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# The Role of the Tumor Microenvironment in the Pathogenesis of Cholangiocarcinoma

Matthew Quinn, Matthew McMillin, Gabriel Frampton,  
Syeda Humayra Afroze, Li Huang and Sharon DeMorrow  
*Digestive Disease Research Center, Department of Internal Medicine  
Scott & White Hospital and Texas A&M Health Science Center  
Research Service, Central Texas Veterans Health Care System  
Temple, Texas,  
USA*

## 1. Introduction

Cholangiocarcinoma is a type of liver cancer arising from the neoplastic transformation of the epithelial cells that line the intra- and extrahepatic bile ducts. Symptoms are usually evident only after blockage of the bile duct by the tumor. This is an extremely aggressive tumor, which has very poor prognosis and limited treatment options. Cholangiocarcinoma is relatively resistant to chemotherapy and radiation therapy leaving conventional treatment like surgery as the only option. Therefore, further understanding into the factors that are involved in tumor initiation, promotion and progression is required for designing alternate therapies to combat this devastating disease.

The tumor microenvironment is one of the most important factors regulating tumor angiogenesis, tumor invasion and metastasis. The microenvironment is a well-recognized system that plays a key role in tumor progression. However, the mechanism through which tumor microenvironment regulates tumor progression and invasion is largely unknown. In this review, we discuss the current knowledge about the role of the tumor microenvironment in the pathogenesis of cholangiocarcinoma, the role of the tumor microenvironment in the classification of cholangiocarcinoma and efforts to develop treatments targeting the tumor microenvironment.

## 2. Background

Cholangiocarcinoma arises from the neoplastic transformation of cholangiocytes and can exist as either intrahepatic, perihilar or distal extrahepatic tumors (Alpini et al. 2001). Typically, cholangiocarcinomas are adenocarcinomas and have a poor prognosis and limited treatment options. This is due, at least in part, to the late presentation of symptoms and the relative resistance to current treatment options (Sirica 2005).

The incidence of both intra- and extra-hepatic cholangiocarcinoma is typically more prevalent in Asian countries (Patel 2002). The mortality rates for intrahepatic cholangiocarcinoma have increased since the 1970s, whereas deaths from extrahepatic cholangiocarcinoma have declined in most countries (Patel 2002). There is a slight

preponderance for cholangiocarcinoma in males (Tominaga and Kuroishi 1994) and the incidence in both sexes increases with age (Patel 2002).

## 2.1 Risk factors

Cholangiocarcinoma occurs with varying frequency in different regions of the world. This can be explained in part by the distribution of risk factors in geographic regions and ethnic groups (Ben-Menachem 2007). The common link between these regional risk factors seems to involve chronic inflammation and biliary irritation (Gores 2003).

The prevalence of cholangiocarcinoma in Asian countries shares a relationship with infections such as liver flukes, Hepatitis B and Hepatitis C (Ben-Menachem 2007). In contrast, approximately 90% of patients diagnosed with cholangiocarcinoma in Western countries do not have any recognized risk factors (Ben-Menachem 2007). However, the remaining 10% of cases are associated with certain risk factors. Apart from factors related to chronic inflammation, both intra- and extrahepatic cholangiocarcinomas are well-known complications of primary sclerosing cholangitis (de Groen et al. 1999). Other known risk factors include obesity, hepatolithiasis, bacterial infection and/or bile stasis-related chronic cholangitis (Chen 1999; de Groen et al. 1999; Catalano et al. 2009).

## 3. Tumor microenvironment

Neoplastic epithelial cells coexist with a biologically complex stroma composed of various types of stromal cells as well as the extracellular matrix, both of which create the complexity of the tumor microenvironment (Orimo and Weinberg 2006). Mouse models of tumorigenesis have revealed that stromal cells, in particular inflammatory cells, vascular endothelial cells and fibroblasts actively support tumor growth (Olumi et al. 1999; Tlsty 2001; Cunha et al. 2003; Bhowmick et al. 2004). In addition, the microenvironment is now well recognized as playing a role in neoplastic transformation, malignant progression and metastasis and invasion of cancer cells (Tlsty 2001; Bhowmick et al. 2004). Furthermore, the interaction between the cancer cells and the tumor microenvironment is a major factor influencing cancer treatment resistance to radiotherapy and chemotherapy (de Visser and Jonkers 2009; Shinohara and Maity 2009). Research indicates that the interplay between the cancer cells and the stromal cells of the microenvironment is bi-directional and dynamic. For example, neoplastic cells often secrete factors that work in a paracrine manner to recruit and activate a number of types of stromal cells into the tumor microenvironment as required (Rasanen and Vaheri 2010; Rojas et al. 2010; Onimaru and Yonemitsu 2011). Conversely, stromal cells, once recruited and activated, release factors into the extracellular milieu that can either stimulate or inhibit growth of the tumor (Rasanen and Vaheri 2010; Rojas et al. 2010; Onimaru and Yonemitsu 2011). The effects of the components of the tumor microenvironment on tumor growth are summarized in Figure 1. In particular, the proliferation and recruitment of vascular endothelial cells and subsequent formation of new blood vessels brings a nutrient supply thereby allowing growth and metastasis of the tumor. Cancer associated fibroblasts, on the other hand, can stimulate angiogenesis as well promote tumor growth and invasion. The presence of immune cells, in particular tumor-associated macrophages, in the microenvironment, confers resistance to toxic insults and also promotes growth. Lastly, proliferation of lymph endothelial cells and subsequent increase in lymphatic vessel density promotes tumor metastasis.

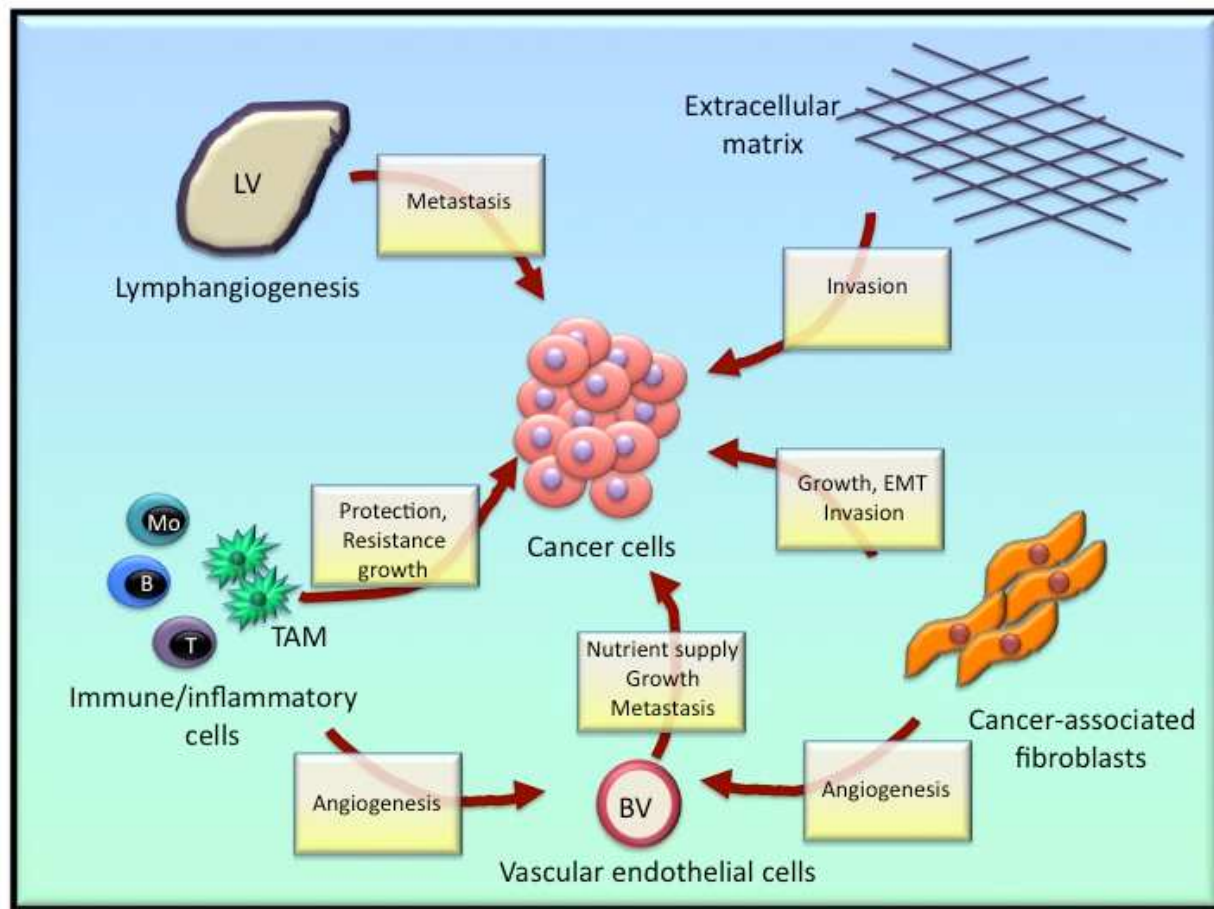


Fig. 1. Schematic representation of the effects of stromal support cells on tumor growth and metastasis. Abbreviations: B, B cell; BV, Blood vessel; EMT, Epithelial-mesenchymal transition; LV, lymph vessel; M, monocyte; T, T cell; TAM, Tumor associated macrophage.

### 3.1 Angiogenesis

The physiological process of the formation of new blood vessels from pre-existing blood vessels is termed angiogenesis. Tumors require the formation of new blood vessels to supply oxygen and other essential nutrients, without which their growth would be severely restricted (McDougall et al. 2006). Generally, the process of angiogenesis involves a sequence of co-ordinated events that is initiated with the expression and release of various angiogenic factors from the tumor cells, such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and fibroblast growth factor (FGF). Once these angiogenic factors bind to their corresponding receptors on the cell surface of the endothelial cells, there is an increase in vascular permeability, leading to extravasation of plasma proteins and dissociation of pericyte coverage (Roberts and Palade 1997; Dvorak 2005). This is followed by proliferation and migration of the endothelial cells to initiate new vessel formation (Ausprunk and Folkman 1977). For new vessel formation to occur, there also needs to be localized degradation of the extracellular matrix, which is performed by the matrix metalloproteinases, cathepsin B and other degradation enzymes, as well as the expression of matrix proteins such as fibronectin and laminin (Mikkelsen et al. 1995; Gladson 1999; Ljubimova et al. 2006). The expression of these essential extracellular matrix proteins largely

occurs in the tumor cells or cancer associated fibroblasts (Rasanen and Vaheri 2010), which then secrete them into the extracellular milieu.

### 3.1.1 Angiogenesis in cholangiocarcinoma

A recent immunohistochemical study of microvessel density and lymphatic microvessel density revealed that intrahepatic cholangiocarcinoma tumors demonstrated tumor-associated angiogenesis (Thelen et al. 2009). Tumors with increased microvessel density were correlated with a higher recurrence rate, lower 5-year survival rates and increased nodal spread which in turn influences patient survival (Thelen et al. 2009). Recent studies have also shown that the overexpression of the angiogenic factors nerve growth factor- $\beta$  (NGF- $\beta$ ) and vascular endothelial growth factor-C (VEGF-C) occurred in approximately 57.1% and 46.4% of cholangiocarcinoma samples, respectively (Xu et al. 2010). A number of human cholangiocarcinoma cell lines and samples have also been shown to overexpress VEGF-A and VEGF receptors (VEGFRs), the angiogenic factors angiopoietin-1, -2, and thrombospondin-1, as well as EGF, EGF receptors (EGFR) and basic fibroblast growth factor (Ogasawara et al. 2001; Alvaro et al. 2006; Tang et al. 2006; Yoshikawa et al. 2008; Harder et al. 2009). Secretion of these factors may individually or co-ordinately bring about increased angiogenesis as demonstrated by increased microvessel density. For example, VEGF-A has been shown to play a role in the neovascularization of extrahepatic cholangiocarcinoma (Mobius et al. 2007).

The factors that drive angiogenesis have also been shown to have distinct effects on cholangiocyte and cholangiocarcinoma growth in an autocrine manner (Gaudio et al. 2006; Tang et al. 2006; Mobius et al. 2007; Yabuuchi et al. 2009; Yoshikawa et al. 2009; Glaser et al. 2010). Indeed, the proliferative effects of estrogen on cholangiocarcinoma cell lines have been attributed to a mechanism involving the upregulation of VEGF expression, as blocking VEGF ameliorates the estrogenic effects on proliferation (Mancino et al. 2009).

Taken together, these data suggest that agents that block angiogenesis (by blocking VEGF expression, for example) may also have a direct effect on cholangiocarcinoma cell proliferation in addition to their anti-angiogenic effects. In support of this notion, inhibition of VEGFR and EGFR signaling with vandetanib (ZD6474, a tyrosine kinase inhibitor) can be an important approach for the management of the subset of cholangiocarcinoma that lack KRAS mutations and/or have EGFR amplification (Yoshikawa et al. 2009). Furthermore, ZD1839 (IRESSA), an orally active, selective inhibitor of EGFR tyrosine kinase has clinical activity against cholangiocarcinoma by stabilizing the cell cycle inhibitor, p27Kip1 and enhancing radiosensitivity in cholangiocarcinoma cell lines (Yabuuchi et al. 2009). Curcumin, a natural phenol found in tumeric has recently been shown to suppress the expression of VEGF and decrease the microvessel density in a hamster model of cholangiocarcinoma (Prakobwong et al. 2011a). In parallel, curcumin also exerts antiproliferative and proapoptotic effects on cholangiocarcinoma cells independent of the effects on angiogenesis (Prakobwong et al. 2011a; Prakobwong et al. 2011b). Similar effects have been shown with inhibitors of histamine synthesis (Francis et al. 2011), H3 histamine receptor agonists (Francis et al. 2009), and Endothelin-1 (Fava et al. 2009) just to name a few. The interaction between angiogenesis, angiogenic factors and cholangiocarcinoma growth and progression is summarized in Figure 2.



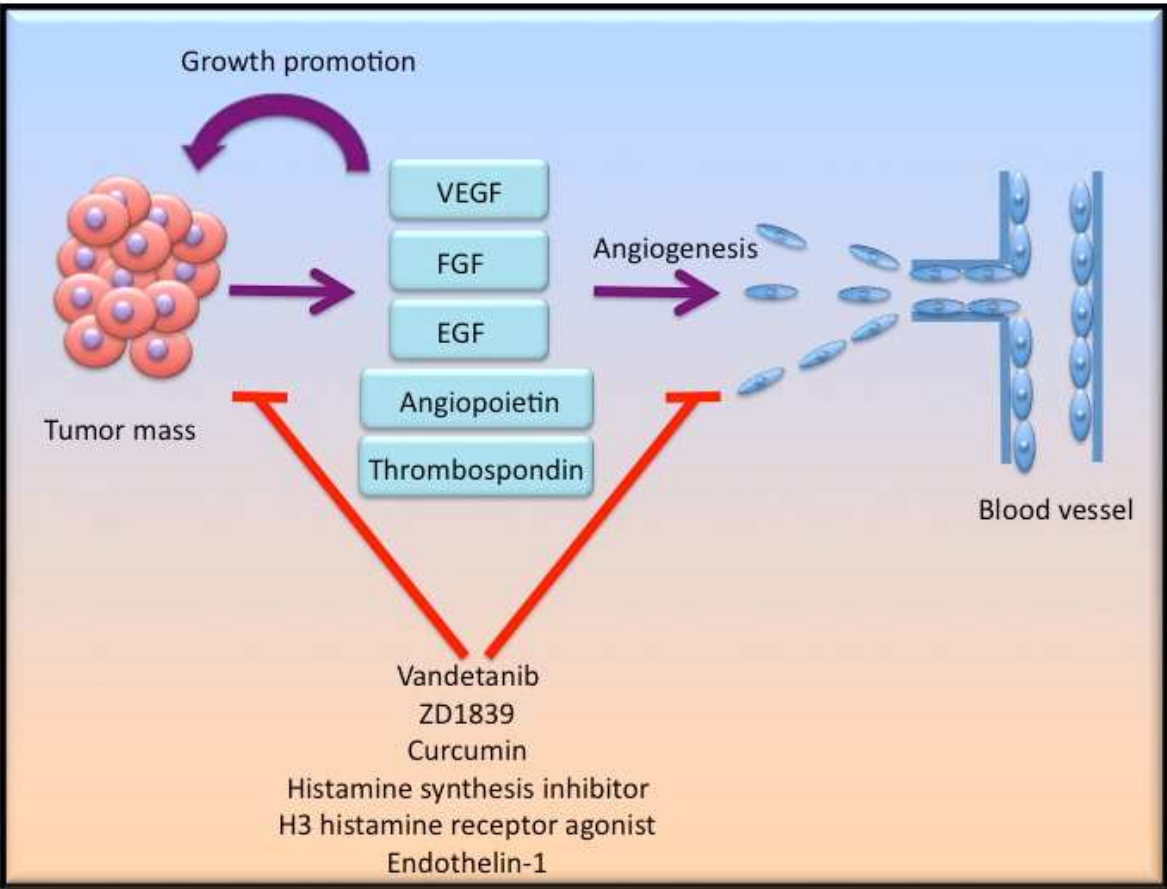


Fig. 2. Schematic representation of the interactions between cholangiocarcinoma and angiogenic factors regulating cell proliferation and angiogenesis

3.2 Cancer associated fibroblasts

Under normal physiological conditions, fibroblasts have a low proliferative index and only secrete factors needed to maintain normal tissue homeostasis (Tuxhorn et al. 2001; Beacham and Cukierman 2005). Indeed, normal fibroblasts provide biochemical cues that constrain epithelial tumor cells within their basement membrane (Tuxhorn et al. 2001; Beacham and Cukierman 2005). In contrast, when homeostasis is disrupted during tissue injury, stromal cells rapidly and reversibly alter their phenotype and proliferation rate (Tuxhorn et al. 2001). However, during tumorigenesis, the fibroblastic wound healing machinery lacks the regulatory mechanisms to revert to normal homeostasis (Tuxhorn et al. 2001). The inability to down-regulate the wound healing response affects stromal dynamics. Tumor-dependent changes in signaling and plasticity of the stroma trigger a continuum of alterations yielding a ‘primed’ stroma that can support and incite tumor initiation or progression (Tuxhorn et al. 2001).

3.2.1 Cancer-associated fibroblasts in cholangiocarcinoma

Cancer-associated fibroblasts are the predominant cell type in the stroma of cholangiocarcinoma tumors (Sirica et al. 2009). Increased  $\alpha$ -smooth muscle actin-positive fibroblasts were correlated with shorter survival times and larger tumor sizes in resected

cholangiocarcinoma tissue (Chuaysri et al. 2009; Okabe et al. 2009). The origin of these cancer-associated fibroblasts is unknown, although a number of possibilities have been suggested, including hepatic stellate cells (Okabe et al. 2009), portal fibroblasts (Dranoff and Wells 2010) or circulating bone marrow-derived precursor cells (Shimoda et al. 2010). Given the apparent heterogeneous population of cancer-associated fibroblasts observed in cholangiocarcinoma tumors, it is highly likely that these fibroblasts are derived from more than one source. Recently, researchers have performed genetic screening to determine the differences in gene expression between cholangiocarcinoma-derived cancer-associated fibroblasts and non-malignant liver fibroblasts and showed a number of genes associated with angiogenesis, cell proliferation and motility (Utispan et al. 2010). In particular, periostin, a cell adhesion molecule, was shown to be significantly upregulated correlating with shorter survival time in patients and increased cell proliferation and invasive properties *in vitro* (Utispan et al. 2010). Another gene specifically expressed by cholangiocarcinoma-derived cancer-associated fibroblasts is the extracellular matrix protein tenascin-C (Aishima et al. 2003; Iguchi et al. 2009). This gene was expressed predominantly in the stroma near the invasion front of the tumor (Aishima et al. 2003) and was associated with poor prognosis in intrahepatic cholangiocarcinoma (Aishima et al. 2003; Iguchi et al. 2009). Furthermore, the expression of thrombospondin-1 by cancer-associated fibroblasts correlated with increased metastasis (Kawahara et al. 1998; Tang et al. 2006).

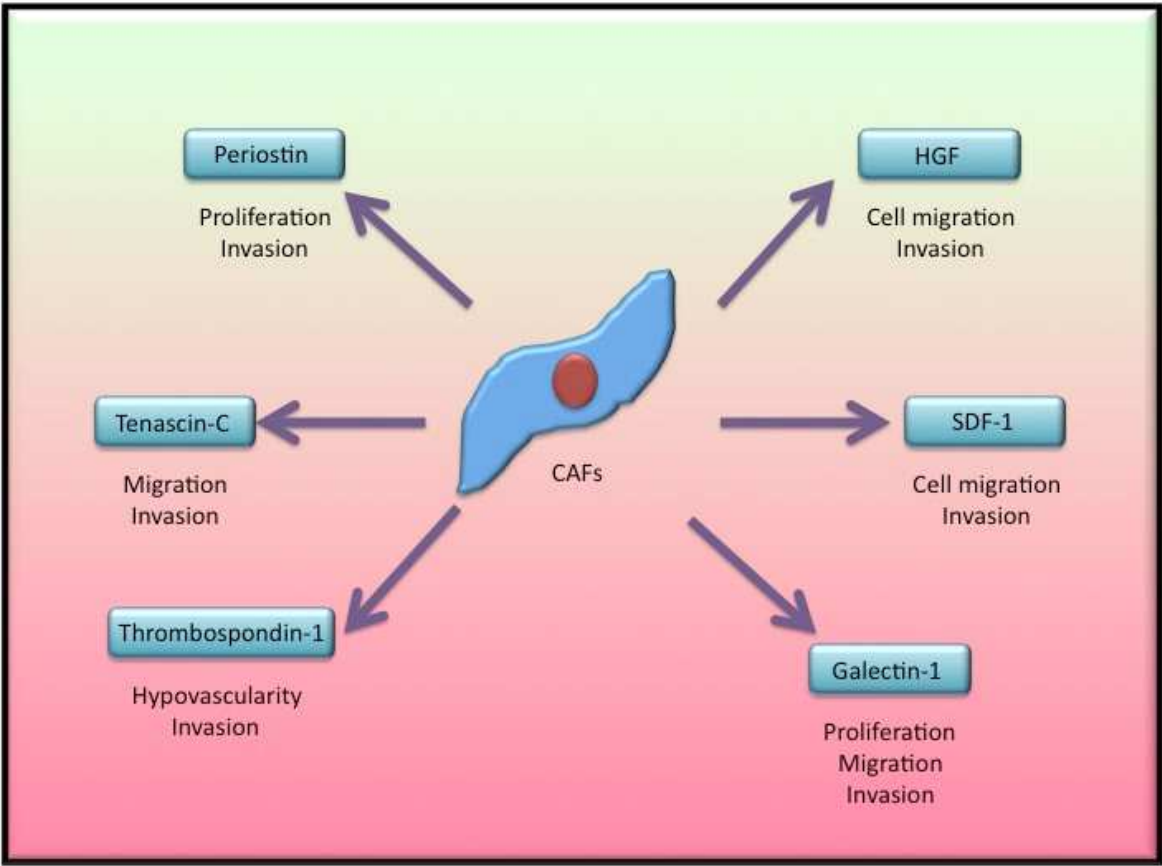


Fig. 3. Summary of the signalling molecules released by cholangiocarcinoma-derived cancer-associated fibroblasts and their known effects on cholangiocarcinoma progression. CAFs; cancer-associated fibroblasts, HGF; hepatocyte growth factor, SDF-1; stromal derived factor-1.

One last cancer-associated fibroblast gene of note is the expression of the chemokine, stromal-derived factor 1, which is released from stromal fibroblasts and stimulates the invasion and migration of cholangiocarcinoma cells via interaction with the chemokine receptor, CXCR4 (Ohira et al. 2006). A summary of these and other cholangiocarcinoma-derived cancer-associated fibroblasts can be found in Figure 3.

The preponderance of data demonstrating a role for cancer-associated fibroblasts in the growth and invasion of cholangiocarcinoma suggest that targeting molecular signals released from cancer-associated fibroblasts may be a viable option, in addition to strategies for suppressing cholangiocarcinoma cell proliferation, for the treatment of cholangiocarcinoma.

3.3 Tumor-associated macrophages

Inflammation and the immune system share a long-standing relationship with tumor initiation and progression. Indeed, the primary risk factor for the development of a number of different tumor types is chronic inflammation of the target organ (Sica 2010). Once a tumor is initiated, tumor-associated macrophages (TAMs) are the major immune cell found within tumors. Macrophages generally have the potential to express and secrete pro- and anti-inflammatory molecules, and as such, may have pro- and anti-tumor activities depending upon the activation stimulus (Sica 2010). For example, macrophages activated with tumor necrosis factor  $\alpha$ , (considered M1 activation), have anti-tumor activity and signal tissue destruction (Mantovani et al. 2002). Alternatively, in response to interleukin-4, macrophages undergo M2 activation and are involved in tissue repair, remodelling and tumor promotion (Mantovani et al. 2002).

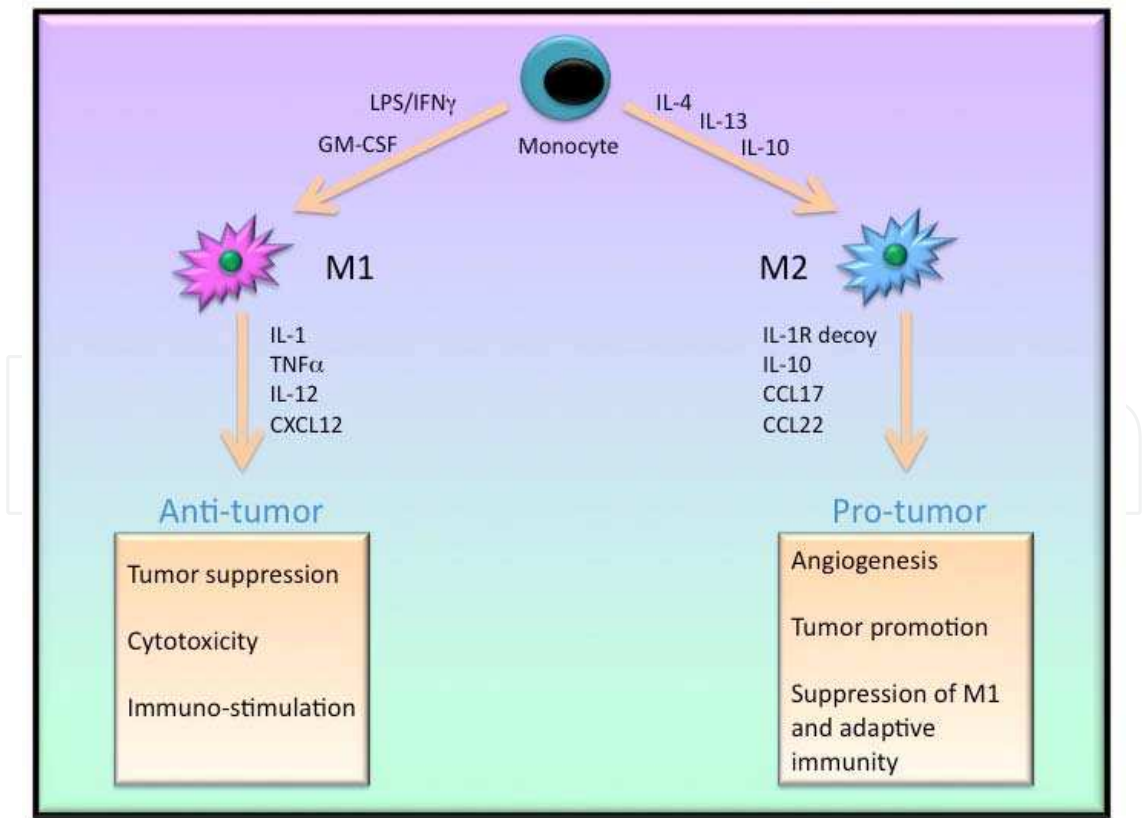


Fig. 4. Schematic representation of the pro- (M1) and anti-(M2) inflammatory activation of macrophages and their effect on tumor growth.



Logically, most TAMs have an M2-like phenotype (Mantovani and Sica 2010) thought to be brought about by various signals expressed within the tumor microenvironment, including interleukin-10, transforming growth factor- $\beta$  and colony stimulating factor-1 (Sica 2010). These signals responsible for the M2-activation of macrophages have been reported to come from myeloid-derived suppressor cells, IL-10+ B lymphocytes, Th2 subtype of T helper cells and the tumor cells themselves (Sica 2010). Once alternatively activated, TAMs exhibit reduced anti-tumor activities, while increasing the production of mediators of angiogenesis such as VEGF and IL-10 (Mantovani and Sica 2010), as well as M2-specific genes that are known to be involved in promoting cell proliferation (Mantovani and Sica 2010). These events are summarized in Figure 4.

It has been proposed that strategies to inhibit the M2- and activation of the M1-inducing signals may lead to the restoration of the anti-tumor functions of TAM and help to remove the protective signals originating from the M2 TAM (Sica and Bronte 2007), which may trigger an innate immune response, thereby reducing tumor size (Sica 2010).

### 3.3.1 Tumor-associated macrophages in cholangiocarcinoma

As mentioned previously, cholangiocarcinoma shares a long-standing relationship with chronic inflammation (Gores 2003). Indeed, cholangiocarcinoma cells are known to over-produce many inflammatory cytokines, with IL-6 being the most studied (Isomoto et al. 2007). The role of TAMs in the development and progression of cholangiocarcinoma is poorly understood. However, recent studies have demonstrated that the density of infiltrating macrophages (as demonstrated using the MAC387 antibody to specifically stain macrophages) was high in over half of the tumor samples studied and that a high density of MAC387-positive cells correlated to a poor survival rate although conclusive proof that these cells were of the M2-phenotype is lacking (Subimerb et al. 2010a). Similarly, a subset of monocytes (CD14<sup>+</sup>CD16<sup>+</sup>) thought to be the precursors of tissue-resident macrophages are increased in the blood from cholangiocarcinoma patients, the levels of which were correlated with the density of MAC387-positive infiltrating macrophages (Subimerb et al. 2010b). The circulating CD14<sup>+</sup>CD16<sup>+</sup> monocytes also expressed higher levels of angiogenic factors such as VEGF and the chemokine CXCL3 (Subimerb et al. 2010b). Lastly, Hasita et al. demonstrated that the macrophages infiltrating intrahepatic cholangiocarcinoma are mainly of the M2 phenotype (using CD163 as a marker of M2-type macrophages); their number correlates closely with neovascularization and infiltration of FOXP3<sup>+</sup> regulatory T cells (Hasita et al. 2010). Furthermore, treatment of macrophages in culture with the supernatant from a number of CCA cells induced macrophage polarization toward the M2 phenotype and induced the macrophage-derived expression and secretion of VEGF-A, IL-10 and TGF $\beta$  (Hasita et al. 2010). Taken together, these data suggest that TAMs may play a role in cholangiocarcinoma progression. However, the molecules regulating the crosstalk between M2-type TAMs and cholangiocarcinoma cells needs to be further clarified.

### 3.4 Lymphangiogenesis in cancer

Tumor metastasis is the most lethal aspect of cancer. The spread of tumor cells is often via the lymphatic vasculature and the presence of tumor foci in lymph nodes is considered an adverse prognostic factor in most carcinomas (Achen and Stacker 2008). Metastatic spread of tumor cells via the lymphatic system was previously thought to be via a passive process by

which detached tumor cells enter pre-existing lymphatic vessels in the vicinity of the tumor (Achen and Stacker 2008). However, recent studies suggest that the formation of new lymphatic vessels in the tumor microenvironment correlates with lymphatic metastasis (Achen et al. 2005).

To date, the growth factors recognized to be associated with the control of lymphangiogenesis are similar to those that control angiogenesis. That is, the most characterized factors are VEGF-C and VEGF-D, which are secreted from the tumors, and then activate VEGFR-3 expressed on lymphatic endothelium (Lymboussaki et al. 1998). Activation of VEGFR-3 induces the proliferation of lymphatic endothelial cells *in vitro* (Makinen et al. 2001) and the formation of new lymphatic vessels *in vivo* (Veikkola et al. 2001). Other identified lymphangiogenic factors include VEGF-A (Nagy et al. 2002), fibroblast growth factor-2 (Kubo et al. 2002), angiopoietin-2 (Gale et al. 2002) and platelet-derived growth factor-BB (Cao et al. 2004).

Because of the overlap in angiogenic and lymphangiogenic activity of the above-mentioned factors, agents designed to block angiogenesis may also be effective in blocking lymphangiogenesis. For example, inhibitors that block the VEGF-C/VEGF-D/VEGFR3 signalling mechanism might have the potential to not only block angiogenesis, but to also block lymphangiogenesis and hence to block lymphogenous metastatic spread (Baldwin et al. 2002; Stacker et al. 2002a; Stacker et al. 2002b). Indeed, a neutralizing VEGF-D monoclonal antibody designed to block the interaction between VEGF-D and its receptors, inhibited angiogenesis, lymphangiogenesis and metastatic spread via the lymphatics in a mouse tumor model (Stacker et al. 2001). Further studies into therapeutic strategies designed to block lymphangiogenesis are required in an attempt to stop the metastatic spread of tumors.

### 3.4.1 Lymphangiogenesis in cholangiocarcinoma

The role of lymphangiogenesis in cholangiocarcinoma metastasis and progression is largely unknown and controversial. However, recent studies suggest that there is a correlation between lymphangiogenesis and lymph node metastases and prognosis; patients diagnosed with cholangiocarcinoma tumors exhibiting low lymphatic vessel density have a longer survival rate than those with higher lymphatic vessel density (Thelen et al. 2008). In addition, in intrahepatic cholangiocarcinoma tumors, high lymphatic vessel density correlated with increased nodal spread and higher recurrence rate (Thelen et al. 2009). Conversely, other researchers demonstrated that in intrahepatic cholangiocarcinoma tumors, lymph node metastasis did not correlate with lymphangiogenesis, but did correlate with VEGF-C expression and the presence of a subset of myofibroblasts expressing the same markers as lymphendothelial cells (Aishima et al. 2008), which may explain the discrepancy in conclusions.

NGF has previously been linked to tumor progression and growth (Sortino et al. 2000; Descamps et al. 2001a; Descamps et al. 2001b) as well as VEGF expression (Lazarovici et al. 2006a; Lazarovici et al. 2006b) in a number of other cell types. Therefore, Xu et al. assessed the correlation of NGF- $\beta$  expression with lymphangiogenesis, lymph node metastasis or VEGF-C expression in hilar cholangiocarcinoma tissue (Xu et al. 2010). Indeed, high NGF expression was correlated with VEGF-C overexpression, lymphatic vessel density, and lymph node metastasis suggesting that NGF may also be responsible for stimulating lymphangiogenesis in cholangiocarcinoma tumors.

#### 4. Conclusions

The work highlighted in this review clearly demonstrates a role for the tumor microenvironment in the growth, progression and metastatic invasion of cholangiocarcinoma. There is obviously a strong interplay between the cells found in the stroma and cholangiocarcinoma cells with signaling molecules passing back and forth between the cell types to co-ordinately support an environment that nurtures tumor growth and suppresses innate immunity while conferring resistance to cytotoxic insults (both endogenous and chemotherapeutic). The mechanism by which each of the support cells found in the stroma of cholangiocarcinoma tumors are recruited and activated is still largely unknown. Therapeutic strategies designed to target the microenvironment rather than specifically targeting the cholangiocarcinoma cells might prove fruitful in the quest to combat this devastating cancer.

#### 5. Acknowledgements

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#### 6. References

- Achen, M., McColl, B., & Stacker, S. (2005). Focus on lymphangiogenesis in tumor metastasis. *Cancer Cell* Vol. 7 Issue 2 (Feb 2005). pp 121-7. ISSN 1535-6108
- Achen, M. & Stacker, S (2008). Molecular control of lymphatic metastasis. *Ann N Y Acad Sci* Vol. 1131 (May 2008), pp 225-34. ISSN 0077-8923
- Aishima, S., Nishihara, Y., Iguchi, T., Taguchi, K., Taketomi, A., Maehara, Y., & Tsuneyoshi, M. (2008). Lymphatic spread is related to VEGF-C expression and D2-40-positive myofibroblasts in intrahepatic cholangiocarcinoma. *Mod Pathol* Vol 21, Issue 3(Mar 2008), pp 256-64. ISSN 0893-3952.
- Aishima, S., Taguchi, K., Terashi, T., Matsuura, S., Shimada, M., & Tsuneyoshi, M. (2003). Tenascin expression at the invasive front is associated with poor prognosis in intrahepatic cholangiocarcinoma. *Mod Pathol* Vol 16, issue 10 (Oct 2003). pp 1019-27. ISSN 0893-3952
- Alpini, G., Prall, R., & LaRusso, NF. (2001). The pathobiology of biliary epithelia. *The Liver; Biology & Pathobiology*, 4E: pp 421-435.
- Alvaro, D., Barbaro, B., Franchitto, A., Onori, P., Glaser, S., Alpini, G., Francis, H., Marucci, L., Sterpetti, P., Ginanni-Corradini, S., Onetti Muda, A., Dostal, D., De Santis, A., Atilli, A., Benedetti, A., & Gaudio, E. (2006). Estrogens and insulin-like growth factor 1 modulate neoplastic cell growth in human cholangiocarcinoma. *Am J Pathol* Vol 169, Issue 3 (Sep 2006), pp 877-88. ISSN 0002-9440.
- Ausprunk, D. H. & Folkman J. (1977). Migration and proliferation of endothelial cells in preformed and newly formed blood vessels during tumor angiogenesis. *Microvasc Res* Vol 14, Issue 1 (Jul 1977) pp 53-65. ISSN 0026-2862.
- Baldwin, M. E., Stacker, S.A & Achen, M.G. (2002). Molecular control of lymphangiogenesis. *Bioessays* Vol 24, issue 11 (Nov 2002) pp 1030-40. ISSN 0265-9247.

- Beacham, D. A. & Cukierman E. (2005). Stromagenesis: the changing face of fibroblastic microenvironments during tumor progression. *Semin Cancer Biol* Vol 15, Issue 5 (Oct, 2005), pp 329-41. ISSN 1044-579X.
- Ben-Menachem, T. (2007). Risk factors for cholangiocarcinoma. *Eur J Gastroenterol Hepatol* Vol 19, Issue 8 (Aug 2007), pp 615-7. ISSN 0954-691X
- Bhowmick, N. A., Neilson, E. G. & Moses H.L (2004). Stromal fibroblasts in cancer initiation and progression. *Nature* Vol 432, Issue 7015 (Nov 2004) pp 332-7. ISSN 1476-4687
- Cao, R., Bjorndahl, M.A., Religa, P., Clasper, S., Garvin, S., Galter, D., Meister, B., Ikomi, F., Tritsarlis, K., Dissing, S., Ohhashi, T., Jackson, D.G., & Cao Y (2004). PDGF-BB induces intratumoral lymphangiogenesis and promotes lymphatic metastasis. *Cancer Cell* Vol 6, Issue 4 (Oct 2004), pp 333-45. ISSN 1535-6108.
- Catalano, O.A., Sahani, D.V., Forcione, D.G., Czermak, B., Liu, C.H., Soricelli, A., Arellano, R.S., Muller, P.R., & Hahn, P.F. (2009). Biliary infections: spectrum of imaging findings and management. *Radiographics* Vol 29, Issue 7 (Nov 2009), pp 2059-80. ISSN 1527-1323.
- Chen, M. F. (1999). Peripheral cholangiocarcinoma (cholangiocellular carcinoma): clinical features, diagnosis and treatment. *J Gastroenterol Hepatol* Vol 14 Issue 12 (Dec 1999) pp 1144-9. ISSN 0815-9319.
- Chuaysri, C., Thuwajit P., Paupairoj, A., Chau-In, S., Suthiphongchai, T., & Thuwajit, C. (2009). Alpha-smooth muscle actin-positive fibroblasts promote biliary cell proliferation and correlate with poor survival in cholangiocarcinoma. *Oncol Rep* Vol 21, Issue 4 (Apr 2009) pp 957-69. ISSN 1021-335X.
- Cunha, G. R., Hayward S. W., Wang, Y.Z., & Ricke, W.A. (2003). Role of the stromal microenvironment in carcinogenesis of the prostate. *Int J Cancer* Vol 107 Issue 1 (Oct 2003), pp 1-10. ISSN 0020-7136.
- de Groen, P. C., Gores G. J., LaRusso, N.F., Gunderson, L.L., & Nagorney, D.M. (1999). Biliary tract cancers. *N Engl J Med* Vol 341, Issue 18 (Oct 1999) pp 1368-78. ISSN 0028-4793.
- de Visser, K. E. & Jonkers, J. (2009). Towards understanding the role of cancer-associated inflammation in chemoresistance. *Curr Pharm Des* Vol 15 Issue 16 (Jun 2009) pp 1844-53. ISSN 1873-4286.
- Descamps, S., Pawlowski V., Revillion, F., Hornez, L., Hebbar, M., Boilly, B., Hondermarck, H., & Peyrat, J.P. (2001a). Expression of nerve growth factor receptors and their prognostic value in human breast cancer. *Cancer Res* Vol 61, Issue 11 (Jun 2001), pp 4337-40. ISSN 0008-5472.
- Descamps, S., Toillon R. A., Adriaenssens, E., Pawlowski, V., Cool, S.M., Nurcombe, V., Le Bourhis, X., Boilly, B., Peyrat, J.P., & Hondermarck, H. (2001b). Nerve growth factor stimulates proliferation and survival of human breast cancer cells through two distinct signaling pathways. *J Biol Chem* Vol 276 Issue 21 (May 2001) pp 17864-70. ISSN 0021-9258.
- Dranoff, J. A. & Wells, R.G. (2010). Portal fibroblasts: Underappreciated mediators of biliary fibrosis. *Hepatology* Vol 51 Issue 4 (Apr 2010), pp 1438-44. ISSN 1527-3350.
- Dvorak, H. F. (2005). Angiogenesis: update 2005. *J Thromb Haemost* Vol 3, Issue 8 (Aug 2005) pp 1835-42. ISSN 1538-7933.
- Fava, G., DeMorrow S., Gaudio, E., Franchitto, A., Onori, P., Carpino, G., Glaser, S., Francis, H., Coufal, M., Marucci, L., Alvaro, D., Marzioni, M., Horst, T., Mancielli, R., Benedetti, A., & Alpini, G. (2009). Endothelin inhibits cholangiocarcinoma growth



- by a decrease in the vascular endothelial growth factor expression. *Liver Int* Vol 29 Issue 7 (August 2009), pp 1031-42. ISSN 1478-3231.
- Francis, H., DeMorrow S., Venter, J., Onori, P., White, M., Gaudio, E., Francis, T., Greene, J., Tran, S., Meininger, C., & Alpini, G. (2011). Inhibition of histidine decarboxylase ablates the autocrine tumorigenic effects of histamine in human cholangiocarcinoma. *Gut* In press.
- Francis, H., Onori P., Gaudio, E., Franchitto, A., DeMorrow, S., Venter, J., Kopriva, S., Carpino, G., Mancinelli, R., White, M., Meng, F., Vetusch, A., Sferra, R., & Alpini, G. (2009). H3 histamine receptor-mediated activation of protein kinase Calpha inhibits the growth of cholangiocarcinoma in vitro and in vivo. *Mol Cancer Res* Vol 7 Issue 10 (Oct 2009), pp 1704-13. ISSN 1557-3125.
- Gale, N. W., Thurston G., Hackett, S.f., Renard, R., Wang, Q., McClain, J., Martin, C., Witte, C., Witte, M.H., Jackson, D., Suri, C., Campochiaro, P.A., Wiegand, S.J., & Yancopoulos, G.D. (2002). Angiopoietin-2 is required for postnatal angiogenesis and lymphatic patterning, and only the latter role is rescued by Angiopoietin-1. *Dev Cell* Vol 3, Issue 3 (Sept 2002), pp 411-23. ISSN 1534-5807.
- Gaudio, E., Barbaro B., Alvaro, D., Glaser, S., Francis, H., Ueno, Y., Meininger, C.J., Franchitto, A., Onori, P., Marzoni, M., Taffetani, S., Fava, G., Stoica, G., Venter, J., Reichenbach, R., DeMorrow, S., Summers, R., & Alpini, G. (2006). Vascular endothelial growth factor stimulates rat cholangiocyte proliferation via an autocrine mechanism. *Gastroenterology* Vol 130, Issue 4 (Apr 2006) pp 1270-82. ISSN 0016-5085.
- Gladson, C. L. (1999). The extracellular matrix of gliomas: modulation of cell function. *J Neuropathol Exp Neurol* Vol 58, Issue 10 (Oct 1999), pp 1029-40. ISSN 0022-3069.
- Glaser, S. S., Gaudio E., & Alpini, G. (2010). Vascular factors, angiogenesis and biliary tract disease. *Curr Opin Gastroenterol.* Vol 26, Issue 3 (Jan 2010) pp 246-50. ISSN 1531-7056.
- Gores, G. J. (2003). Cholangiocarcinoma: current concepts and insights. *Hepatology* Vol 37, Issue 5 (May 2003), pp 961-9. ISSN 0270-9139.
- Harder, J., Waiz O., Otto, F., Geissler, M., Olschewski, M., Winhold, B., Blum, H.E., Schmitt0Graeff, A., & Opitz, O.G. (2009). EGFR and HER2 expression in advanced biliary tract cancer. *World J Gastroenterol* Vol 15 Issue 36 (Sep 2009), pp 4511-7. ISSN 1007-9327.
- Hasita, H., Komohara Y., Okabe, H., Masuda, T., Ohnishi, K., Lei, X.F., Beppu, T., Baba, H., & Takeya, M. (2010). Significance of alternatively activated macrophages in patients with intrahepatic cholangiocarcinoma. *Cancer Sci* Vol 101, Issue 8 (Aug 2010) pp 1913-9. ISSN 1349-7006.
- Iguchi, T., Yamashita N., Aishima, S., Kuroda, Y., Terashi, T., Sugimachi, K., Taguchi, K., Taketomi, A., Maehara, Y., & Tsuneyoshi, M. (2009). A comprehensive analysis of immunohistochemical studies in intrahepatic cholangiocarcinoma using the survival tree model. *Oncology* Vol 76 Issue 4 (Sep 2009) pp 293-300. ISSN 1423-0232.
- Isomoto, H., Mott, J.L., Kobayashi, S., Werneburg, N.W., Bronk, S.F., Haan, S., & Gores, G.J. (2007). Sustained IL-6/STAT-3 signaling in cholangiocarcinoma cells due to SOCS-3 epigenetic silencing. *Gastroenterology* Vol 132, Issue 1 (Jan 2007), pp 384-96.
- Kawahara, N., Ono, M., Taguchi, K., Okamoto, M., Shimada, M., Takenaka, K., Hayashi, K., Mosher, D.F., Sugimachi, K., Tsuneyoshi, M., & Kuwano, M. (1998). Enhanced expression of thrombospondin-1 and hypovascularity in human



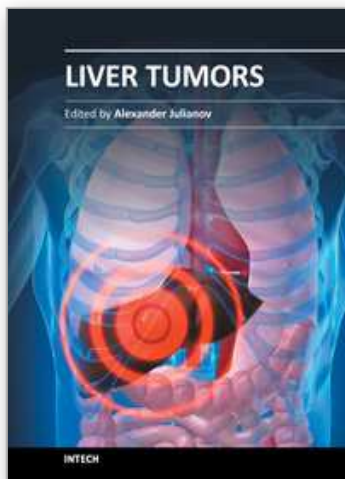
- cholangiocarcinoma. *Hepatology* Vol 28 Issue 6 (Dec 1998), pp 1512-7. ISSN 0270-9139.
- Kubo, H., Cao, R., Brakenhielm, E., Makinen, T., Cao, Y., & Alitalo, K. (2002). Blockade of vascular endothelial growth factor receptor-3 signaling inhibits fibroblast growth factor-2-induced lymphangiogenesis in mouse cornea. *Proc Natl Acad Sci U S A* Vol 99, Issue 13 (Jun 2002), pp 8868-73. ISSN 0027-8424.
- Lazarovici, P., Gazit, A., Staniszewska, I., Marcinkiewicz, C., & Lelkes, P.I. (2006a). Nerve growth factor (NGF) promotes angiogenesis in the quail chorioallantoic membrane. *Endothelium* Vol 13 Issue 1 (Jan-Feb 2006) pp 51-9. ISSN 1062-3329.
- Lazarovici, P., Marcinkiewicz C., & Lelkes, P.I. (2006b). Cross talk between the cardiovascular and nervous systems: neurotrophic effects of vascular endothelial growth factor (VEGF) and angiogenic effects of nerve growth factor (NGF)-implications in drug development. *Curr Pharm Des* Vol 12 Issue 21 (Nov 2006) pp 2609-22. ISSN 1381-6128.
- Ljubimova, J. Y., Fujita M., Khazenzon, N.M., Ljubimov, A.V., & Black, K.L. (2006). Changes in laminin isoforms associated with brain tumor invasion and angiogenesis. *Front Biosci* Vol 11 (Nov 2006) pp 81-8. ISSN 1093-4715.
- Lymboussaki, A., Partanen T. A., Olofsson, B., Thomas-Crusells, J., Fletcher, C.D., de Waal, R.M., Kaipainen, A., & Alitalo, K. (1998). Expression of the vascular endothelial growth factor C receptor VEGFR-3 in lymphatic endothelium of the skin and in vascular tumors. *Am J Pathol* Vol 153, Issue 2 (Aug 1998) pp 395-403. ISSN 0002-9440.
- Makinen, T., Veikkola T., Mustjoki, S., Karpanen, T., Catimel, B., Nice, E.C., Wise, L., Mercer, A., Kowalski, H., Kerjaschki, D., Stacker, S.A., Achen, M.G., & Alitalo, K. (2001). Isolated lymphatic endothelial cells transduce growth, survival and migratory signals via the VEGF-C/D receptor VEGFR-3. *EMBO J* Vol 20, Issue 17, (Sept 2001), pp 4762-73. ISSN 0261-4189.
- Mancino, A., Mancino M. G., Glaser, S.S., Alpini, G., Bolognese, A., Izzo, L., Francis, H., Onori, P., Franchitto, A., Ginanni-Corradini, S., Gaudio, E., & Alvaro, D. (2009). Estrogens stimulate the proliferation of human cholangiocarcinoma by inducing the expression and secretion of vascular endothelial growth factor. *Dig Liver Dis* Vol 41, Issue 2 (Feb 2009), pp 156-63. ISSN 1878-3562.
- Mantovani, A. and Sica A. (2010). Macrophages, innate immunity and cancer: balance, tolerance, and diversity. *Curr Opin Immunol* Vol 22, Issue 2 (Apr 2010) pp 231-7. ISSN 1879-0372.
- Mantovani, A., Sozzani S., Locati, M., Allavena, P., & Sica, A. (2002). Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol* Vol 23, Issue 11 (Nov 2002), pp 549-55. ISSN 1471-4906.
- McDougall, S. R., Anderson A. R., & Chaplain, M.A. (2006). Mathematical modelling of dynamic adaptive tumour-induced angiogenesis: clinical implications and therapeutic targeting strategies. *J Theor Biol* Vol 241, Issue 3 (Aug 2006), pp 564-89. ISSN 0022-5193.
- Mikkelsen, T., Yan P. S., Ho, K.L., Sameni, M., Sloane, B.F., & Rosenblum, M.L. (1995). Immunolocalization of cathepsin B in human glioma: implications for tumor invasion and angiogenesis. *J Neurosurg* Vol 83, Issue 2 (Aug 1995), pp 285-90. ISSN 0022-3085.

- Mobius, C., Demuth C., Aigner, T., Wiedmann, M., Wittekind, C., Mossner, J., Hauss, J., & Witzigmann, H. (2007). Evaluation of VEGF A expression and microvascular density as prognostic factors in extrahepatic cholangiocarcinoma. *Eur J Surg Oncol* Vol 33, Issue 8 (Oct 2007), pp 1025-9. ISSN 0748-7983.
- Nagy, J. A., Vasile E., Feng, D., Sundberg, C., Brown, L.F., Detmar, M.J., Lawitts, J.A., Benjamin, L., Tan, X., Manseau, E.J., Dvorak, A.M., & Dvorak, H.F.(2002). Vascular permeability factor/vascular endothelial growth factor induces lymphangiogenesis as well as angiogenesis. *J Exp Med* Vol 196, Issue 11 (Dec 2002), pp 1497-506. ISSN 0022-1007.
- Ogasawara, S., Yano H., Higaki, K., Takayama, A., Akiba, J., Shiota, K., & Kojiro, M. (2001). Expression of angiogenic factors, basic fibroblast growth factor and vascular endothelial growth factor, in human biliary tract carcinoma cell lines. *Hepatol Res* Vol 20, Issue 1 (May 2001), pp 97-113. ISSN 1386-6346.
- Ohira, S., Sasaki M., Harada, K., Sato, Y., Zen, Y., Isse, K., Kozaka, K., Ishikawa, A., Oda, DK., Nimura, Y., & Nakanuma, Y. (2006). Possible regulation of migration of intrahepatic cholangiocarcinoma cells by interaction of CXCR4 expressed in carcinoma cells with tumor necrosis factor-alpha and stromal-derived factor-1 released in stroma. *Am J Pathol* Vol 168, Issue 4 (Apr 2006), pp 1155-68. ISSN 0002-9440.
- Okabe, H., Beppu T., Hayashi, H., Horino, K., Masuda, T., Komori, H., Ishikawa, S., Watanabe, M., Takamori, H., Iyama, K., & Baba, H. (2009). Hepatic stellate cells may relate to progression of intrahepatic cholangiocarcinoma. *Ann Surg Oncol* Vol 16 Issue 9 (Sep 2009), pp 2555-64. ISSN 1534-4681.
- Olumi, A. F., Grossfeld G. D., Hayward, S.W., Carroll, P.R., Tlsty, T.D., & Cunha, G.R. (1999). Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium. *Cancer Res* Vol 59, Issue 19 (Oct 1999), pp 5002-11. ISSN 0008-5472.
- Onimaru, M. and Yonemitsu Y. (2011). Angiogenic and lymphangiogenic cascades in the tumor microenvironment. *Front Biosci (Schol Ed)* Vol 3, pp 216-25. ISSN 1945-0524.
- Orimo, A. and Weinberg R. A. (2006). Stromal fibroblasts in cancer: a novel tumor-promoting cell type. *Cell Cycle* Vol 5, Issue 15 (Aug 2006) pp 1597-601. ISSN 1551-4005.
- Patel, T. (2002). Worldwide trends in mortality from biliary tract malignancies. *BMC Cancer* Vol 2 (May 2002), pp 10. ISSN 1471-2407.
- Prakobwong, S., Gupta S. C., Kim, J.H., Sung, B., Pinlaor, P., Hiraku, Y., Wongkham, S., Sripa, B., Pinlaor, S., & Aggarwal, B.B. (2011). Curcumin suppresses proliferation and induces apoptosis in human biliary cancer cells through modulation of multiple cell signaling pathways. *Carcinogenesis*. In press ISSN 1460-2180.
- Prakobwong, S., Khoontawad, J., Yongvanit, P., Pairojkul, C., Hiraku, Y., Sithithaworn, P., Pinlaor, P., Aggarwal, B.B., & Pinlaor, S. (2011). Curcumin decreases cholangiocarcinogenesis in hamsters by suppressing inflammation-mediated molecular events related to multistep carcinogenesis. *Int J Cancer* Vol 129 Issue 1 (Jul 2011), pp 88-100. ISSN 1097-0215.
- Rasanen, K. and Vaheri A. (2010). Activation of fibroblasts in cancer stroma. *Exp Cell Res* Vol 316, Issue 17 (Oct 2010), pp 2713-22. ISSN 1090-2422.

- Roberts, W. G. and Palade G. E. (1997). Neovasculature induced by vascular endothelial growth factor is fenestrated. *Cancer Res* Vol 57, Issue 4 (Feb 1997), pp 765-72. ISSN 0008-5472.
- Rojas, A., Figueroa H., & Morales, E. (2010). Fueling inflammation at tumor microenvironment: the role of multiligand/RAGE axis. *Carcinogenesis* Vol 31 Issue 3 (Mar 2010), pp 334-41. ISSN 1460-2180.
- Shimoda, M., Mellody K. T., & Orimo, A. (2010). Carcinoma-associated fibroblasts are a rate-limiting determinant for tumour progression. *Semin Cell Dev Biol* Vol 21, Issue 1 (Feb 2010), pp 19-25. ISSN 1096-3634.
- Shinohara, E. T. and Maity A. (2009). Increasing sensitivity to radiotherapy and chemotherapy by using novel biological agents that alter the tumor microenvironment. *Curr Mol Med* Vol 9, Issue 9 (Dec 2009), pp 1034-45. ISSN 1875-5666.
- Sica, A. (2010). Role of tumour-associated macrophages in cancer-related inflammation. *Exp Oncol* Vol 32, Issue 3 (Sep 2010), pp 153-8. ISSN 1812-9269.
- Sica, A. and Bronte V. (2007). Altered macrophage differentiation and immune dysfunction in tumor development. *J Clin Invest* Vol 117 Issue 5 (May 2007) pp 1155-66. ISSN 0021-9738.
- Sirica, A. E. (2005). Cholangiocarcinoma: molecular targeting strategies for chemoprevention and therapy. *Hepatology* Vol 41, Issue 1 (Jan 2005), pp 5-15.
- Sirica, A. E., Dumur C. I., Campbell, D.J., Almenara, J.A., Ogunwobi, O.O., & Dewitt, J.L. (2009). Intrahepatic cholangiocarcinoma progression: prognostic factors and basic mechanisms. *Clin Gastroenterol Hepatol* Vol 7 Issue 11 Suppl (Nov 2009), pp S68-78. ISSN 1542-7714.
- Sortino, M. A., Condorelli F., Vancheri, C., Chiarenza, A., Bernardini, R., Consoli, U., & Canonico, P.L. (2000). Mitogenic effect of nerve growth factor (NGF) in LNCaP prostate adenocarcinoma cells: role of the high- and low-affinity NGF receptors. *Mol Endocrinol* Vol 14 Issue 1 (Jan 2000), pp 124-36. ISSN 0888-8809.
- Stacker, S. A., Achen M. G., Jussila, L., Baldwin, M.E., & Alitalo, K. (2002a). Lymphangiogenesis and cancer metastasis. *Nat Rev Cancer* Vol 2 Issue 8 (Aug 2002) pp 573-83. ISSN 1474-175X
- Stacker, S. A., Baldwin M. E., & Achen, M.G.. (2002b). The role of tumor lymphangiogenesis in metastatic spread. *FASEB J* Vol 16, Issue 9 (Jul 2002), pp 922-34. ISSN 1530-6860.
- Stacker, S. A., Caesar C., Baldwin, M.E., Thornton, G.E., Williams, R.A., Prevo, R., Jackson, D.G., Nishikawa, S., Kubo, H., & Achen, M.G. (2001). VEGF-D promotes the metastatic spread of tumor cells via the lymphatics. *Nat Med* Vol 7, Issue 2 (Feb 2001) pp 186-91. ISSN 1078-8956.
- Subimerb, C., Pinlaor S., Khuntikeo, N., Leelayuwat, C., Morris, A., McGrath, M.S., & Wongkham, S. (2010a). Tissue invasive macrophage density is correlated with prognosis in cholangiocarcinoma. *Mol Med Report* Vol 3 Issue 4 (Jul-Aug 2010) pp 597-605. ISSN 1791-3004.
- Subimerb, C., Pinlaor S., Lulitanond, V., Khuntikeo, N., Okada, S., McGrath, M.S., & Wongkham, S. (2010b). Circulating CD14(+) CD16(+) monocyte levels predict tissue invasive character of cholangiocarcinoma. *Clin Exp Immunol* Vol 161 Issue 3 (Sep 2010) pp 471-9. ISSN 1365-2249.
- Tang, D., Nagano H., Yamamoto, H., Wada, H., Nakamura, M., Kondo, M., Ota, H., Yoshioka, S., Kato, H., Damdinsuren, B., Marubashi, S., Miyamoto, A., Takeda, Y.,

- Umeshita, K., Dono, K., Wakasa, K., & Monden, M. (2006). Angiogenesis in cholangiocellular carcinoma: expression of vascular endothelial growth factor, angiopoietin-1/2, thrombospondin-1 and clinicopathological significance. *Oncol Rep* Vol 15 Issue 3 (Mar 2006), pp 525-32. ISSN 1021-335X.
- Thelen, A., A. Scholz, et al. (2008). Tumor-associated lymphangiogenesis correlates with lymph node metastases and prognosis in hilar cholangiocarcinoma. *Ann Surg Oncol* Vol 15 Issue 3 (Mar 2008), pp 791-9.
- Thelen, A., Scholz A., Benckert, C., Weichert, W., Dietz, E., Wiedenmann, B., Neuhaus, P., & Jonas, S. (2010). Tumor-Associated Angiogenesis and Lymphangiogenesis Correlate With Progression of Intrahepatic Cholangiocarcinoma. *Am J Gastroenterol.* Vol 105, Issue 5 (Mar 2010) pp 1123-32. ISSN 1534-4681.
- Tlsty, T. D. (2001). Stromal cells can contribute oncogenic signals. *Semin Cancer Biol* Vol 11 Issue 2 (Apr 2001) pp 97-104. ISSN 1044-579X.
- Tominaga, S. and Kuroishi T. (1994). Biliary tract cancer. *Cancer Surv* Vol 19-20, pp 125-37. ISSN 0261-2429.
- Tuxhorn, J. A., Ayala G. E., & Rowley, D.R. (2001). Reactive stroma in prostate cancer progression. *J Urol* Vol 166, Issue 6 (Dec 2001), pp 2472-83. ISSN 0022-5347.
- Utispan, K., Thuwajit P., Abiko, Y., Charngkaew, K., Paupairoj, A., Chau-in, S., & Thuwajit, C. (2010). Gene expression profiling of cholangiocarcinoma-derived fibroblast reveals alterations related to tumor progression and indicates periostin as a poor prognostic marker. *Mol Cancer* Vol 9, pp 13. ISSN 1476-4598.
- Veikkola, T., Jussila L., Makinen, T., Karpanen, T., Jeltsch, M., Petrova, T.V., Kubo, H., Thurston, G., McDonald, D.M., Achen, M.G., Stacker, S.A., & Alitalo, K. (2001). Signalling via vascular endothelial growth factor receptor-3 is sufficient for lymphangiogenesis in transgenic mice. *EMBO J* Vol 20 Issue 6 (Mar 2001), pp 1223-31. ISSN 0261-4189.
- Xu, L. B., Liu C., Gao, G.Q., Yu, X.H., Zhang, R., & Wang, J. (2010). Nerve growth factor-beta expression is associated with lymph node metastasis and nerve infiltration in human hilar cholangiocarcinoma. *World J Surg* Vol 34, Issue 5 (May 2010), pp 1039-45. ISSN 1432-2323.
- Yabuuchi, S., Katayose Y., Oda, A., Mizuma, M., Shirasou, S., Sasaki, T., Yamamoto, K., Oikawa, M., Rikiyama, T., Onogawa, T., Yoshia, H., Ohtuska, H., Motoi, F., Egawa, S., & Unno, M. (2009). ZD1839 (IRESSA) stabilizes p27Kip1 and enhances radiosensitivity in cholangiocarcinoma cell lines. *Anticancer Res* Vol 29 Issue 4 (Apr 2009) pp 1169-80. ISSN 0250-7005.
- Yoshikawa, D., Ojima H., Iwasaki, M., Hiraoka, N., Kosuge, T., Kasai, S., Hirohashi, S., & Shibata, T. (2008). Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. *Br J Cancer* Vol 98, Issue 2 (Jan 2008), pp 418-25. ISSN 0007-0920.
- Yoshikawa, D., Ojima H., Kokubu, A., Ochiya, T., Kasai, S., Hirohashi, S., & Shibata, T. (2009). Vandetanib (ZD6474), an inhibitor of VEGFR and EGFR signalling, as a novel molecular-targeted therapy against cholangiocarcinoma. *Br J Cancer* Vol 100, Issue 8 (Apr 2009), pp 1257-66. ISSN 1532-1827.





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This book is oriented towards clinicians and scientists in the field of the management of patients with liver tumors. As many unresolved problems regarding primary and metastatic liver cancer still await investigation, I hope this book can serve as a tiny step on a long way that we need to run on the battlefield of liver tumors.

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Phone: +86-21-62489820  
Fax: +86-21-62489821



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