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EDITORIAL

Nestin in gastrointestinal and other cancers: Effects on cells and tumor angiogenesis

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Abstract

Nestin is a class Ⅵ intermediate filament protein that was originally described as a neuronal stem cell marker during central nervous system (CNS) development, and is currently widely used in that capacity. Nestin is also expressed in non-neuronal immature or progenitor cells in normal tissues. Under pathological conditions, nestin is expressed in repair processes in the CNS, muscle, liver, and infarcted myocardium. Furthermore, increased nestin expression has been reported in various tumor cells, including CNS tumors, gastrointestinal stromal tumors, pancreatic cancer, prostate cancer, breast cancer, malignant melanoma, dermatofibrosarcoma protuberances, and thyroid tumors. Nestin is reported to correlate with aggressive growth, metastasis, and poor prognosis in some tumors; however, the roles of nestin in cancer cells have not been well characterized. Furthermore, nestin is more specifically expressed in proliferating small-sized tumor vessels in glioblastoma and gastric, colorectal, and prostate cancers than are other tumor vessel markers. These findings indicate that nestin may be a marker for newly synthesized tumor vessels and a therapeutic target for tumor angiogenesis. It has received a lot of attention recently as a cancer stem cell marker in various cancer cells including brain tumors, malignant rhabdoid tumors, and uterine, cervical, prostate, bladder, head and neck, ovarian, testicular, and pancreatic cancers. The purpose of this review is to clarify the roles of nestin in cancer cells and in tumor angiogenesis, and to examine the association between nestin and cancer stem cells. Nestin has the potential to serve as a molecular target for cancers with nestin-positive cancer cells and nestin-positive tumor vasculature.

Key words: Cancer growth; Intermediate filament protein; Cancer invasion; Tumor migration; Nestin; Stem cell marker; Tumor angiogenesis

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INTRODUCTION

Nestin is an intermediate filament (IF) protein that was originally described in 1990 as a neuronal stem cell/progenitor cell marker during central nervous system (CNS) development[1]. Cytoskeletal proteins mainly consist of microfilaments, IFs, and microtubules. The diameter of microfilaments (actin) is 5-7 nm and that of microtubules is 20-25 nm, while the diameter of IFs falls between the two at 10 nm, giving them their name. IFs are

classified into six subtypes[2,3], and the IF protein members are expressed in specific cell types, for example, keratin in epithelial cells, vimentin in mesenchymal cells, desmin in muscular cells, neurofilament in neuronal cells, and glial fibrillar acidic protein in glial cells.

Nestin is expressed in dividing cells during the early stages of development in the CNS, peripheral nervous system, and myogenic and other tissues. With differentiation, nestin is downregulated and replaced by tissue-specific IF proteins, and therefore, is widely used as a neuronal stem cell marker. Nestin is also expressed in immature or progenitor cells in non-neuronal cells in normal tissues[4-7]. High levels of nestin expression have been detected in oligodendroglial lineage cells, ependymocytes, Sertoli cells, enteric glia, hair follicle cells, podocytes of renal glomeruli, pancreatic stellate cells, pericytes, islets, optic nerve, and odontoblasts[8-14]. Recent work has shown that nestin is also expressed in follicle stem cells and their immediate, differentiated progeny, and the hair follicle bulge area has been noted as an easily accessible source of actively growing pluripotent adult stem cells[15]. In adult organisms, nestin-expressing cells are restricted to defined locations, where they may function as a cellular reserve that is capable of proliferation, differentiation, and migration after reactivation[16].

In pathological conditions, nestin is expressed in repair processes in the CNS, muscle, liver[17-20], and infarcted myocardium[21]. Furthermore, increased nestin expression has been reported in various tumor cells, including CNS tumors, pancreatic cancer, gastrointestinal stromal tumors (GISTs), prostate cancer, breast cancer, malignant melanoma, dermatofibrosarcoma protuberances, and thyroid tumors[22-28] (Table 1). Expression of nestin in several tumors has been reported to be closely correlated with poor prognosis. Recently, nestin has also received attention as a cancer stem cell marker in various tumor cells including brain tumors, uterine and cervical cancers, prostate cancer, bladder cancer, head and neck cancers, ovarian cancer, testicular cancer, pancreatic cancer, and malignant rhabdoid tumors[29-36]. In the tumor tissues, proliferating vascular endothelial cells also highly express nestin, and nestin is therefore closely correlated with tumor angiogenesis[37-40] (Table 2). Detailed analyses of expression patterns of nestin in various tumor tissues and tumor angiogenesis, including gastrointestinal cancer, will be helpful for examining the roles of nestin in mechanisms of tumor growth and invasion and for finding novel therapeutic targets.

Table 1 Expression and roles of nestin in cancers

	Expression patterns	Roles
Glioblastoma[66-69]	Tumor cells and tumor vessels	*In vitro* and *in vivo* growth
	Glioma << glioblastoma	G1/S arrest
		Migration, invasion
Pancreatic cancer[87,90]	30% of PDAC	Nerve invasion, migration
		Initiation of PanIN
GIST[25,96]	Tumor cells and interstitial cells of Cajal	
Prostate cancer[27]	Androgen-insensitive cancer cells	Migration, invasion *in vitro*
	75% of lethal androgen-independent prostate cancer	Lung metastasis
Breast cancer[26,101-103]	Basal breast cancer subtype	Shorter survival
	Triple-negative breast cancer	Independent prognostic factor
	Lymphovascular embolus of inflammatory breast cancer	
Malignant melanoma[24,106-108,112,113]	Tumor cells and endothelial cells	Advanced stage
	Ulceration of primary tumors	Metastasis
	Infiltrating front of tumors	Shorter survival
	Primary tumor << metastatic tumor	
	Stage Ⅳ >> Ⅲ/Ⅳ with no evidence of disease in blood	

PanIN: Pancreatic intraepithelial neoplasia; GIST: Gastrointestinal stromal tumor; PDAC: Pancreatic ductal adenocarcinoma.

Table 2 Expression and roles of nestin in tumor angiogenesis

	Expression patterns	Roles
Gastric adenocarcinoma[37]	Tumor blood vessels	Shorter survival
Colorectal cancer[38]	Small-sized and proliferating tumor vessels	Shorter survival
Prostate cancer[39,40]	Proliferating vascular cells	Shorter survival
	Endothelial cells in metastatic bone	Recurrence
		Skeletal metastasis
Glioblastoma[131]	Proliferating endothelial cells	
Malignant melanoma[108]	Endothelial cells	Shorter survival

STRUCTURE AND REGULATION OF NESTIN

Nestin is a large protein (> 1600 amino acids) with a highly conserved α-helical core domain of 300-330 amino acids flanked by N- and C-terminal domains and classified into type Ⅵ IFs[1,3,41]. Nestin contains a short N terminus and an unusually long C terminus, which interacts with other IFs including vimentin, desmin, or internexin, forming heterodimers and mixed polymers[42-44], but in contrast to other IFs, nestin cannot form homopolymers[2]. Nestin is known to contribute to the disassembly of vimentin during mitosis[45]. It has been suggested that the long C-terminal portion of nestin protrudes from the filament body and may function as a linker or cross-bridge between IFs and microtubules[2]. The assembly and disassembly of cytoskeletal IFs modulate a variety of signaling cascades, and several lines of evidence suggest that nestin participates in this regulation[46]. Nestin may thus play a role in

connecting the three components of the cytoskeleton and coordinate changes in cell dynamics.

Nestin has a high molecular weight (about 240 kDa), which differs among organs because of modifications to the protein[47]. It has multiple phosphorylation sites and glycosylated side chains, and the phosphorylated and glycosylated forms of nestin may affect intracellular localization or act as a means of functional regulation in specific cell types or brain regions[48]. Nestin is known to be phosphorylated at Thr^{316} by cdc2 kinase[49] and/or cyclin-dependent kinase 5[50], and modulates mitosis-associated cytoplasmic reorganization during mitosis. However, the roles of glycosylation have not been closely examined[51].

The minimal promoter of the mouse nestin gene resides in the region -11 to +183 of the 5' non-coding and upstream flanking regions, and two adjacent Sp1-binding sites are necessary for promoter activity. Sp1 and Sp3 proteins are reported to regulate the expression of the mouse nestin gene[52]. The nestin gene has four exons and three introns, and neural cell-specific expression is reported to be regulated by the second intron, whereas nestin expression in tumor endothelium is enhanced by the first intron[53]. Nestin expression in muscle precursor cells is regulated by temporally and spatially restricted enhancer elements in the first intron[54]. Furthermore, the epigenetic regulation of nestin transcripts has been reported; histone acetylation is sufficient to mediate the activation of nestin transcription, but DNA demethylation is not[55]. Tissue- and cell-specific and spatiotemporal regulation of nestin is important for cell behavior during development or in pathological conditions. These observations also suggest that nestin is more than just a structural protein that serves as a progenitor stem cell marker.

NESTIN IN CNS TUMORS

Nestin has been implicated in the rapid proliferation of progenitor cells during neurogenesis[56]. However, when precursor cells differentiate into neural or glial cell types, nestin expression is downregulated or disappears[54,57]. Nestin mRNA is expressed at a high level in the cerebrum of the developing rat embryo on embryonic day 15, and the level decreases toward postnatal day 12, disappearing from postnatal day 18 to the adult stage[1]. Cells that express nestin have been found at the ventricular border in mammalian brains, and these cells give rise to neurons and glia in avian models[58,59]. Nestin expression has not been detected in normal astrocytes but is transiently detected in reactive astrocytes accompanying, for example, trauma, tumor growth, or neurodegenerative diseases in brain tissue[19,60-62].

Nestin expression has been reported in tumor cells originating from the CNS, including astrocytoma, ependymoma, oligodendroglioma, glioblastoma, and primitive neuroectodermal tumors[63-66]. Nestin has been detected in human gliomas, including low and high grade, but its expression has been observed more frequently in high-grade than in low-grade gliomas, such as pilocytic astrocytomas[66,67]. The downregulation of nestin in glioblastomas induces cell cycle arrest at the G1/S phase[68]. However, the roles of nestin in glial cell tumors have not been well clarified. Recent work has shown that nestin expression does not influence the *in vitro* proliferation of glioblastoma cell lines, while subclones characterized by high levels of nestin form larger tumors *in vivo* than those with low expression. Furthermore, blocking the expression of nestin in glioblastoma tumors via intratumoral injection of short hairpin RNA (shRNA) significantly slows tumor growth and volume[69]. We have also found that expression of nestin correlates with cell growth, migration, and invasion in low- and high-grade gliomas. These findings demonstrate that nestin plays important roles in the development of glioblastomas and may potentially be a target for treatment of the disease.

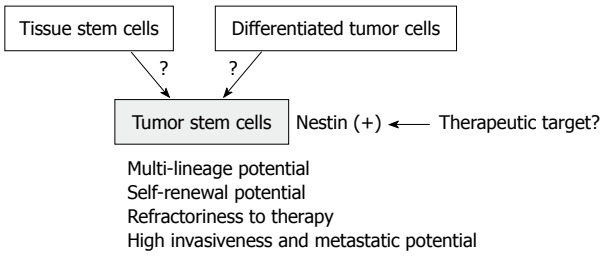

Figure 1 Tumor stem cells and nestin. Tumor stem cells have specific characteristics, including multi-lineage potential, self-renewal potential, refractoriness to therapy, and high invasiveness and metastatic potential. The origin of tumor stem cells has not been well clarified, but it is known that some tumor stem cells express nestin in their cytoplasm. Nestin in tumor stem cells thus is considered to be a novel therapeutic target.

Brain tumor stem cells (BTSCs), obtained by cell sorting of dissociated suspensions of tumor cells for the NSC marker CD133[70,71], also express nestin but not differentiated neural lineage markers. These $CD133^+$, $nestin^+$ cells represent a minority fraction of the entire brain tumor cell population, exclusively generate clonal tumor spheres in suspension culture, and exhibit increased self-renewal capacity. These findings suggest that nestin serves as a BTSC marker. Furthermore, it has been reported that tumor stem cells play crucial roles in tumor proliferation, invasion, and metastasis; therefore, nestin may be closely associated with these tumor stem cell functions. The origin of tumor stem cells has been controversial, but nestin may be a novel therapeutic target to suppress them (Figure 1).

NESTIN IN PANCREATIC CANCER

During early embryonic development, neuronal and islet cells in the pancreas share many phenotypic properties, and developing islet cells express several neuronal-specific markers[72-74]. In the adult pancreas, nestin-positive cells were initially described as a specific subpopulation of cells located in the endocrine islets, with a possible stem cell function[75]. Nestin-expressing cells also reside in the pancreatic ducts, where they may function as possible progenitor cells[76]. Nestin has been used as a selection marker for neuronal and pancreatic endocrine precursor cells[77,78] dur-

ing differentiation assays using embryonic and adult stem cells. Additionally, the isolation of nestin-expressing cells from rat and human islets, and their *in vitro* differentiation into pancreatic endocrine and exocrine cells, has led to the suggestion that nestin-positive cells have a role as multipotent pancreatic stem cells[76]. Moreover, nestin-positive cells do not necessarily serve as endocrine precursors during pancreas development in mice, rats and humans, or in a regenerating model of adult rat pancreas[11,79-81].

Lineage-tracing experiments have indicated that exocrine cells are derived from nestin-expressing progenitor cells in the pancreas[82-85]. In adult pancreas, localization of nestin has been reported in vascular endothelial cells and acinar cells at different levels but not in endocrine cells[86-89]. In the regenerative process of a rat acute pancreatitis model, nestin expression was observed in proliferating capillary endothelial cells, stellate cells surrounding ductular structures, and submesothelial cells[82].

Concerning nestin and pancreatic cancer, it has been demonstrated that activation of oncogenic K-ras in the nestin cell lineage is sufficient for initiation of premalignant pancreatic intraepithelial neoplasia in mice[90]. We have reported that nestin immunoreactivity is present in the cancer cells in about 30% of pancreatic ductal adenocarcinoma (PDAC) cases, and nestin expression in pancreatic cancer cells correlates with nerve invasion and the presence of cancer cells at the tumor resection margins[87]. We recently found that nestin expression also correlates with migration, invasion, and metastasis of pancreatic cancer cells.

Regarding pancreatic tumors other than PDAC, nestin expression has been reported in acinar cell carcinoma, pancreatoblastoma, solid-pseudopapillary neoplasm, and serous cystadenoma[91]. However, nestin is rarely detected in intraductal papillary-mucinous neoplasms, mucinous cystic neoplasm, or undifferentiated carcinoma cases.

NESTIN IN GISTs

Mesenchymal tumors consisting of spindle-shaped cells develop in the gastrointestinal tract, and they were at first believed to originate from smooth muscle or neuronal cells. However, subsequent studies have shown that most of the tumors do not have the typical features of smooth muscle or neuronal cells; therefore, the most common mesenchymal tumors that differ from leiomyomas or schwannomas are designated as GISTs. Most GISTs express *c-kit* receptor tyrosine kinase (KIT) and CD34; both of which are expressed in hematopoietic stem cells[92-95]. In some studies, nestin expression has been identified in most GIST cases examined but not in leiomyomas[25,96]. However, a subsequent study from the same group has shown that nestin is also highly expressed in gastrointestinal schwannomas; thus, nestin may not be a definitive marker for GIST[96]. Nestin expression has also been reported in granular cell tumors, considered to be benign neoplasms of Schwann cell origin in the gastrointestinal tract[97].

In the normal gastrointestinal tract, intestinal cells of Cajal (ICCs), which are localized between the circular and longitudinal muscle layers, express KIT and CD34. ICCs are assumed to originate from mesenchymal progenitor cells that can also differentiate into smooth muscle cells[98,99]. Expression of nestin in the ICCs and GIST supports the hypothesis that GIST is derived from ICCs.

NESTIN IN PROSTATE CANCER

Nestin is highly expressed in androgen-insensitive prostate cancer cell lines, but it has not been detected in androgen-dependent prostate cancer cells[27]. Furthermore, nestin has been localized in 75% of lethal androgen-independent prostate cancer cases, but is undetectable in localized androgen-deprived tumors and in metastases without prior androgen deprivation. Work using shRNA against nestin has shown a marked decrease of migration and invasion of prostate cancer cells *in vitro*, and nestin knockdown in prostate cancer cells inhibits lung metastasis of the cells[27]. Furthermore, it has been reported that nestin is a tumor stem cell marker of prostate cancer[36,100]. The underlying mechanisms have not been well examined, but nestin may be a novel therapeutic target for preventing the metastatic and cancer stem cell potential of prostate cancer.

NESTIN IN BREAST CANCER

In normal human breast tissues, nestin is expressed in the cells within the basal/myoepithelial layers[26,101,102] and may be used as a myoepithelial marker. In one of these cell types, nestin is co-expressed with ΔN-p63. This finding, coupled with the role of ΔN-p63 in preservation of self-renewal, suggests that nestin may be expressed in the regenerative compartment within the mammary gland. Furthermore, nestin and ΔN-p63 are coordinately expressed during pregnancy in the murine mammary gland[26].

Among the breast cancer subtypes, nestin is highly expressed in basal breast cancer subtype ($ER\alpha^-/PR^-/Her2^-$) but not in the Her2 subtype ($ER\alpha^-/PR^-/Her2^+$) or luminal epithelial phenotype ($ER\alpha^+/PR^+$)[26]. The other group showed that triple-negative breast cancers, which do not express ER, PR, and Her2, have higher expression rates for nestin than other breast cancers[103]. Furthermore, nestin expression has been associated with shorter survival and shown to be an independent prognostic factor of breast cancer[103]. Another group has reported significantly high nestin expression in basal-like and triple-negative breast cancers in a cohort of 245 patients with invasive breast cancer treated with surgery followed by anthracycline-based chemotherapy[104]. These findings indicate that nestin is a selective marker of the basal breast cancer subtype (triple negative), which displays aggressive growth and has a poor prognosis. Co-expression of nestin and melatonin receptor 1 (MT 1) in breast cancer cells has been reported in patients with higher stages (T Ⅱ/Ⅲ) and with a high risk of relapse. Co-expression of nestin and MT 1 may correlate with invasive breast cancer and ad-

vanced tumors[102]. Lymphovascular emboli of inflammatory breast cancer, a particularly lethal form of breast cancer characterized by exaggerated lymphovascular invasion, express stem cell markers including nestin[105]. These data indicate that nestin correlates with an aggressive growth phenotype and lymphatic invasion.

NESTIN IN MALIGNANT MELANOMA

Nestin is expressed in benign nevi and melanoma but not in basal cell carcinoma[106]. Nestin expression is higher at the advanced stage in melanoma and in metastatic foci of melanoma cells[24,107]. Nestin staining in stage Ⅰ and Ⅱ melanoma patients significantly predicts poor survival, with lower survival rates in cases with nestin positivity in tumoral and endothelial cells[108]. Furthermore, the 5-year survival rate exceeded 80% in nestin-negative melanoma at all stages of tumor development[109]. Nestin and SOX9 and SOX10 transcription factors are co-expressed in melanoma cells, and downregulation of SOX9 and SOX10 markedly decreases nestin levels[110,111]. Furthermore, nestin has been significantly associated with the presence of ulceration in primary tumors of melanoma and with SOX9 in the more advanced state. These findings indicate that nestin and SOX9 may be negative prognostic markers in melanoma. Nestin protein has been shown to occur most abundantly at the infiltrating front of the tumors, suggesting that nestin plays important roles in melanoma cell migration and invasion[106].

Nestin expression in the peripheral blood of melanoma patients has been examined using flow cytometry, and expression is higher in stage Ⅳ patients as compared with stage Ⅲ/Ⅳ with no evidence of the disease[112,113]. Nestin thus may be an additional marker of interest for circulating melanoma cells in the future.

Immunohistochemically, melanoma antigen-encoding-1 (MAGE-1), melanocyte-specific transcription factor, tyrosinase, and Melan-A have been reported as useful markers in the diagnosis of melanotic parts when HMB-45 is negative[114]. However, nestin has been more specifically detected in HMB-45-negative melanoma cells in the dermal portions of melanotic and amelanotic nodular melanomas[115]. Nestin thus also may be a useful diagnostic marker for HMB-45-negative melanoma.

NESTIN IN OTHER TUMORS

Few reports have addressed nestin expression in other types of tumor cells. Its expression has been reported in various kinds of thyroid tumors, and nestin mRNA has been detected in differentiated thyroid tumors but not in anaplastic carcinoma[22]. Nestin mRNA is also expressed in normal thyroid tissues, therefore, the authors of the above study have suggested that nestin mRNA is not associated with the malignant characteristics of thyroid tumors. Dermatofibrosarcoma protuberans (DFSP) is a dermal and subcutaneous neoplasm of intermediate malignancy that is invasive and locally aggressive with frequent recurrence. Histopathologically, the differential diagnosis between DFSP and dermatofibroma (DF) is important because DF is benign[28]. In one study, nestin was found to be strongly expressed in DFSP, while all DFs examined were nestin negative. Based on these findings, nestin may serve as an additional marker for DFSP and for surgical margin evaluation of DFSP.

NESTIN IN TUMOR ANGIOGENESIS

Tumor angiogenesis is an important factor in the proliferation, metastasis, and drug sensitivity of human neoplasms. A possible explanation of this metastatic mechanism is that the increased number of tumor vessels increases the chances for tumor cells to enter the circulation. Newly formed tumor vessels or capillaries have leaky and weak basement membranes; thus, tumor cells can penetrate these more easily than they can mature vessels[116]. Furthermore, increased tumor vessels supply abundant oxygen and nutrition to the tumor cells. Angiogenesis in malignant tumors, as measured by microvessel density (MVD), has been reported to correlate with clinicopathological factors or survival in breast, ovarian, esophageal, gastric, colorectal, and prostate cancers, malignant melanoma, and non-small-cell lung carcinoma[117-124]. CD34, CD31, and factor-Ⅷ-related antigen are commonly used as endothelial cell markers of tumor vessels, and MVD is determined based on staining of blood vessels with these markers[125-127]. However, the markers identify not only newly formed small tumor blood vessels but also pre-existing large blood vessels[128].

Nestin expression in endothelial cells accompanying the process of angiogenesis has been reported[129]. In pathological conditions, nestin is strongly expressed in proliferating endothelial cells in acute pancreatitis[82] and vascular malformations[130]. Furthermore, nestin has been reported to be a marker of proliferating endothelial cells in brain tumor tissues[131] (Table 2). In gastric adenocarcinoma, MVD determined by nestin correlates better with patient survival than MVD determined by CD34 when the size of the carcinoma exceeds 5 cm[37]. We examined the effectiveness of nestin as an angiogenic marker in colorectal cancer[38]. Diameters of nestin-positive and CD34-positive vessels were compared in subcutaneous colorectal cancer tumors formed in nude mice. Nestin was localized in the endothelial cells in small tumor blood vessels, whereas CD34 was localized in large blood vessels in nude mice. Furthermore, the diameter of nestin-positive vessels was smaller than that of CD34-positive vessels in human colorectal cancer. The ratio of proliferating cell nuclear antigen (PCNA)-positive to nestin-positive vascular endothelial cells was higher than that of PCNA-positive to CD34-positive cells. These findings indicate that nestin is expressed in small-sized and proliferating tumor vessels in colorectal cancer. Further, prognosis is worse in the highly nestin-positive MVD population of colorectal cancer patients. In pancreatic cancer tissues, CD31 is expressed in endothelial cells of most blood vessels, while nestin is

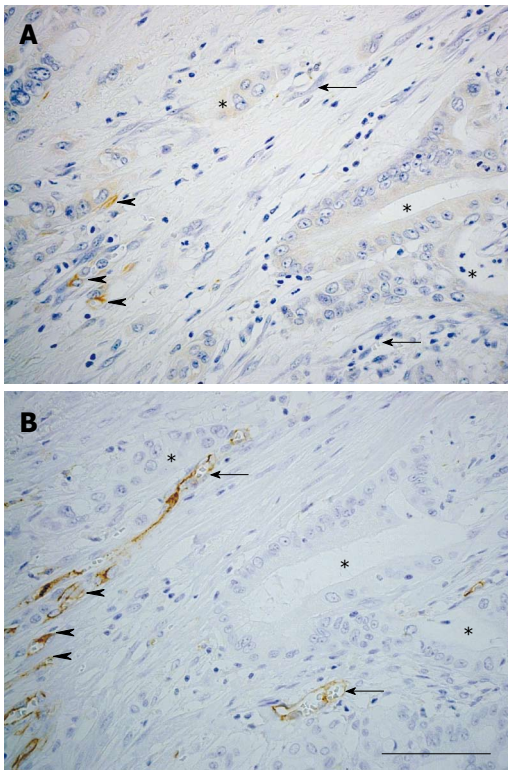

Figure 2 Expression of nestin and CD31 in pancreatic cancer tissues. Nestin is expressed in endothelial cells of small blood vessels (A, arrowheads) and cancer cells (asterisks), whereas it is not detected in large blood vessels (arrows). CD31 is expressed in endothelial cells of most blood vessels (B, arrowheads and arrows), but not in cancer cells (B, asterisks) in pancreatic tissues. Immunohistochemistry: bar, 100 μm.

specifically expressed in those of small-sized blood vessels (Figure 2).

Recently, co-expression of nestin and Ki-67 has been shown to be a vascular proliferation marker in prostate cancer[39], and vascular proliferation is of independent prognostic importance among prostate cancer. Furthermore, vascular proliferation is significantly increased in castration-resistant cases and metastatic lesions compared with localized cancers. Very recently, nestin expression has been reported in the endothelial cells of bone metastatic lesions of prostate cancer[40]. These results indicate that nestin correlates with tumor angiogenesis in primary and metastatic lesions, and that nestin may be a novel molecular target for inhibition of tumor angiogenesis, as are vascular endothelial growth factor receptors (Figure 3).

CONCLUSION

Nestin is highly expressed in various kinds of cancer cells and proliferating tumor vasculature. The roles of nestin in cancer cells have not been clarified fully, although nestin correlates with growth, migration, invasion, and metastasis of some cancers. Nestin is also highly expressed in proliferating vascular endothelial cells in cancer tissues and metastatic lesions. These findings indicate that this protein may become a new molecular target for nestin-positive

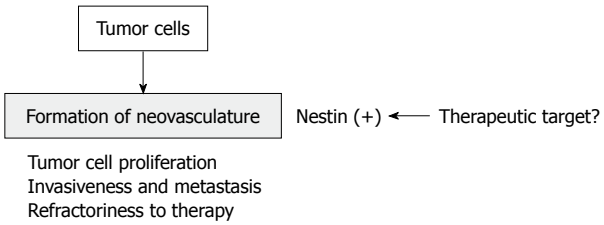

Figure 3 Tumor angiogenesis and nestin. Tumor cells induce neovascular formation, known as tumor angiogenesis. Formation of the neovasculature leads to tumor aggressiveness through tumor cell proliferation, invasiveness, metastasis, and refractoriness to therapy. Nestin expression has been reported in tumor vessels, and nestin may be a new molecular target for tumor angiogenesis.

cancer cells and tumor vessels. Furthermore, nestin is highly expressed in tumor stem cells in various tissues, and research concerning its expression and roles in various tumors may provide us important information about the origin of cancer stem cells and differentiation of cancer stem cells into cancer cells.

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