, investigators suggested that PCa cells grow along the path of least resistance after entering nerves, which was thought to be the perineural space (Rodin et al., 1967; Bockman et al., 1994; di Mola & di Sebastiano, 2008). Indeed, a higher proliferative index and decreased apoptosis in the perineural space could previously be shown for prostate cancer cells invading nerves (Ayala et al., 2004). However, newer studies could demonstrate that limiting PCa cells' presence around nerves to the local physical circumstances may be an oversimplification of the utmost frequent NI in Pca (Demir et al., 2010). In particular, the development of novel in vitro research tools to study NI in PCa has enabled the discovery of a true cancer-nerve affinity as an important biological mechanism in Pca (Zhu et al., 1999; Zhu et al., 2002). Especially, we know today that peripheral nerves in the tumor microenvironment can serve a source of tumor-trophic factors and cancer-attracting molecules (Zhu et al., 1999; Ceyhan et al., 2008; Gil et al., 2010). This "biological cancer-nerve affinity" in PCa is today one of the cardinal pathomechanistic concepts in our understanding of NI in Pca (Zhu et al., 1999; Ceyhan et al., 2008; Demir et al., 2010; Gil et al., 2010).

This increased appreciation of cancer-nerve affinity in PCa was largely possible owing to increased efforts to develop novel advanced in vitro models of NI in PCa. These models generally employ heterotypic co-cultures of neurons and PCa cells as in of the earliest models by Dai et al (Dai et al., 2007). In their study, the investigators co-cultivated the human PCa cell line MiaPaCa-2 with neurons from mouse dorsal root ganglia (DRG). In accordance with the hypothesized trophic effect of nerves, PCa cells which were co-cultured with DRG exhibited stronger growth than non-co-cultured control PCa cells and over-expressed prosurvival genes like MALT1 and TRAF (Dai et al., 2007). As a frequent observation also made by other current models, also PCa cells supported the growth of the neurons, as evidenced by their increased neurite growth (Dai et al., 2007).

This mutual trophic effect gained a further dimension in a recent study by our group where we presented another in vitro model which allows a precise spatiotemporal monitoring of NI by PCa cells (Ceyhan et al., 2008). As shown in the original article, different PCa cell lines were co-cultured together with rat DRG or myenteric plexus (MP) cells in a three-dimensional (3D) extracellular matrix (ECM)-based migration assay (Ceyhan et al., 2008).

The presented assay offers several advantages: First, it initiates from a clear-cut physical separation of PCa cells and neurons, as it is the case under *in vivo* conditions. Therefore, the model allows exact monitoring of cell behavior from the very beginning. Second, the model includes a pre-defined migration path for PCa cells, i.e. defined ECM-bridges, which allows the generation of a chemical gradient for any chemotactic factor (Ceyhan et al., 2008). Using this novel assay, we could demonstrate that PCa cells react to the presence of neurons with a characteristic morphological alteration including cell flattening, grouping, colony formation and spike-like cellular polarization directed towards neurites. Following their targeted migration towards neurons, PCa cells established physical contact with neurites along which they were guided in their migration (Ceyhan et al., 2008). Similar to the findings by Dai et al., we also observed increased neurite growth from DRG neurons towards PCa cells when compared to non-co-cultured DRG neurons (Ceyhan et al., 2008). Moreover, the presented 3D-migration assay for the first time included a neuronal subtype which represents the intrinsic pancreatic neurons, i.e. neurons of the enteric nervous system (ENS). The key role of neurotrophins which was initially demonstrated by Zhu et al. for NGF could be confirmed by means of this novel assay where we monitored the quantitative alterations in the expression of neurotrophins, their receptors and the members of the glial-cell-derived neurotrophic factor (GDNF) family (Zhu et al., 1999; Ceyhan et al., 2008). As opposed to several members of the GDNF family, the nerve growth factor (NGF) increased continuously throughout the migration process of 120 hours (Ceyhan et al., 2008). Certainly, this novel 3D migration assays is at the same time a novel tool to investigate the contribution of numerous molecular factors from different cellular sources to NI in PCa. A very similar model, though without pre-defined paths for chemical gradient generation, has been recently reported by Gil et al. where the investigators could demonstrate a potent chemotactic effect of GDNF from DRG neurons upon PCa cells (Gil et al., 2010). In a further study, our group showed the potent enhancer effect of the neurotrophic factor artemin, a member of the GDNF family of neurotrophic factors, upon invasiveness of PCa cells (Ceyhan et al., 2006).

In the presence of an increasing number of studies on the role of neurotrophic factors in NI in PCa, there is only a limited of reports on the role of chemokines in NI in PCa (Marchesi et al., 2008; Marchesi et al., 2010; Marchesi et al., 2010). In one of the first studies where the potential role of chemokines was recognized, Marchesi et al could show that the neural immunoreactivity for the receptor of the chemokine fractalkine, i.e. CX3CR1, was significantly higher in perineural invasive lesions of PCa (Marchesi et al., 2008). By using CX3CR1-overexpressing PCa cells for an *in vivo* implantation model, they could also demonstrate that CX3CR1-overexpressing PCa cells exhibited a more pronounced infiltration of peripheral nerves (Marchesi et al., 2008). This study stands out in the literature due to the seminal investigation of chemokines in the generation of NI in PCa and pointed to the CX3CR1-CX3CL1 as a potential therapeutic target.

Interestingly, beyond molecules with chemoattractive potential, other nerve-derived molecules have also been the focus of recent research on NI in PCa. From these, in a mouse perineural invasion and orthotopic transplantation model, the stable knockdown of synuclein gamma (synuclein- γ) via by short hairpin RNA significantly reduced the incidence of perineural invasion and liver and lymph node metastasis (Hibi et al., 2009). In another study where the investigators provided a novel perspective on NI in PCa, Swanson

et al. showed that Schwann cells of peripheral nerves express myelin-associated glycoprotein (MAG) which can serve as a receptor for the transmembrane mucin MUC1 on PCa cells (Swanson et al., 2007). Hence, based on this study, it seems that nerves in PCa tissue not only chemo-attract PCa cells but also can undergo direct physical contact, as initially observed by Bockman (Swanson et al., 2007; Demir et al., 2010).

It is conceivable that the presented *in vitro* models in the literature would enable the identification of a gene set which would reflect the differentially upregulated genes in NI in PCa. Accordingly, in a recent study, Abiatari et al. aimed at obtaining a transcriptome signature of NI in PCa by means of an *in vitro* / *ex vivo* model (Abiatari et al., 2009). Specifically, they confronted human PCa cell lines with explanted rat vagus nerves and quantified the differentially regulated genes in highly versus less nerve-invasive PCa cells (Abiatari et al., 2009). Interestingly, the differentially regulated genes which were identified by this study were primarily related to cell motility, including kinesin family member 14 (KIF14) and Rho-GDP dissociation inhibitor beta (ARHGDIbeta), a gene set which they could expand in a subsequent by two molecules, i.e., the microtubule-associated protein MAPRE2 and the nuclear protein YPEL2 (Abiatari et al., 2009; Abiatari et al., 2009; Abiatari et al., 2009). Based on these important observations, the investigators underlined the importance of increased PCa cell motility in the generation of NI in PCa as additional molecular biological mechanism (Abiatari et al., 2009; Abiatari et al., 2009).

7.2 In vivo models

The increasing number of efforts to elucidate the pathomechanism of NI in PCa necessitated the creation of *in vivo* models which better mimic NI in human PCa. The common characteristic of these models is that they involve implantation of PCa cells as xenograft tumors in one out of several locations, e.g. into the pancreas, under the skin or in the proximity of large-diameter peripheral nerves to allow NI by PCa cells. In the first one of these models, Eibl et al. aimed at creating a model to simulate the high rates of local recurrence and NI after curative resection (Eibl&Reber, 2005). For this purpose, they performed complete surgical resection of the tumor at 4, 6, and 8 weeks after orthotopic implantation of the PCa cell lines MiaPaCa-2 (undifferentiated) and Capan-2 (well-differentiated) in nude mice pancreas. Six weeks after tumor implantation, local tumor recurrence with extensive retroperitoneal nerve invasion and distant organ metastasis were observed in nude mice who had received MiaPaCa-2 cells (Eibl&Reber, 2005). Astonishingly, although the investigators achieved a successful simulation of the local recurrence and NI associated with PCa in this murine model, there has since been no application of this model to identify further pathomechanistic features of NI in PCa. Certainly, the model is probably not suitable to study the initial, early events leading to PCa, however, it can possibly be employed to examine the therapeutic potential of different agents on NI in PCa in an animal model of PCa. In another model, Koide et al. subcutaneously (s.c.) implanted different PCa cell lines with or without human peripheral nerves in nonobese diabetes/severe combined immunodeficient mice and analyzed the frequency of NI by these different cell lines (Koide et al., 2006). Furthermore, they performed an oligonucleotide microarray to obtain the expression profiles of high and low perineurally invasive cell lines. Interestingly, only two well-differentiated cell lines (Capan-1 and Capan-2) demonstrated invasion of mouse s.c. nerves. In these invasive cell lines, they

identified over-expression of CD74 in the specifically perineural invasive cells, which they confirmed in human PCa tissue specimens (Koide et al., 2006). Despite the implantation of PCa cells under skin and not the actual organ of origin (i.e. the pancreas), this model sticks out owing to its uncomplicated performance. Still, it has to be underlined that none of these *in vivo* models has so far found widespread application.

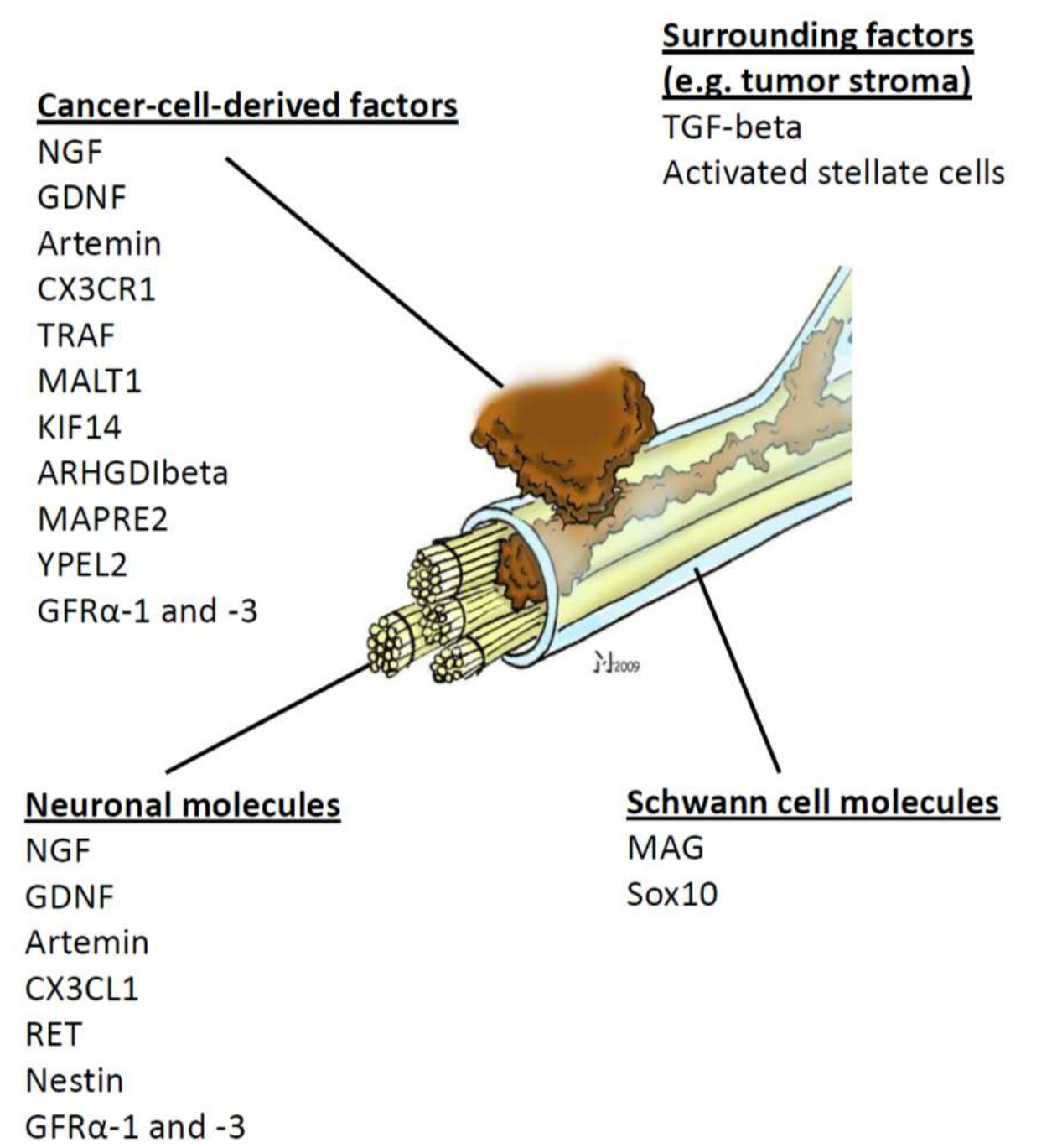


Fig. 2. Different sources of molecular actors in neural invasion (NI) in pancreatic cancer (PCa). Research from the past 15 years revealed that NI results from a complicated interplay of numerous molecular agents derived from different sources, e.g. PCa cells, neurons, Schwann cells and stromal cells. Please refer to the main text for the respective references

Investigator	Model characteristics	Advantages	Limitations
<i>In Vitro Models</i>			
Dai et al.	Matrigel-based heterotypic co-culture	One of the initial models Apt for studying expression changes	No pre-defined chemical gradient for chemo-attractants No remark on the initial cellular reactions Different species of confronted cells (murine neurons vs. human PCa cells)
Ceyhan et al.	ECM-based three-dimensional heterotypic migration assay	Initial physical separation of different cells Observation of initial cellular morphological reactions “Bridges” to enable chemical gradient generation Usage of myenteric neurons	Different species of confronted cells (murine neurons vs. human PCa cells)
Abiatari et al.	Ex vivo co-culture of rat nerves with PCa cells	Easy to perform	Confrontation with the “large-caliber” vagal nerve Different species of confronted cells (murine neurons vs. human PCa cells)
<i>In Vivo Models</i>			
Eibl et al.	Orthotopic PCa cell injection followed by tumor resection (murine)	Simulation of extrapancreatic NI	Lacking monitoring of initial pathophysiological events
Gil et al.	Tumor injection onto murine sciatic nerve	Easy to perform Therapeutic monitoring by observing degree of paralysis	Confrontation with the “large-caliber” sciatic nerve

Table 1. Experimental models of neural invasion (NI) in pancreatic cancer (PCa). The listed in vitro and in vivo models represent complicated heterotypic culture systems and possess several differences among each other. Their advantages, however, clearly overweigh their limitations. ECM: extracellular matrix. Please refer to the manuscript for the respective references.

8. Efforts of controlling neural invasion in PCa

Among all studies in the literature, there are so far two *in vivo* models of NI in PCa where a primarily therapeutic goal was pursued: In the first study, Gil et al. aimed at treating NI by means of an attenuated, replication-competent, oncolytic herpes simplex virus which inhabits nerves (Gil et al., 2007). After injection of PCa cell lines into the perineurium of the sciatic nerve of athymic mice, they monitored limb function for 9 days after injection. Excitingly, a single injection of the oncolytic herpes simplex virus 7 days after PCa cell injection effectively eradicated NI without compromising physiologic nerve function (Gil et al., 2007). The same group utilized this model in a subsequent study for intraoperative diagnosis of NI: By using enhanced green fluorescent protein (eGFP)-expressing oncolytic herpes virus, they could detect invaded nerves following intrasciatic implantation of PCa cell lines via intraoperative fluorescent stereoscopic imaging (Gil et al., 2008). Thereby, they proposed a novel tool for enhanced diagnosis and therapy of NI in PCa and for facilitated detection of invaded nerves in cases where an extended resection may be considered (Gil et al., 2008). In a third study, the group applied PCa cell injection onto mouse sciatic nerves and subsequently treated the mice with pyrazolopyrimidine-1, a tyrosine kinase inhibitor targeting the RET pathway (Gil et al., 2010). Strikingly, systemic therapy with this agent diminished nerve invasion toward the spinal cord and prevented limb paralysis (Gil et al., 2010). Still, the sensitivity and true effectiveness of their method remains to be confirmed in future studies.

9. Future directions in research on NI in PCa

Today, research on NI in PCa is in an era of “data collection” and “expansion of knowledge”. The increasing number of *in vitro* and *in vivo* models, together with the rapidly growing scientific interest in NI, create the best possible conditions to learn and discover about this peculiar histopathological phenomenon. However, we are convinced that future studies should aim at the generation of models with an increasingly therapeutic intention, because there is urgent need to employ additional, novel tools to treat PCa. Furthermore, the main pathomechanistic hypothesis for the generation of NI, i.e. the neuro-affinity of PCa cells, has to be carefully reviewed. It should certainly be considered that PCa cells may not be responsible for every aspect of NI, but rather be reacting to the signals coming from the nerves. The increasing number of nerve-derived molecules like neurotrophic factors or neuronal chemokines which are continuously shown to contribute to NI should serve as a motivation to delve deeper into the involvement of neuronal molecules during NI.

While novel *in vitro* models of NI in PCa are being steadily developed, the currently available *in vivo* models still exhibit major deficits. In particular, these models lack:

1. Tumors that directly originate from the pancreas
2. Histopathological confirmation of the tumor phenotype as ductal adenocarcinoma
3. The confirmation of the presence of NI even at early stages of tumor development and progression
4. The specific extension of NI towards the extrapancreatic neural plexus
5. Accompanying neuropathic and desmoplastic alterations
6. Neuropathic pain sensation

Therefore, future *in vivo* models of NI in PCa should be superior to the current ones in the above-mentioned aspects, especially because they should increasingly be employed to deduce therapeutic targets and strategies.

10. Summary and conclusion

Neural invasion in PCa bears a unique importance in the biology of this disease due its impact on patient survival, local tumor recurrence and neuropathic pain sensation. Higher interest in NI has paved path for increased research on the biology of NI and accelerated the development of numerous experimental models. The discussed *in vitro* and *in vivo* models which shall help to elucidate the pathomechanisms of NI in PCa may provide novel tools to control and to reduce NI in this highly aggressive human malignancy. Considering the dismal average prognosis associated with PCa, one may wonder about the actual benefit of reducing the specific invasion of nerves in this tumor entity. Here, it should be underlined that reduction of NI can be regarded as one of several possibilities to control tumor growth, just as adjuvant therapy as an oncological therapy regimen aims at reaching microscopic tumor presence and reducing the systemic tumor burden. The control of NI, however, bears a further special importance since NI is not only the probably most common mode of spread for PCa, but also because nerves represent the most frequent site of local tumor recurrence in PCa. Moreover, limitation of NI is likely to have a considerable impact upon the neuropathic pain syndrome and thus quality of life of patients with PCa. Therefore, NI may find increased attention in the future as an additional therapeutic target for increased survival, enhanced postoperative outcome and improved quality of life among all patients with this dreadful malignancy.

11. Acknowledgements

The authors are grateful to Dr. Matthias Maak for his assistance with the figures.

12. References

- Abiatari, I., DeOliveira, T., Kerkadze, V., Schwager, C., Esposito, I., Giese, N. A., Huber, P., Bergman, F., Abdollahi, A., Friess, H. & Kleeff, J. (2009). "Consensus transcriptome signature of perineural invasion in pancreatic carcinoma." *Mol Cancer Ther* 8(6): 1494-504.
- Abiatari, I., Gillen, S., DeOliveira, T., Klose, T., Bo, K., Giese, N. A., Friess, H. & Kleeff, J. (2009). "The microtubule-associated protein MAPRE2 is involved in perineural invasion of pancreatic cancer cells." *Int J Oncol* 35(5): 1111-6.
- Abiatari, I., Kiladze, M., Kerkadze, V., Friess, H. & Kleeff, J. (2009). "Expression of YPEL1 in pancreatic cancer cell lines and tissues." *Georgian Med News*(175): 60-2.
- Ayala, G. E., Dai, H., Ittmann, M., Li, R., Powell, M., Frolov, A., Wheeler, T. M., Thompson, T. C. & Rowley, D. (2004). "Growth and survival mechanisms associated with perineural invasion in prostate cancer." *Cancer Res* 64(17): 6082-90.
- Bachmann, J., Michalski, C. W., Martignoni, M. E., Buchler, M. W. & Friess, H. (2006). "Pancreatic resection for pancreatic cancer." *HPB (Oxford)* 8(5): 346-51.
- Bockman, D. E., Buchler, M. & Beger, H. G. (1994). "Interaction of pancreatic ductal carcinoma with nerves leads to nerve damage." *Gastroenterology* 107(1): 219-30.

- Bradley, E. L., 3rd & Bem, J. (2003). "Nerve blocks and neuroablative surgery for chronic pancreatitis." *World J Surg* 27(11): 1241-8.
- Ceyhan, G. O., Bergmann, F., Kadihasanoglu, M., Altintas, B., Demir, I. E., Hinz, U., Muller, M. W., Giese, T., Buchler, M. W., Giese, N. A. & Friess, H. (2009). "Pancreatic neuropathy and neuropathic pain--a comprehensive pathomorphological study of 546 cases." *Gastroenterology* 136(1): 177-186 e1.
- Ceyhan, G. O., Demir, I. E., Altintas, B., Rauch, U., Thiel, G., Muller, M. W., Giese, N. A., Friess, H. & Schafer, K. H. (2008). "Neural invasion in pancreatic cancer: a mutual tropism between neurons and cancer cells." *Biochem Biophys Res Commun* 374(3): 442-7.
- Ceyhan, G. O., Demir, I. E., Rauch, U., Bergmann, F., Muller, M. W., Buchler, M. W., Friess, H. & Schafer, K. H. (2009). "Pancreatic neuropathy results in "neural remodeling" and altered pancreatic innervation in chronic pancreatitis and pancreatic cancer." *Am J Gastroenterol* 104(10): 2555-65.
- Ceyhan, G. O., Giese, N. A., Erkan, M., Kersch, A. G., Wente, M. N., Giese, T., Buchler, M. W. & Friess, H. (2006). "The neurotrophic factor artemin promotes pancreatic cancer invasion." *Ann Surg* 244(2): 274-81.
- Ceyhan, G. O., Liebl, F., Maak, M., Schuster, T., Becker, K., Langer, R., Demir, I. E., Hartel, M., Friess, H. & Rosenberg, R. (2011). "The severity of neural invasion is a crucial prognostic factor in rectal cancer independent of neoadjuvant radiochemotherapy." *Ann Surg* 252(5): 797-804.
- Ceyhan, G. O., Michalski, C. W., Demir, I. E., Muller, M. W. & Friess, H. (2008). "Pancreatic pain." *Best Pract Res Clin Gastroenterol* 22(1): 31-44.
- Chakravarty, K. D., Hsu, J. T., Liu, K. H., Yeh, C. N., Yeh, T. S., Hwang, T. L., Jan, Y. Y. & Chen, M. F. (2011). "Prognosis and feasibility of en-bloc vascular resection in stage II pancreatic adenocarcinoma." *World J Gastroenterol* 16(8): 997-1002.
- Dai, H., Li, R., Wheeler, T., Ozen, M., Ittmann, M., Anderson, M., Wang, Y., Rowley, D., Younes, M. & Ayala, G. E. (2007). "Enhanced survival in perineural invasion of pancreatic cancer: an in vitro approach." *Hum Pathol* 38(2): 299-307.
- Dang, C., Zhang, Y., Ma, Q. & Shimahara, Y. (2006). "Expression of nerve growth factor receptors is correlated with progression and prognosis of human pancreatic cancer." *J Gastroenterol Hepatol* 21(5): 850-8.
- Demir, I. E., Ceyhan, G. O., Liebl, F., J.G., D. H., Maak, M. & Friess, H. (2010). "Neural Invasion in Pancreatic Cancer: The Past, Present and Future." *Cancers* 2(3): 1513-1527.
- Demir, I. E., Ceyhan, G. O., Rauch, U., Altintas, B., Klotz, M., Muller, M. W., Buchler, M. W., Friess, H. & Schafer, K. H. (2010). "The microenvironment in chronic pancreatitis and pancreatic cancer induces neuronal plasticity." *Neurogastroenterol Motil* 22(4): 480-90, e112-3.
- di Mola, F. F. & di Sebastiano, P. (2008). "Pain and pain generation in pancreatic cancer." *Langenbecks Arch Surg* 393(6): 919-22.
- Eibl, G. & Reber, H. A. (2005). "A xenograft nude mouse model for perineural invasion and recurrence in pancreatic cancer." *Pancreas* 31(3): 258-62.

- Gil, Z., Cavel, O., Kelly, K., Brader, P., Rein, A., Gao, S. P., Carlson, D. L., Shah, J. P., Fong, Y. & Wong, R. J. (2010). "Paracrine regulation of pancreatic cancer cell invasion by peripheral nerves." *J Natl Cancer Inst* 102(2): 107-18.
- Gil, Z., Kelly, K. J., Brader, P., Shah, J. P., Fong, Y. & Wong, R. J. (2008). "Utility of a herpes oncolytic virus for the detection of neural invasion by cancer." *Neoplasia* 10(4): 347-53.
- Gil, Z., Rein, A., Brader, P., Li, S., Shah, J. P., Fong, Y. & Wong, R. J. (2007). "Nerve-sparing therapy with oncolytic herpes virus for cancers with neural invasion." *Clin Cancer Res* 13(21): 6479-85.
- Hibi, T., Mori, T., Fukuma, M., Yamazaki, K., Hashiguchi, A., Yamada, T., Tanabe, M., Aiura, K., Kawakami, T., Ogiwara, A., Kosuge, T., Kitajima, M., Kitagawa, Y. & Sakamoto, M. (2009). "Synuclein-gamma is closely involved in perineural invasion and distant metastasis in mouse models and is a novel prognostic factor in pancreatic cancer." *Clin Cancer Res* 15(8): 2864-71.
- Hirai, I., Kimura, W., Ozawa, K., Kudo, S., Suto, K., Kuzu, H. & Fuse, A. (2002). "Perineural invasion in pancreatic cancer." *Pancreas* 24(1): 15-25.
- Hirano, S., Kondo, S., Hara, T., Ambo, Y., Tanaka, E., Shichinohe, T., Suzuki, O. & Hazama, K. (2007). "Distal pancreatectomy with en bloc celiac axis resection for locally advanced pancreatic body cancer: long-term results." *Ann Surg* 246(1): 46-51.
- Hirano, S., Kondo, S., Tanaka, E., Shichinohe, T., Tsuchikawa, T., Kato, K. & Matsumoto, J. "Postoperative bowel function and nutritional status following distal pancreatectomy with en-bloc celiac axis resection." *Dig Surg* 27(3): 212-6.
- Hiraoka, T., Watanabe, E., Katoh, T., Hayashida, N., Mizutani, J., Kanemitsu, K. & Miyauchi, Y. (1986). "A new surgical approach for control of pain in chronic pancreatitis: complete denervation of the pancreas." *Am J Surg* 152(5): 549-51.
- Imamura, M., Hosotani, R. & Kogire, M. (1999). "Rationale of the so-called extended resection for pancreatic invasive ductal carcinoma." *Digestion* 60 Suppl 1: 126-9.
- Kayahara, M., Nagakawa, T., Futagami, F., Kitagawa, H., Ohta, T. & Miyazaki, I. (1996). "Lymphatic flow and neural plexus invasion associated with carcinoma of the body and tail of the pancreas." *Cancer* 78(12): 2485-91.
- Kayahara, M., Nagakawa, T., Konishi, I., Ueno, K., Ohta, T. & Miyazaki, I. (1991). "Clinicopathological study of pancreatic carcinoma with particular reference to the invasion of the extrapancreatic neural plexus." *Int J Pancreatol* 10(2): 105-11.
- Kayahara, M., Nagakawa, T., Tsukioka, Y., Ohta, T., Ueno, K. & Miyazaki, I. (1994). "Neural invasion and nodal involvement in distal bile duct cancer." *Hepatogastroenterology* 41(2): 190-4.
- Kayahara, M., Nagakawa, T., Ueno, K., Ohta, T., Takeda, T. & Miyazaki, I. (1993). "An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined by autopsy and diagnostic imaging." *Cancer* 72(7): 2118-23.
- Kayahara, M., Nagakawa, T., Ueno, K., Ohta, T., Tsukioka, Y. & Miyazaki, I. (1995). "Surgical strategy for carcinoma of the pancreas head area based on clinicopathologic analysis of nodal involvement and plexus invasion." *Surgery* 117(6): 616-23.
- Kayahara, M., Nakagawara, H., Kitagawa, H. & Ohta, T. (2007). "The nature of neural invasion by pancreatic cancer." *Pancreas* 35(3): 218-23.

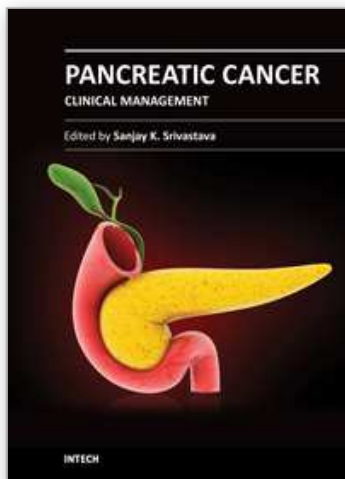
- Kirchgessner, A. L. & Gershon, M. D. (1990). "Innervation of the pancreas by neurons in the gut." *J Neurosci* 10(5): 1626-42.
- Kirchgessner, A. L. & Gershon, M. D. (1991). "Innervation and regulation of the pancreas by neurons in the gut." *Z Gastroenterol Verh* 26: 230-3.
- Koide, N., Yamada, T., Shibata, R., Mori, T., Fukuma, M., Yamazaki, K., Aiura, K., Shimazu, M., Hirohashi, S., Nimura, Y. & Sakamoto, M. (2006). "Establishment of perineural invasion models and analysis of gene expression revealed an invariant chain (CD74) as a possible molecule involved in perineural invasion in pancreatic cancer." *Clin Cancer Res* 12(8): 2419-26.
- Kondo, S., Katoh, H., Omi, M., Hirano, S., Ambo, Y., Tanaka, E., Okushiba, S., Morikawa, T., Kanai, M. & Yano, T. (2001). "Radical distal pancreatectomy with en bloc resection of the celiac artery, plexus, and ganglions for advanced cancer of the pancreatic body: a preliminary report on perfect pain relief." *Jop* 2(3): 93-7.
- Li, J. & Ma, Q. (2008). "Hyperglycemia promotes the perineural invasion in pancreatic cancer." *Med Hypotheses* 71(3): 386-9.
- Li, J., Ma, Q., Liu, H., Guo, K., Li, F., Li, W., Han, L., Wang, F. & Wu, E. (2011). "Relationship between neural alteration and perineural invasion in pancreatic cancer patients with hyperglycemia." *PLoS One* 6(2): e17385.
- Liebig, C., Ayala, G., Wilks, J. A., Berger, D. H. & Albo, D. (2009). "Perineural invasion in cancer: a review of the literature." *Cancer* 115(15): 3379-91.
- Liu, B. & Lu, K. Y. (2002). "Neural invasion in pancreatic carcinoma." *Hepatobiliary Pancreat Dis Int* 1(3): 469-76.
- Marchesi, F., Locatelli, M., Solinas, G., Erreni, M., Allavena, P. & Mantovani, A. (2010). "Role of CX3CR1/CX3CL1 axis in primary and secondary involvement of the nervous system by cancer." *J Neuroimmunol* 224(1-2): 39-44.
- Marchesi, F., Piemonti, L., Fedele, G., Destro, A., Roncalli, M., Albarello, L., Doglioni, C., Anselmo, A., Doni, A., Bianchi, P., Laghi, L., Malesci, A., Cervo, L., Malosio, M., Reni, M., Zerbi, A., Di Carlo, V., Mantovani, A. & Allavena, P. (2008). "The chemokine receptor CX3CR1 is involved in the neural tropism and malignant behavior of pancreatic ductal adenocarcinoma." *Cancer Res* 68(21): 9060-9.
- Marchesi, F., Piemonti, L., Mantovani, A. & Allavena, P. (2010). "Molecular mechanisms of perineural invasion, a forgotten pathway of dissemination and metastasis." *Cytokine Growth Factor Rev* 21(1): 77-82.
- Mitsunaga, S., Hasebe, T., Kinoshita, T., Konishi, M., Takahashi, S., Gotohda, N., Nakagohri, T. & Ochiai, A. (2007). "Detail histologic analysis of nerve plexus invasion in invasive ductal carcinoma of the pancreas and its prognostic impact." *Am J Surg Pathol* 31(11): 1636-44.
- Nagakawa, T., Konishi, I., Ueno, K., Ohta, T., Akiyama, T., Kayahara, M. & Miyazaki, I. (1991). "Surgical treatment of pancreatic cancer. The Japanese experience." *Int J Pancreatol* 9: 135-43.
- Nagakawa, T., Nagamori, M., Futakami, F., Tsukioka, Y., Kayahara, M., Ohta, T., Ueno, K. & Miyazaki, I. (1996). "Results of extensive surgery for pancreatic carcinoma." *Cancer* 77(4): 640-5.

- Nakao, A., Harada, A., Nonami, T., Kaneko, T. & Takagi, H. (1996). "Clinical significance of carcinoma invasion of the extrapancreatic nerve plexus in pancreatic cancer." *Pancreas* 12(4): 357-61.
- Ozaki, H., Hiraoka, T., Mizumoto, R., Matsuno, S., Matsumoto, Y., Nakayama, T., Tsunoda, T., Suzuki, T., Monden, M., Saitoh, Y., Yamauchi, H. & Ogata, Y. (1999). "The prognostic significance of lymph node metastasis and intrapancreatic perineural invasion in pancreatic cancer after curative resection." *Surg Today* 29(1): 16-22.
- Rodin, A. E., Larson, D. L. & Roberts, D. K. (1967). "Nature of the perineural space invaded by prostatic carcinoma." *Cancer* 20(10): 1772-9.
- Sperti, C., Berselli, M. & Pedrazzoli, S. "Distal pancreatectomy for body-tail pancreatic cancer: is there a role for celiac axis resection?" *Pancreatology* 10(4): 491-8.
- Stefaniak, T., Basinski, A., Vingerhoets, A., Makarewicz, W., Connor, S., Kaska, L., Stanek, A., Kwiecinska, B., Lachinski, A. J. & Sledzinski, Z. (2005). "A comparison of two invasive techniques in the management of intractable pain due to inoperable pancreatic cancer: neurolytic celiac plexus block and videothoracoscopic splanchnicectomy." *Eur J Surg Oncol* 31(7): 768-73.
- Swanson, B. J., McDermott, K. M., Singh, P. K., Eggers, J. P., Crocker, P. R. & Hollingsworth, M. A. (2007). "MUC1 is a counter-receptor for myelin-associated glycoprotein (Siglec-4a) and their interaction contributes to adhesion in pancreatic cancer perineural invasion." *Cancer Res* 67(21): 10222-9.
- Takahashi, S., Hasebe, T., Oda, T., Sasaki, S., Kinoshita, T., Konishi, M., Ueda, T., Ochiai, T. & Ochiai, A. (2001). "Extra-tumor perineural invasion predicts postoperative development of peritoneal dissemination in pancreatic ductal adenocarcinoma." *Anticancer Res* 21(2B): 1407-12.
- Takahashi, T., Ishikura, H., Motohara, T., Okushiba, S., Dohke, M. & Katoh, H. (1997). "Perineural invasion by ductal adenocarcinoma of the pancreas." *J Surg Oncol* 65(3): 164-70.
- Takamori, H., Hiraoka, T., Kanemitsu, K., Tsuji, T., Tanaka, H., Chikamoto, A., Horino, K., Beppu, T., Hirota, M. & Baba, H. (2008). "Long-term outcomes of extended radical resection combined with intraoperative radiation therapy for pancreatic cancer." *J Hepatobiliary Pancreat Surg* 15(6): 603-7.
- Wong, G. Y., Schroeder, D. R., Carns, P. E., Wilson, J. L., Martin, D. P., Kinney, M. O., Mantilla, C. B. & Warner, D. O. (2004). "Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial." *Jama* 291(9): 1092-9.
- Yan, B. M. & Myers, R. P. (2007). "Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer." *Am J Gastroenterol* 102(2): 430-8.
- Yokoyama, Y. & Nagino, M. (2011). "Role of extended surgery for pancreatic cancer: critical review of the four major RCTs comparing standard and extended surgery." *J Hepatobiliary Pancreat Sci*.
- Zhang, Y., Dang, C., Ma, Q. & Shimahara, Y. (2005). "Expression of nerve growth factor receptors and their prognostic value in human pancreatic cancer." *Oncol Rep* 14(1): 161-71.

- Zhu, Z., Friess, H., diMola, F. F., Zimmermann, A., Graber, H. U., Korc, M. & Buchler, M. W. (1999). "Nerve growth factor expression correlates with perineural invasion and pain in human pancreatic cancer." *J Clin Oncol* 17(8): 2419-28.
- Zhu, Z., Kleeff, J., Kaye, H., Wang, L., Korc, M., Buchler, M. W. & Friess, H. (2002). "Nerve growth factor and enhancement of proliferation, invasion, and tumorigenicity of pancreatic cancer cells." *Mol Carcinog* 35(3): 138-47.

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Edited by Prof. Sanjay Srivastava

ISBN 978-953-51-0394-3

Hard cover, 312 pages

Publisher InTech

Published online 28, March, 2012

Published in print edition March, 2012

This book covers pancreatic cancer risk factors, treatment and clinical procedures. It provides an outline of pancreatic cancer genetic risk factors, biomarkers and systems biology for the better understanding of disease. As pancreatic cancer suffers from lack of early diagnosis or prognosis markers, this book encompasses stem cell and genetic makers to identify the disease in early stages. The book uncovers the rationale and effectiveness of monotherapy and combination therapy in combating the devastating disease. As immunotherapy is emerging as an attractive approach to cease pancreatic cancer progression, the present book covers various aspects of immunotherapy including innate, adaptive, active, passive and bacterial approaches. Management of anesthesia during surgery and pain after surgery has been discussed. Book also takes the reader through the role of endoscopy and fine needle guided biopsies in diagnosing and observing the disease progression.

How to reference

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Ihsan Ekin Demir, Helmut Friess and Güralp O. Ceyhan (2012). Generation and Impact of Neural Invasion in Pancreatic Cancer, Pancreatic Cancer - Clinical Management, Prof. Sanjay Srivastava (Ed.), ISBN: 978-953-51-0394-3, InTech, Available from: <http://www.intechopen.com/books/pancreatic-cancer-clinical-management/generation-and-impact-of-neural-invasion-in-pancreatic-cancer>

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