REVIEW

Inflammation and cancer

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Abstract

There is evidence supporting the hypothesis that inflammation participates in providing conditions that lead to cancer. An unresolved inflammation due to any failure in the precise control of the immune response can continue to perturb the cellular microenvironment, thereby leading to alterations in cancer-related genes and posttranslational modification in crucial cellular proteins involved in the cell cycle, DNA repair and apoptosis. In addition, there are data indicating that inflammatory cells and immunomodulatory mediators present in the tumor microenvironment influence tumor progression and metastasis. Historically, tumor-infiltrating leukocytes have been considered to be manifestations of an intrinsic defence mechanism against developing tumors. However, increasing evidence indicates that leukocyte infiltration can promote tumor phenotypes, such as angiogenesis, growth and invasion. This may be due to inflammatory cells that probably can influence cancer promotion by secreting cytokines, growth factors, chemokines and proteases, which stimulate proliferation and invasiveness of cancer cells. Consequently, events and molecules implicated in this cross talk between the tumor microenvironment and inflammatory process may emerge as attractive targets in anticancer therapeutic interventions with significant clinical impact.

INTRODUCTION

That continuous irritation over long periods of time can lead to cancer was described in Ayurveda (means the science of long life), written as far back as 5000 years ago. Aulus Cornelius Celsus, a Roman medic in the first century, defined inflammation as: "rubor" (redness), "tumor" (swelling), "calor" (heat) and "dolor" (pain). Rodolf Virchow postulated that microinflammation that results from irritation leads to the development of most chronic diseases, including cancer[1]. Although this concept has long been suspected, only recently experimental and clinical studies have confirmed this hypothesis, which is now a generally accepted paradigm[2,3]. It is estimated that underlying infections and inflammatory reactions are linked to 15%-20% of all cancer deaths.

CHRONIC INFLAMMATION AS A PREDISPOSITION TO CANCER

The first evidence that non-cancerous cells might affect the formation and growth of tumors derives from the field of inflammation. Today, there is evidence supporting the hypothesis that inflammation participates in providing conditions that lead to cancer. It is estimated that underlying infections and inflammatory reactions are linked to 25% of all cancer cases. In many epidemio-

logical studies, the role of chronic inflammation in the carcinogenesis process was examined through studies of pro-inflammatory and anti-inflammatory cytokines along with other factors, including viral infections and genetic markers that take part in the inflammatory response[4].

There are well known associations between inflammatory processes and cancer, such as bowel disease (Crohn's disease and especially ulcerative colitis) and colorectal cancer[5,6], viral hepatitis B and C or alcoholic liver cirrhosis and hepatocarcinoma[7], chronic reflux esophagitis resulting in Barrett's esophagus and esophageal carcinoma[6], cervical infection by human papillomavirus and cervical cancer, prostatitis and prostate cancer, pancreatitis and pancreatic cancer, or gastric infection from *Helicobacter pylori*, which increases gastric cancer risk by 75%[8,9].

Tissue injury, whether physical, chemical or infectious, triggers a sequence of events that constitutes the inflammatory response. Inflammation is an important mechanism that can eliminate the agent responsible for the injury and initiate tissue repair by launching a well-coordinated immune response. The inflammatory mechanism involves both innate and adaptive immunity, which is characterized by coordinated blood borne delivery to injured tissues of cells and soluble mediators. After the elimination of the invading pathogen and wound healing, inflammation subsides. However, an unresolved inflammation on account of any failure in the precise control of the immune response can continue to perturb the cellular microenvironment, thereby leading to alterations in cancer-related genes and posttranslational modification in key cell signaling proteins involved in cell cycle, DNA repair and apoptosis. In fact, it is of note that mononuclear inflammatory cells (MICs) are often present at the very early stage of tumor development, in close association with areas of hyperplasia and atypia[10,11]. These findings support the concept that MICs themselves are a driving force that contributes to tumor initiation and/or initial tumoral progression. In addition to macrophages, mast cells and neutrophils can also support tumoral development by leading to upregulation of non-specific pro-inflammatory cytokines, such as interferon-γ, tumor necrosis factor (TNF), interleukin (IL)-1α/β or IL-6[12,13]. Likewise, activated nuclear factor-κB (NF-κB) transcription factor is one of the main links between inflammation and tumorogenesis and may be key to allowing both preneoplastic and malignant cells to escape from apoptosis[14,15]. Therefore, all of these factors may act as initiators and promoters of carcinogenesis by directly increasing the proliferation of epithelial cells. Table 1 shows studies reporting the relationship between overexpression of molecular components from inflammation pathway and gastrointestinal carcinogenesis.

On the other hand, it is noteworthy that increased toll-like receptors (TLRs) expression has been described in different human tumors[16-24]. It is an interesting finding because TLRs are considered a link between innate (non-specific) and adaptive (specific) immunity and contribute to the immune system's capacity to efficiently combat

pathogens[17]. As molecular sensors, TLRs detect pathogen-derived products and couple to different adapter proteins that trigger specific signaling pathways, such as the IL-1 receptor-associated kinase family and serine/threonine-protein kinase (TBK-1). These adapters initiate pathways leading to the activation of their respective transcription factors, NF-κB and interferon regulatory factor 3 (IRF3). Both NF-κB and IRF3 induce the release of various immune and inflammatory cytokines, such as TNF and IL6, which proved to be excellent targets for inflammatory diseases[25]. TLR-deficient mice were found to be protected from or develop less inducible tumors in experimental models[16,24]. In addition, for example, components of bacteria and viruses have been identified within pathological specimens of men with prostate cancer. There is evidence that the presence of pathogens in the urinary system may contribute to the malignant transformation of prostate epithelia through the activation of TLRs[19,26,27]. Therefore, all of this evidence indicates that biological signals elicited from TLR-activated tumor cells might also be a molecular link between inflammation and cancer.

TUMOR MICROENVIRONMENT AND ITS CONTRIBUTION TO TUMOR PROGRESSION TOWARDS METASTASIS

Tumors are composed not only of cancer cells but also of other cell types constituting the stroma. These stromal cells include cancer associated fibroblasts, endothelial cells, pericytes and variable representation of leukocytes. Leukocytes can account for as much 50% of the total tumor mass in invasive breast carcinomas. Initially, tumor cells and cells of the tumor microenvironment respond to tumor hypoxia and necrosis, secondary to excessive tumor cell proliferation, by releasing a number of growth factors and cytokines that are chemoattractive for monocytes and macrophages. These latter factors include colony stimulating factor (CSF)-1, granulocyte-monocyte-CSF, transforming growth factor (TGF)-β and chemokines[13]. In addition, macrophage-tumor cell interaction leads to the release of macrophage-derived cytokines, chemokines and growth/motility factors, such as IL-8 and fibroblast growth factor, which in turn promote the recruitment of additional inflammatory cells[28].

Historically, tumor-infiltrating leukocytes have been considered to be manifestations of an intrinsic defence mechanism against developing tumors[29,30]. The presence of leukocytes in tumors was subsequently interpreted as an aborted attempt of the immune system to reject the tumor. However, increasing evidence indicates that leukocyte infiltration can promote tumor phenotypes, such as angiogenesis, growth and invasion[31,32]. This may be due to inflammatory cells that can probably influence cancer promotion by secreting cytokines, growth factors, chemokines and proteases, which stimulate proliferation and invasiveness of cancer cells[28,33,34]. These factors reported

Factors	Gastrointestinal cancers
NF-κB	Differential expression and constitutive activation was correlated with severity of oral lesions in the course of oral cancer development[112]
	Elevated activated nuclear factor-κB-regulated cytokines were found in oral lichen planus patients and in the saliva of patients with oral squamous cell carcinoma[113,114]
	Associated with hepatocarcinogenesis induced by viral hepatitis B or viral hepatitis C infection[115,116]
COX-2	Associated with pathogenesis in mucositis[117]
	Associated in Barrett's metaplasia with a change in the local inflammatory reaction[118]
	Important overexpression in the pathogenesis of cholangiocarcinomas[119]
	Contribute to suppression of local immune responses and enhancement of metastatic potential in human hepatocellular carcinoma[120]
	Predictive marker in the early stages of hepatocarcinogenesis[121]
	Related to the histological grade of intraductal papillary-mucinous tumor of the pancreas[122]
	Gene expression was elevated in human colorectal cancer compared to normal mucosa[123]
	Associated with prognosis and intestinal pathways in gastric carcinogenesis[124,125]
STAT-3	Associated with the tumorigenesis of colorectal carcinoma[126]
	Associated with cell survival in gastric cancer[127]
	Associated with the development and proliferation of colorectal cancer[128]
IL-6	Associated with the development of apoptosis resistance Barrett's esophagus[129]
	Associated with the growth and proliferation in human colorectal cancer[130,131]
NOS	Correlated with Barrett's-associated neoplastic progression[132]
5-LOX	Associated with the development of pancreatic cancer[133]

Table 1 Overexpression of inflammatory factors in gastrointestinal carcinogenesis

NF-κB: Nuclear factor-κB; COX-2: Cyclooxygenase-2; STAT-3: Signal transducer and activator transcription 3; IL-6: Interleukin-6; NOS: Nitric oxide lipoxygenase; 5-LOX: 5-lipoxygenase.

as released by recruited MICs, included TNF, vascular endothelial growth factor (VEGF)- A and -C, hepatocyte growth factor (HGF), epidermal growth factor (EGF) family members, basic fibroblast growth factor, platelet-derived growth factor and chemokines, such as chemokine ligand 12 (CXCL12) and IL-8[4,13,35]. In addition, it is also remarkable that MICs bring in much of the cyclo-oxygenase-2 (COX-2) present in the tumor environment. It is because COX-2 expression and prostaglandins production within the tumor environment stimulate tumor cell proliferation, survival and motility, but also tumor angiogenesis[36].

CLINICAL RELEVANCE OF INFLAMMATORY COMPONENTS IN TUMOR PROGRESSION

Accumulating clinical data for solid tumors shows a correlation between high-density leukocytic infiltration into tumors and poor outcome of patients with malignancies of different origins, such as breast[37,38], bladder[39], rectum[40], endometrium[41], melanomas[42], gliomas[43] or leiomyosarcomas[44]. In addition, deficient monocyte recruitment at tumor sites in mice lacking CSF-1 expression was shown to attenuate late-stage progression and metastasis formation, suggesting that monocytes contribute to tumor progression[45]. Nevertheless, the presence of inflammatory cells can be an indicator of favorable prognosis in some tumor types, as for example, the presence of macrophages in colorectal cancer[46,47], gastric[48] or ovarian carcinomas[49]. These latter data suggest that, at least in some situations, inflammatory cells may be able to eliminate tumor cells just as they can destroy normal cells. On the other hand, one of the reasons why the

prognostic significance of the lymphoid infiltrate at the tumor site remains controversial is perhaps because the evaluation criteria for tumor infiltrates are not sufficiently standardized to yield reliable and reproducible results in different institutions. Leukocyte infiltrate includes a variable representation of leukocytes, including macrophages, neutrophils, mast cells and T and B lymphocytes[31,50]. In addition, there is evidence indicating that different types of leukocyte infiltration occur in different carcinomas and that probably these are induced by different abilities to control tumor growth according to the tumor dissemination[51]. Therefore, inflammatory cells and immunomodulatory mediators present in the tumor microenvironment polarize host immune response toward specific phenotypes impacting tumor progression.

Macrophages are often the most abundant immune cell population in the tumor microenvironment. Recruitment of monocyte precursors circulating in the blood leads to their differentiation into tumor-associated macrophages. It has been reported that, once recruited into tumors, macrophages can assume two different phenotypes: M1 or M2, based on environmental stimuli and each expressing specialized functional properties[52]. The M1 phenotype is associated with inflammation and microbial killing activity, whereas the M2 phenotype is associated with activities which are predominant and key events in cancer, including inhibition of T helper 1 adaptive immunity by immunosuppressive mediators [TGFβ, IL-10 or prostaglandin E2 (PGE2)], production of growth and survival factors (EGF, IL-6 and CXCL8), secretion of angiogenic factors (VEGF, TGFα or PGE2), production of matrix metalloproteases (MMPs) which degrade extracellular matrix, and chemokines able to recruit more inflammatory cells (CCL17, CCL18 or CCL22)[33,52,53].

In this sense, we recently identified a phenotype of

Table 2 Different factors associated with poor prognosis in gastrointestinal tumors

Factors	Gastrointestinal cancers
NF-κB	An independent prognostic indicator of poor outcome in patients with esophageal adenocarcinoma[134]
	High expression of activated nuclear factor-κB indicates poor patient survival in pancreatic cancer[135]
	Activation in hepatocellular carcinoma was implicated in a poor patient outcome[136]
	Associated with a shorter overall survival rate and prognosis biomarker in gastric cancer[137-139]
	Nuclear factor-κB positivity after radiotherapy was linked with worse clinical outcome in rectal cancer[140]
COX-2	The most important predictor of poor survival in oropharyngeal squamous cell carcinoma[141]
	Correlated with tumor progression and an unfavorable prognostic factor in esophageal carcinomas [142-146]
	Prognostic factor after surgical resection in patients affected by cancer of ampulla of vater[147]
	Associated with liver metastasis and poor survival in primary colorectal cancer[148-152]
	Associated with invasion, metastasis and implicated a poor prognosis in gastric carcinoma[153]
	Linked to an increased risk of hematogenous metastatic spread in rectal carcinoma[154]
CXCR-4	Associated with poor clinical outcome in esophageal cancer patients[155]
	Associated with lymph node metastasis and early distant relapse in colorectal cancer[156,157]
VEGF	An independent prognostic factor for patients with nasopharyngeal carcinoma[158]
	Associated with prognosis in squamous cell carcinoma of the esophagus[159]
	VEGF-C and VEGF-D expression was associated with lymphatic metastasis and prognosis in patients with pancreatic adenocarcinoma and induced lymphangiogenesis[160]
	Associated with prognosis in patients with hepatocellular carcinoma[161]
	Associated with prognosis in colorectal cancer patients[162,163]
	Associated with angiogenesis and metastasis in gastric cancer[164]
	Associated with lymph node metastasis and progression of ampullary carcinoma[165]
IL-6	Interleukin-1β and Interleukin-6 expression was associated with the growth and progression of human gastric carcinoma[166]
	Associated with progression and poor prognosis of colorectal carcinoma[167,168]
IL-8	Associated with the tumor progression and hepatic metastasis in patients with colorectal cancer[169-171]
	Associated with metastatic potential, angiogenesis and cell proliferation in human hepatocellular carcinoma[172]
	Associated with prognosis in human gastric carcinoma[173]
MMP-9	Correlated with the metastasis of lymph node in gastric cancer[174]
	Associated with tumor cell differentiation, vessel permeation, lymph node metastasis in esophageal squamous cell carcinoma[175]
NOS	Associated with angiogenesis of hepatocellular carcinoma[176]
	Correlated with the progression in gastric cancer patients[177]

NF-κB: Nuclear factor-κB; COX-2: Cyclooxygenase-2; CXCR: Chemokine receptor type 4; VEGF: Vascular endothelial growth factor; IL: Interleukin; MMP: Metalloproteases; NOS: Nitric oxide lipoxygenase.

MICs at the intratumor stroma of 40% of breast carcinomas, which is associated with the development of distant metastasis. These MICs were characterized by overexpression of metalloproteases (MMP)-7, 9, 11, 13 and 14, and tissue inhibitors of metalloproteases (TIMP)-1 and 2[54,55]. This may be because MMPs play an essential role in the degradation of the stromal connective tissue and basement membrane components, which are key elements in tumor invasion and metastasis. MMPs are also able to impact *in vivo* on tumor cell behavior as a consequence of their capacity to cleave growth factors, cell surface receptors, cell adhesion molecules and chemokines/cytokines[56-58]. Furthermore, by cleaving proapoptotic factors, MMPs produce a more aggressive phenotype *via* generation of apoptotic resistant cells[56]. MMPs also regulate cancer-related angiogenesis, positively through their ability to mobilize or activate proangiogenic factors[59], and negatively *via* generation of angiogenesis inhibitors, such as angiostatin and endostatin, cleaved from large protein precursors[60]. In addition, inflammatory cells from tumor stroma play a role in tumor angiogenesis by releasing other factors, such as VEGF, HGF or IL-8, which are able to stimulate and activate endothelial cells. On the other hand, it is now accepted that TIMPs are multifactorial proteins also involved in the induction of proliferation and the inhibition of apoptosis[61,62].

It is noteworthy that many of these molecules which have been identified as playing a critical role in inflammation are regulated by NF-κB. This is a transcription factor that is ubiquitous to all cell types and present in the cytoplasm in its resting stage. There is evidence pointing to the role of NF-κB in tumoral progression. Thus, NF-κB has also been linked with the survival of cancer stem cells[63]. NF-κB regulates the expression of most antiapoptotic gene products associated with the survival of tumors [bcl2-like 1 (bcl-xl), B-cell lymphoma 2 (bcl-2), X-linked inhibitor of apoptosis protein, cellular FLICE-inhibitory protein, inhibitor of apoptosis (IAP)-1 and IAP-2 and surviving], as well as gene products linked with proliferation of tumors (cyclin D1, c-myc and COX-2). In addition, recent data supports a role of the NF-κB-regulated inflammatory network in the progression, diagnosis, prognosis, recurrence and treatment of cancer in patients[64]. Table 2 shows several studies reporting the relationship between NF-κB and/or related molecules with poor prognosis in gastrointestinal tumors.

On the other hand, as mentioned above, elevated TLRs expression has been described in different human tumors[16-24]. It is noteworthy because cancer cells activated by TLR signals may release cytokines and chemokines that in turn may recruit immune cells and stimulate them to release further cytokines and chemokines. This

process results in a cytokine profile that is associated with immune tolerance, cancer progression and propagation of the tumor microenvironment[22]. In fact, recent studies by our group revealed that breast carcinomas with high TLR3 expression by tumor cell or with high TLR4 expression by MICs were significantly associated with higher probability of metastasis[65]. Likewise, we found that samples of prostate carcinomas with recurrence exhibited a significant increase in the mRNA levels of TLR3, TLR4 and TLR9. In addition, the tumors that showed high level expression of TLR3 or TLR9 were significantly associated with higher probability of biochemical recurrence[66]. However, we also found that breast tumors with high TLR9 expression by fibroblast-like cells were associated with a low metastasis rate. Although the biological significance of TLR9 expression by stromal fibroblast-like cells is currently unknown, there are data pointing to a protective role against tumor progression. Indeed, it was demonstrated that stimulation of TLR9 activates human plasmacytoid dendritic cells and B cells and this induces potent innate immune responses in preclinical tumor models as well as in patients[67]. The increasing interest in using bindings of nucleic acid-sensing TLR9 as a pharmacological intervention in various diseases is thus understandable. All of these data suggest that further studies of the expression of TLRs in malignant tumors may help to better understand the process that links inflammation and cancer, as well as to assess the biological and clinical importance of the interaction between tumor and stroma.

IMMUNOTHERAPY AND ANTI-INFLAMMATORY THERAPY IN CANCER

It is considered that the main mechanism of tumor immunity is due to an antitumoral T cell response[68]. This antitumor response can be due to the direct killing of tumor cells by CD8 cytotoxic T lymphocytes which recognize major histocompatibility complex class I and other antigens expressed on the surface of tumor cells. However, it is generally assumed that during growth, tumors develop strategies to evade or limit the effects of the host's immune responses[69]. In most cases, the adaptive immune response against tumor cells is very weak and largely inefficient, since the tumor itself and the surrounding microenvironment tumor induce immunosuppression by the down-regulation of CD8 cytotoxic T lymphocytes response[68]. It has also been suggested that increasing immune activity or immunotherapy will exacerbate the rate of immune escape and select for a tumor sub-population, which will be resistant to immunotherapy. In addition, the secretion of immunosuppressive cytokines and chemokines into the tumor microenvironment, such as TGF-β, IL-6 and IL-10, which can interfere with multiple steps and pathways in the generation of an effective immune response, has been described in many types of tumors[68]. Nevertheless, it is noteworthy that an alternative approach was recently described in which the expression of

new, and thereby potent, antigens are induced in tumor cells by inhibiting nonsense-mediated messenger RNA decay (NMD)[70,71]. It has been demonstrated that small interfering RNA-mediated inhibition of NMD in tumor cells led to the expression of new antigenic determinants and their immune-mediated rejection[72]. Therefore, it would be of interest to determine whether the NMD-induced antigens are cross-reactive among different tumors in future studies, and if so, to identify the dominant antigens induced by NMD inhibition.

On the other hand, it is clear that several inflammatory markers are expressed in various cancers and mediate their progression. Consequently, agents which suppress these inflammatory markers or the pathways activated by them have a potential for prevention and treatment of cancer. Some of these agents are being tested, such as steroids (dexamethasone and prednisolone)[73,74], TNF inhibitors (humira, remicade, enbrel and thalidomide)[75-77], proteasome inhibitors (velcade)[78] and NF-κB inhibitors (curcumin)[79]. It is also of note that most nutraceuticals derived from fruits, vegetables, legumes or spices have been shown to suppress NF-κB activation pathways, thus leading to suppression of various inflammatory markers. COX-2 has also been proposed as a therapeutic target for cancer prevention and treatment [COX-2 inhibitors (COXIB), such as aspirin and celecoxib][80]. The appearance of cardiovascular complications induced by potent COXIBs has dampened enthusiasm and hampered the widespread use of COXIBs for cancer chemoprevention. TLRs may also represent a good therapeutic target in cancer. In this sense, there are studies that show a variable antineoplastic effect caused by a blockade of TLR3[81,82]. However, the authors suggested that TLR3 plays a role in inhibiting the cell cycle and inducing apoptosis[20]. In addition, the use of TLR3 agonists has been successful in prostate immune-based therapies[83,84]. The implications for therapeutic interventions using TLRs as targets could justify numerous creative strategies. Further study of this association is warranted and therapeutic strategies to boost or block these pathways may be relevant.

Mesenchymal stem cells (MSCs) represent a promising tool for new clinical concepts in supporting cellular therapy. Although bone marrow (BM) has been the main source for the isolation of multipotent MSCs, adipose tissue is another source of this cell[85], but the harvest of BM and adipose tissue is a highly invasive procedure. Therefore, alternative sources from which to isolate MSCs are subject to intensive investigation. One alternative source is umbilical cord blood, which can be obtained by a less invasive method, without harm to the mother or infant[86]. Other sources of MSCs were identified in a variety of other human adult tissues, including placenta[87], scalp tissue[88] and myometrium[89].

MSCs appear to suppress inflammation through secretion of anti-inflammatory cytokines, such as IL-10[90], TGF-β[91], soluble human leukocyte antigen-G[92] and IL-1 receptor antagonist[93], and expression of immune regulatory enzymes, such as cycloxygenase[94] and indolamine 2,3

deoxygenase. MSCs were able to suppress T-lymphocyte activation and proliferation *in vitro*[95-97]. The mechanisms are probably mediated by both direct cell-cell contacts and soluble factors. As regards the effect of MSC on B-lymphocyte function, MSC inhibit immunoglobulin production and arrest B-lymphocytes in the G0/G1 phase of the cell cycle. MSCs have been demonstrated to interfere with dendritic cell differentiation, maturation and function[98-101]. Based on these properties, MSCs are being used in regenerative medicine, for the treatment of autoimmune diseases[102,103], graft versus host disease[104-109] and the tropism of MSCs for human gliomas can also be exploited to therapeutic advantage[110]. These cells can be a new alternative in cancer studies; in fact, recently an inhibiting effect of the MSC on the proliferation of the tumor was described[111].

It seems clear that an understanding of how tumor cells control and benefit from host inflammation responses can open the way towards the identification of therapeutic strategies targeting the molecular mechanisms that underlie relevant tumor-host interactions.

CONCLUSION

Chronic and persistent inflammation contributes to cancer development and even predisposes to carcinogenesis. In addition, cellular and molecular components from tumor-associated inflammation may affect neoplastic progression. Events and molecules implicated in this crosstalk between the tumor and inflammatory microenvironment may emerge as attractive targets in anticancer therapeutic intervention with significant clinical impact. Thus, anti-inflammatory agents should be explored for both prevention and treatment of cancer. Their true potential will be recognized only through well-controlled clinical trials.

REFERENCES

1   **Heidland A**, Klassen A, Rutkowski P, Bahner U. The contribution of Rudolf Virchow to the concept of inflammation: what is still of importance? *J Nephrol* 2006; **19** Suppl 10: S102-S109

2   **Balkwill F**, Charles KA, Mantovani A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer Cell* 2005; **7**: 211-217

3   **Balkwill F**, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001; **357**: 539-545

4   **Lorusso G**, Rüegg C. The tumor microenvironment and its contribution to tumor evolution toward metastasis. *Histochem Cell Biol* 2008; **130**: 1091-1103

5   **Eaden J**, Abrams K, Ekbom A, Jackson E, Mayberry J. Colorectal cancer prevention in ulcerative colitis: a case-control study. *Aliment Pharmacol Ther* 2000; **14**: 145-153

6   **van der Woude CJ**, Kleibeuker JH, Jansen PL, Moshage H. Chronic inflammation, apoptosis and (pre)malignant lesions in the gastro-intestinal tract. *Apoptosis* 2004; **9**: 123-130

7   **Matsuzaki K**, Murata M, Yoshida K, Sekimoto G, Uemura Y, Sakaida N, Kaibori M, Kamiyama Y, Nishizawa M, Fujisawa J, Okazaki K, Seki T. Chronic inflammation associated with hepatitis C virus infection perturbs hepatic transforming growth factor beta signaling, promoting cirrhosis and hepatocellular carcinoma. *Hepatology* 2007; **46**: 48-57

8   **Hussain SP**, Amstad P, Raja K, Ambs S, Nagashima M, Bennett WP, Shields PG, Ham AJ, Swenberg JA, Marrogi AJ, Harris CC. Increased p53 mutation load in noncancerous colon tissue from ulcerative colitis: a cancer-prone chronic inflammatory disease. *Cancer Res* 2000; **60**: 3333-3337

9   **Kuper H**, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. *J Intern Med* 2000; **248**: 171-183

10 **Mantovani A**, Schioppa T, Porta C, Allavena P, Sica A. Role of tumor-associated macrophages in tumor progression and invasion. *Cancer Metastasis Rev* 2006; **25**: 315-322

11 **Pollard JW**. Tumour-educated macrophages promote tumour progression and metastasis. *Nat Rev Cancer* 2004; **4**: 71-78

12 **Aggarwal BB**, Shishodia S, Sandur SK, Pandey MK, Sethi G. Inflammation and cancer: how hot is the link? *Biochem Pharmacol* 2006; **72**: 1605-1621

13 **Robinson SC**, Coussens LM. Soluble mediators of inflammation during tumor development. *Adv Cancer Res* 2005; **93**: 159-187

14 **Karin M**. Nuclear factor-kappaB in cancer development and progression. *Nature* 2006; **441**: 431-436

15 **Naugler WE**, Karin M. NF-kappaB and cancer-identifying targets and mechanisms. *Curr Opin Genet Dev* 2008; **18**: 19-26

16 **Fukata M**, Chen A, Vamadevan AS, Cohen J, Breglio K, Krishnareddy S, Hsu D, Xu R, Harpaz N, Dannenberg AJ, Subbaramaiah K, Cooper HS, Itzkowitz SH, Abreu MT. Toll-like receptor-4 promotes the development of colitis-associated colorectal tumors. *Gastroenterology* 2007; **133**: 1869-1881

17 **Kawai T**, Akira S. TLR signaling. *Cell Death Differ* 2006; **13**: 816-825

18 **Kelly MG**, Alvero AB, Chen R, Silasi DA, Abrahams VM, Chan S, Visintin I, Rutherford T, Mor G. TLR-4 signaling promotes tumor growth and paclitaxel chemoresistance in ovarian cancer. *Cancer Res* 2006; **66**: 3859-3868

19 **Kundu SD**, Lee C, Billips BK, Habermacher GM, Zhang Q, Liu V, Wong LY, Klumpp DJ, Thumbikat P. The toll-like receptor pathway: a novel mechanism of infection-induced carcinogenesis of prostate epithelial cells. *Prostate* 2008; **68**: 223-229

20 **Paone A**, Starace D, Galli R, Padula F, De Cesaris P, Filippini A, Ziparo E, Riccioli A. Toll-like receptor 3 triggers apoptosis of human prostate cancer cells through a PKC-alpha-dependent mechanism. *Carcinogenesis* 2008; **29**: 1334-1342

21 **Salaun B**, Coste I, Rissoan MC, Lebecque SJ, Renno T. TLR3 can directly trigger apoptosis in human cancer cells. *J Immunol* 2006; **176**: 4894-4901

22 **Sato Y**, Goto Y, Narita N, Hoon DS. Cancer Cells Expressing Toll-like Receptors and the Tumor Microenvironment. *Cancer Microenviron* 2009; **2** Suppl 1: 205-214

23 **Stark JR**, Wiklund F, Grönberg H, Schumacher F, Sinnott JA, Stampfer MJ, Mucci LA, Kraft P. Toll-like receptor signaling pathway variants and prostate cancer mortality. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 1859-1863

24 **Swann JB**, Vesely MD, Silva A, Sharkey J, Akira S, Schreiber RD, Smyth MJ. Demonstration of inflammation-induced cancer and cancer immunoediting during primary tumorigenesis. *Proc Natl Acad Sci U S A* 2008; **105**: 652-656

25 **O'Neill LA**, Bryant CE, Doyle SL. Therapeutic targeting of Toll-like receptors for infectious and inflammatory diseases and cancer. *Pharmacol Rev* 2009; **61**: 177-197

26 **Nickel JC**, Moon T. Chronic bacterial prostatitis: an evolving clinical enigma. *Urology* 2005; **66**: 2-8

27 **Tanner MA**, Shoskes D, Shahed A, Pace NR. Prevalence of corynebacterial 16S rRNA sequences in patients with bacterial and "nonbacterial" prostatitis. *J Clin Microbiol* 1999; **37**: 1863-1870

28 **Balkwill F**. Cancer and the chemokine network. *Nat Rev Cancer* 2004; **4**: 540-550

29 **Johnson JP**, Riethmüller G, Schirrmacher V. Tumor immu-

nology: Paul Ehrlich's heritage. *Immunol Today* 1989; **10**: S35-S37

30   **Lin EY**, Pollard JW. Role of infiltrated leucocytes in tumour growth and spread. *Br J Cancer* 2004; **90**: 2053-2058

31   **Coussens LM**, Werb Z. Inflammation and cancer. *Nature* 2002; **420**: 860-867

32   **Daniel D**, Chiu C, Giraudo E, Inoue M, Mizzen LA, Chu NR, Hanahan D. CD4+ T cell-mediated antigen-specific immuno-therapy in a mouse model of cervical cancer. *Cancer Res* 2005; **65**: 2018-2025

33   **Le Bitoux MA**, Stamenkovic I. Tumor-host interactions: the role of inflammation. *Histochem Cell Biol* 2008; **130**: 1079-1090

34   **Sica A**, Bronte V. Altered macrophage differentiation and immune dysfunction in tumor development. *J Clin Invest* 2007; **117**: 1155-1166

35   **Benelli R**, Lorusso G, Albini A, Noonan DM. Cytokines and chemokines as regulators of angiogenesis in health and disease. *Curr Pharm Des* 2006; **12**: 3101-3115

36   **Prescott SM**, Fitzpatrick FA. Cyclooxygenase-2 and carcinogenesis. *Biochim Biophys Acta* 2000; **1470**: M69-M78

37   **Pollard JW**. Macrophages define the invasive microenvironment in breast cancer. *J Leukoc Biol* 2008; **84**: 623-630

38   **Shabo I**, Stål O, Olsson H, Doré S, Svanvik J. Breast cancer expression of CD163, a macrophage scavenger receptor, is related to early distant recurrence and reduced patient survival. *Int J Cancer* 2008; **123**: 780-786

39   **Hanada T**, Nakagawa M, Emoto A, Nomura T, Nasu N, Nomura Y. Prognostic value of tumor-associated macrophage count in human bladder cancer. *Int J Urol* 2000; **7**: 263-269

40   **Shabo I**, Olsson H, Sun XF, Svanvik J. Expression of the macrophage antigen CD163 in rectal cancer cells is associated with early local recurrence and reduced survival time. *Int J Cancer* 2009; **125**: 1826-1831

41   **Salvesen HB**, Akslen LA. Significance of tumour-associated macrophages, vascular endothelial growth factor and thrombospondin-1 expression for tumour angiogenesis and prognosis in endometrial carcinomas. *Int J Cancer* 1999; **84**: 538-543

42   **Jensen TO**, Schmidt H, Møller HJ, Høyer M, Maniecki MB, Sjoegren P, Christensen IJ, Steiniche T. Macrophage markers in serum and tumor have prognostic impact in American Joint Committee on Cancer stage I/II melanoma. *J Clin Oncol* 2009; **27**: 3330-3337

43   **Nishie A**, Ono M, Shono T, Fukushi J, Otsubo M, Onoue H, Ito Y, Inamura T, Ikezaki K, Fukui M, Iwaki T, Kuwano M. Macrophage infiltration and heme oxygenase-1 expression correlate with angiogenesis in human gliomas. *Clin Cancer Res* 1999; **5**: 1107-1113

44   **Lee CH**, Espinosa I, Vrijaldenhoven S, Subramanian S, Montgomery KD, Zhu S, Marinelli RJ, Peterse JL, Poulin N, Nielsen TO, West RB, Gilks CB, van de Rijn M. Prognostic significance of macrophage infiltration in leiomyosarcomas. *Clin Cancer Res* 2008; **14**: 1423-1430

45   **Lin EY**, Nguyen AV, Russell RG, Pollard JW. Colony-stimulating factor 1 promotes progression of mammary tumors to malignancy. *J Exp Med* 2001; **193**: 727-740

46   **Forssell J**, Oberg A, Henriksson ML, Stenling R, Jung A, Palmqvist R. High macrophage infiltration along the tumor front correlates with improved survival in colon cancer. *Clin Cancer Res* 2007; **13**: 1472-1479

47   **Zhou Q**, Peng RQ, Wu XJ, Xia Q, Hou JH, Ding Y, Zhou QM, Zhang X, Pang ZZ, Wan DS, Zeng YX, Zhang XS. The density of macrophages in the invasive front is inversely correlated to liver metastasis in colon cancer. *J Transl Med* 2010; **8**: 13

48   **Ohno S**, Inagawa H, Dhar DK, Fujii T, Ueda S, Tachibana M, Suzuki N, Inoue M, Soma G, Nagasue N. The degree of macrophage infiltration into the cancer cell nest is a significant predictor of survival in gastric cancer patients. *Anticancer Res* 2003; **23**: 5015-5022

49   **Tanaka Y**, Kobayashi H, Suzuki M, Kanayama N, Suzuki M, Terao T. Upregulation of bikunin in tumor-infiltrating macrophages as a factor of favorable prognosis in ovarian cancer. *Gynecol Oncol* 2004; **94**: 725-734

50   **Lin EY**, Pollard JW. Macrophages: modulators of breast cancer progression. *Novartis Found Symp* 2004; **256**: 158-68; discussion 168-72, 259-69

51   **Canevari S**, Pupa SM, Ménard S. 1975-1995 revised anti-cancer serological response: biological significance and clinical implications. *Ann Oncol* 1996; **7**: 227-232

52   **Allavena P**, Sica A, Garlanda C, Mantovani A. The Yin-Yang of tumor-associated macrophages in neoplastic progression and immune surveillance. *Immunol Rev* 2008; **222**: 155-161

53   **Mantovani A**, Sozzani S, Locati M, Allavena P, Sica A. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol* 2002; **23**: 549-555

54   **González LO**, Pidal I, Junquera S, Corte MD, Vázquez J, Rodríguez JC, Lamelas ML, Merino AM, García-Muñiz JL, Vizoso FJ. Overexpression of matrix metalloproteinases and their inhibitors in mononuclear inflammatory cells in breast cancer correlates with metastasis-relapse. *Br J Cancer* 2007; **97**: 957-963

55   **Vizoso FJ**, González LO, Corte MD, Rodríguez JC, Vázquez J, Lamelas ML, Junquera S, Merino AM, García-Muñiz JL. Study of matrix metalloproteinases and their inhibitors in breast cancer. *Br J Cancer* 2007; **96**: 903-911

56   **Egeblad M**, Werb Z. New functions for the matrix metalloproteinases in cancer progression. *Nat Rev Cancer* 2002; **2**: 161-174

57   **Mañes S**, Llorente M, Lacalle RA, Gómez-Moutón C, Kremer L, Mira E, Martínez-A C. The matrix metalloproteinase-9 regulates the insulin-like growth factor-triggered autocrine response in DU-145 carcinoma cells. *J Biol Chem* 1999; **274**: 6935-6945

58   **Noë V**, Fingleton B, Jacobs K, Crawford HC, Vermeulen S, Steelant W, Bruyneel E, Matrisian LM, Mareel M. Release of an invasion promoter E-cadherin fragment by matrilysin and stromelysin-1. *J Cell Sci* 2001; **114**: 111-118

59   **Stetler-Stevenson WG**. Matrix metalloproteinases in angiogenesis: a moving target for therapeutic intervention. *J Clin Invest* 1999; **103**: 1237-1241

60   **Cornelius LA**, Nehring LC, Harding E, Bolanowski M, Welgus HG, Kobayashi DK, Pierce RA, Shapiro SD. Matrix metalloproteinases generate angiostatin: effects on neovascularization. *J Immunol* 1998; **161**: 6845-6852

61   **Jiang Y**, Goldberg ID, Shi YE. Complex roles of tissue inhibitors of metalloproteinases in cancer. *Oncogene* 2002; **21**: 2245-2252

62   **Würtz SØ**, Schrohl AS, Sørensen NM, Lademann U, Christensen IJ, Mouridsen H, Brünner N. Tissue inhibitor of metalloproteinases-1 in breast cancer. *Endocr Relat Cancer* 2005; **12**: 215-227

63   **Guzman ML**, Rossi RM, Neelakantan S, Li X, Corbett CA, Hassane DC, Becker MW, Bennett JM, Sullivan E, Lachowicz JL, Vaughan A, Sweeney CJ, Matthews W, Carroll M, Liesveld JL, Crooks PA, Jordan CT. An orally bioavailable parthenolide analog selectively eradicates acute myelogenous leukemia stem and progenitor cells. *Blood* 2007; **110**: 4427-4435

64   **Aggarwal BB**, Gehlot P. Inflammation and cancer: how friendly is the relationship for cancer patients? *Curr Opin Pharmacol* 2009; **9**: 351-369

65   **González-Reyes S**, Marín L, González L, González LO, del Casar JM, Lamelas ML, González-Quintana JM, Vizoso FJ. Study of TLR3, TLR4 and TLR9 in breast carcinomas and their association with metastasis. *BMC Cancer* 2010; **10**: 665

66   **González-Reyes S**, Fernández JM, González LO, Aguirre A, Suárez A, González JM, Escaff S, Vizoso FJ. Study of TLR3, TLR4, and TLR9 in prostate carcinomas and their association

with biochemical recurrence. *Cancer Immunol Immunother* 2011; **60**: 217-226

67   **Flores-Reséndiz D**, Castellanos-Juárez E, Benítez-Bribiesca L. [Proteases in cancer progression]. *Gac Med Mex* 2009; **145**: 131-142

68   **Mantovani A**, Romero P, Palucka AK, Marincola FM. Tumour immunity: effector response to tumour and role of the microenvironment. *Lancet* 2008; **371**: 771-783

69   **Drake CG**, Jaffee E, Pardoll DM. Mechanisms of immune evasion by tumors. *Adv Immunol* 2006; **90**: 51-81

70   **Maquat LE**. Nonsense-mediated mRNA decay: splicing, translation and mRNP dynamics. *Nat Rev Mol Cell Biol* 2004; **5**: 89-99

71   **Mühlemann O**, Eberle AB, Stalder L, Zamudio Orozco R. Recognition and elimination of nonsense mRNA. *Biochim Biophys Acta* 2008; **1779**: 538-549

72   **Pastor F**, Kolonias D, Giangrande PH, Gilboa E. Induction of tumour immunity by targeted inhibition of nonsense-mediated mRNA decay. *Nature* 2010; **465**: 227-230

73   **Tannock IF**, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Théodore C, James ND, Turesson I, Rosenthal MA, Eisenberger MA. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; **351**: 1502-1512

74   **Venkitaraman R**, Thomas K, Huddart RA, Horwich A, Dearnaley DP, Parker CC. Efficacy of low-dose dexamethasone in castration-refractory prostate cancer. *BJU Int* 2008; **101**: 440-443

75   **Adams GP**, Weiner LM. Monoclonal antibody therapy of cancer. *Nat Biotechnol* 2005; **23**: 1147-1157

76   **Eisen T**, Boshoff C, Mak I, Sapunar F, Vaughan MM, Pyle L, Johnston SR, Ahern R, Smith IE, Gore ME. Continuous low dose Thalidomide: a phase II study in advanced melanoma, renal cell, ovarian and breast cancer. *Br J Cancer* 2000; **82**: 812-817

77   **Madhusudan S**, Foster M, Muthuramalingam SR, Braybrooke JP, Wilner S, Kaur K, Han C, Hoare S, Balkwill F, Talbot DC, Ganesan TS, Harris AL. A phase II study of etanercept (Enbrel), a tumor necrosis factor alpha inhibitor in patients with metastatic breast cancer. *Clin Cancer Res* 2004; **10**: 6528-6534

78   **Orlowski RZ**, Kuhn DJ. Proteasome inhibitors in cancer therapy: lessons from the first decade. *Clin Cancer Res* 2008; **14**: 1649-1657

79   **Singh S**, Khar A. Biological effects of curcumin and its role in cancer chemoprevention and therapy. *Anticancer Agents Med Chem* 2006; **6**: 259-270

80   **Xu XC**. COX-2 inhibitors in cancer treatment and prevention, a recent development. *Anticancer Drugs* 2002; **13**: 127-137

81   **Khan AL**, Richardson S, Drew J, Larsen F, Campbell M, Heys SD, Ah-See AK, Eremin O. Polyadenylic-polyuridylic acid enhances the natural cell-mediated cytotoxicity in patients with breast cancer undergoing mastectomy. *Surgery* 1995; **118**: 531-538

82   **Lacour F**, Lacour J, Spira A, Michelson M, Petit JY, Delage G, Contesso G, Merlin-Nahon E, Sarrazin D, Viguier J. [Adjuvant immunotherapy using polyadenylic acid and polyuridylic acid (Poly A., Poly U.) in operable carcinoma of the breast (author's transl)]. *Chirurgie* 1980; **106**: 737-743

83   **Chin AI**, Miyahira AK, Covarrubias A, Teague J, Guo B, Dempsey PW, Cheng G. Toll-like receptor 3-mediated suppression of TRAMP prostate cancer shows the critical role of type I interferons in tumor immune surveillance. *Cancer Res* 2010; **70**: 2595-2603

84   **Nicodemus CF**, Wang L, Lucas J, Varghese B, Berek JS. Toll-like receptor-3 as a target to enhance bioactivity of cancer immunotherapy. *Am J Obstet Gynecol* 2010; **202**: 608.e1-608.e8

85   **Dicker A**, Le Blanc K, Aström G, van Harmelen V, Götherström C, Blomqvist L, Arner P, Rydén M. Functional studies of mesenchymal stem cells derived from adult human adi-

pose tissue. *Exp Cell Res* 2005; **308**: 283-290

86   **Kern S**, Eichler H, Stoeve J, Klüter H, Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. *Stem Cells* 2006; **24**: 1294-1301

87   **In 't Anker PS**, Scherjon SA, Kleijburg-van der Keur C, de Groot-Swings GM, Claas FH, Fibbe WE, Kanhai HH. Isolation of mesenchymal stem cells of fetal or maternal origin from human placenta. *Stem Cells* 2004; **22**: 1338-1345

88   **Shih DT**, Lee DC, Chen SC, Tsai RY, Huang CT, Tsai CC, Shen EY, Chiu WT. Isolation and characterization of neurogenic mesenchymal stem cells in human scalp tissue. *Stem Cells* 2005; **23**: 1012-1020

89   **Gálvez BG**, Martín NS, Salama-Cohen P, Lazcano JJ, Coronado MJ, Lamelas ML, Alvarez-Barrientos A, Eiró N, Vizoso F, Rodríguez C. An adult myometrial pluripotential precursor that promotes healing of damaged muscular tissues. *In Vivo* 2010; **24**: 431-441

90   **Nasef A**, Chapel A, Mazurier C, Bouchet S, Lopez M, Mathieu N, Sensebé L, Zhang Y, Gorin NC, Thierry D, Fouillard L. Identification of IL-10 and TGF-beta transcripts involved in the inhibition of T-lymphocyte proliferation during cell contact with human mesenchymal stem cells. *Gene Expr* 2007; **13**: 217-226

91   **Ryan JM**, Barry F, Murphy JM, Mahon BP. Interferon-gamma does not break, but promotes the immunosuppressive capacity of adult human mesenchymal stem cells. *Clin Exp Immunol* 2007; **149**: 353-363

92   **Selmani Z**, Naji A, Zidi I, Favier B, Gaiffe E, Obert L, Borg C, Saas P, Tiberghien P, Rouas-Freiss N, Carosella ED, Deschaseaux F. Human leukocyte antigen-G5 secretion by human mesenchymal stem cells is required to suppress T lymphocyte and natural killer function and to induce CD4+CD25highFOXP3+ regulatory T cells. *Stem Cells* 2008; **26**: 212-222

93   **Ortiz LA**, Dutreil M, Fattman C, Pandey AC, Torres G, Go K, Phinney DG. Interleukin 1 receptor antagonist mediates the antiinflammatory and antifibrotic effect of mesenchymal stem cells during lung injury. *Proc Natl Acad Sci U S A* 2007; **104**: 11002-11007

94   **English K**, Barry FP, Field-Corbett CP, Mahon BP. IFN-gamma and TNF-alpha differentially regulate immunomodulation by murine mesenchymal stem cells. *Immunol Lett* 2007; **110**: 91-100

95   **Bartholomew A**, Sturgeon C, Siatskas M, Ferrer K, McIntosh K, Patil S, Hardy W, Devine S, Ucker D, Deans R, Moseley A, Hoffman R. Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. *Exp Hematol* 2002; **30**: 42-48

96   **Di Nicola M**, Carlo-Stella C, Magni M, Milanesi M, Longoni PD, Matteucci P, Grisanti S, Gianni AM. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. *Blood* 2002; **99**: 3838-3843

97   **Tse WT**, Pendleton JD, Beyer WM, Egalka MC, Guinan EC. Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation. *Transplantation* 2003; **75**: 389-397

98   **Jiang XX**, Zhang Y, Liu B, Zhang SX, Wu Y, Yu XD, Mao N. Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells. *Blood* 2005; **105**: 4120-4126

99   **Li YP**, Paczesny S, Lauret E, Poirault S, Bordigoni P, Mekhloufi F, Hequet O, Bertrand Y, Ou-Yang JP, Stoltz JF, Miossec P, Eljaafari A. Human mesenchymal stem cells license adult CD34+ hemopoietic progenitor cells to differentiate into regulatory dendritic cells through activation of the Notch pathway. *J Immunol* 2008; **180**: 1598-1608

100   **Nauta AJ**, Kruisselbrink AB, Lurvink E, Willemze R, Fibbe WE. Mesenchymal stem cells inhibit generation and func-

tion of both CD34+-derived and monocyte-derived dendritic cells. *J Immunol* 2006; **177**: 2080-2087

101 **Ramasamy R**, Fazekasova H, Lam EW, Soeiro I, Lombardi G, Dazzi F. Mesenchymal stem cells inhibit dendritic cell differentiation and function by preventing entry into the cell cycle. *Transplantation* 2007; **83**: 71-76

102 **Augello A**, Tasso R, Negrini SM, Cancedda R, Pennesi G. Cell therapy using allogeneic bone marrow mesenchymal stem cells prevents tissue damage in collagen-induced arthritis. *Arthritis Rheum* 2007; **56**: 1175-1186

103 **Parekkadan B**, Tilles AW, Yarmush ML. Bone marrow-derived mesenchymal stem cells ameliorate autoimmune enteropathy independently of regulatory T cells. *Stem Cells* 2008; **26**: 1913-1919

104 **Ball L**, Bredius R, Lankester A, Schweizer J, van den Heuvel-Eibrink M, Escher H, Fibbe W, Egeler M. Third party mesenchymal stromal cell infusions fail to induce tissue repair despite successful control of severe grade IV acute graft-versus-host disease in a child with juvenile myelo-monocytic leukemia. *Leukemia* 2008; **22**: 1256-1257

105 **Le Blanc K**, Frassoni F, Ball L, Locatelli F, Roelofs H, Lewis I, Lanino E, Sundberg B, Bernardo ME, Remberger M, Dini G, Egeler RM, Bacigalupo A, Fibbe W, Ringdén O. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. *Lancet* 2008; **371**: 1579-1586

106 **Le Blanc K**, Rasmusson I, Sundberg B, Götherström C, Hassan M, Uzunel M, Ringdén O. Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. *Lancet* 2004; **363**: 1439-1441

107 **Müller I**, Kordowich S, Holzwarth C, Isensee G, Lang P, Neunhoeffer F, Dominici M, Greil J, Handgretinger R. Application of multipotent mesenchymal stromal cells in pediatric patients following allogeneic stem cell transplantation. *Blood Cells Mol Dis* 2008; **40**: 25-32

108 **Ning H**, Yang F, Jiang M, Hu L, Feng K, Zhang J, Yu Z, Li B, Xu C, Li Y, Wang J, Hu J, Lou X, Chen H. The correlation between cotransplantation of mesenchymal stem cells and higher recurrence rate in hematologic malignancy patients: outcome of a pilot clinical study. *Leukemia* 2008; **22**: 593-599

109 **Ringdén O**, Uzunel M, Rasmusson I, Remberger M, Sundberg B, Lönnies H, Marschall HU, Dlugosz A, Szakos A, Hassan Z, Omazic B, Aschan J, Barkholt L, Le Blanc K. Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease. *Transplantation* 2006; **81**: 1390-1397

110 **Nakamizo A**, Marini F, Amano T, Khan A, Studeny M, Gumin J, Chen J, Hentschel S, Vecil G, Dembinski J, Andreeff M, Lang FF. Human bone marrow-derived mesenchymal stem cells in the treatment of gliomas. *Cancer Res* 2005; **65**: 3307-3318

111 **Zhu Y**, Sun Z, Han Q, Liao L, Wang J, Bian C, Li J, Yan X, Liu Y, Shao C, Zhao RC. Human mesenchymal stem cells inhibit cancer cell proliferation by secreting DKK-1. *Leukemia* 2009; **23**: 925-933

112 **Mishra A**, Bharti AC, Varghese P, Saluja D, Das BC. Differential expression and activation of NF-kappaB family proteins during oral carcinogenesis: Role of high risk human papillomavirus infection. *Int J Cancer* 2006; **119**: 2840-2850

113 **Rhodus NL**, Cheng B, Myers S, Bowles W, Ho V, Ondrey F. A comparison of the pro-inflammatory, NF-kappaB-dependent cytokines: TNF-alpha, IL-1-alpha, IL-6, and IL-8 in different oral fluids from oral lichen planus patients. *Clin Immunol* 2005; **114**: 278-283

114 **Rhodus NL**, Ho V, Miller CS, Myers S, Ondrey F. NF-kappaB dependent cytokine levels in saliva of patients with oral preneoplastic lesions and oral squamous cell carcinoma. *Cancer Detect Prev* 2005; **29**: 42-45

115 **O'Neil BH**, Bůzková P, Farrah H, Kashatus D, Sanoff H, Goldberg RM, Baldwin AS, Funkhouser WK. Expression of nuclear factor-kappaB family proteins in hepatocellular car-

cinomas. *Oncology* 2007; **72**: 97-104

116 **Tai DI**, Tsai SL, Chang YH, Huang SN, Chen TC, Chang KS, Liaw YF. Constitutive activation of nuclear factor kappaB in hepatocellular carcinoma. *Cancer* 2000; **89**: 2274-2281

117 **Logan RM**, Gibson RJ, Sonis ST, Keefe DM. Nuclear factor-kappaB (NF-kappaB) and cyclooxygenase-2 (COX-2) expression in the oral mucosa following cancer chemotherapy. *Oral Oncol* 2007; **43**: 395-401

118 **Ling FC**, Baldus SE, Khochfar J, Xi H, Neiss S, Brabender J, Metzger R, Drebber U, Dienes HP, Bollschweiler E, Hoelscher AH, Schneider PM. Association of COX-2 expression with corresponding active and chronic inflammatory reactions in Barrett's metaplasia and progression to cancer. *Histopathology* 2007; **50**: 203-209

119 **Karamitopoulou E**, Tornillo L, Zlobec I, Cioccari L, Carafa V, Borner M, Schaffner T, Brunner T, Diamantis I, Zimmermann A, Terracciano L. Clinical significance of cell cycle- and apoptosis-related markers in biliary tract cancer: a tissue microarray-based approach revealing a distinctive immunophenotype for intrahepatic and extrahepatic cholangiocarcinomas. *Am J Clin Pathol* 2008; **130**: 780-786

120 **Gao YW**, Chen YX, Wang ZM, Zhou LD, Li XY, Li LX, Luo QZ, Tian W, Fu CY, Zhou JH. Correlation between expression of cyclooxygenase-2 and the presence of CD4+ infiltrating T-lymphocyte in human primary hepatocellular carcinoma. *Hepatogastroenterology* 2008; **55**: 345-350

121 **El-Bassiouny AE**, Zoheiry MM, Nosseir MM, El-Ahwany EG, Ibrahim RA, El-Bassiouni NE. Expression of cyclooxygenase-2 and transforming growth factor-beta1 in HCV-induced chronic liver disease and hepatocellular carcinoma. *MedGenMed* 2007; **9**: 45

122 **Niijima M**, Yamaguchi T, Ishihara T, Hara T, Kato K, Kondo F, Saisho H. Immunohistochemical analysis and in situ hybridization of cyclooxygenase-2 expression in intraductal papillary-mucinous tumors of the pancreas. *Cancer* 2002; **94**: 1565-1573

123 **Eberhart CE**, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, DuBois RN. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. *Gastroenterology* 1994; **107**: 1183-1188

124 **Joo YE**, Oh WT, Rew JS, Park CS, Choi SK, Kim SJ. Cyclooxygenase-2 expression is associated with well-differentiated and intestinal-type pathways in gastric carcinogenesis. *Digestion* 2002; **66**: 222-229

125 **Yamagata R**, Shimoyama T, Fukuda S, Yoshimura T, Tanaka M, Munakata A. Cyclooxygenase-2 expression is increased in early intestinal-type gastric cancer and gastric mucosa with intestinal metaplasia. *Eur J Gastroenterol Hepatol* 2002; **14**: 359-363

126 **Ma XT**, Wang S, Ye YJ, Du RY, Cui ZR, Somsouk M. Constitutive activation of Stat3 signaling pathway in human colorectal carcinoma. *World J Gastroenterol* 2004; **10**: 1569-1573

127 **Kanda N**, Seno H, Konda Y, Marusawa H, Kanai M, Nakajima T, Kawashima T, Nanakin A, Sawabu T, Uenoyama Y, Sekikawa A, Kawada M, Suzuki K, Kayahara T, Fukui H, Sawada M, Chiba T. STAT3 is constitutively activated and supports cell survival in association with survivin expression in gastric cancer cells. *Oncogene* 2004; **23**: 4921-4929

128 **Zhang H**, Wang S, Zhang YC, Ye YJ, Cui ZR, Fang WG. [Correlation between Stat3 signal transduction pathway and expression of cyclooxygenase-2 in colorectal cancer cells]. *Zhonghua Yi Xue Za Zhi* 2005; **85**: 2899-2904

129 **Dvorakova K**, Payne CM, Ramsey L, Holubec H, Sampliner R, Dominguez J, Dvorak B, Bernstein H, Bernstein C, Prasad A, Fass R, Cui H, Garewal H. Increased expression and secretion of interleukin-6 in patients with Barrett's esophagus. *Clin Cancer Res* 2004; **10**: 2020-2028

130 **Kinoshita T**, Ito H, Miki C. Serum interleukin-6 level reflects the tumor proliferative activity in patients with colorectal carcinoma. *Cancer* 1999; **85**: 2526-2531

131 **Komoda H**, Tanaka Y, Honda M, Matsuo Y, Hazama K, Takao T. Interleukin-6 levels in colorectal cancer tissues. *World J Surg* 1998; **22**: 895-898

132 **Wilson KT**, Fu S, Ramanujam KS, Meltzer SJ. Increased expression of inducible nitric oxide synthase and cyclooxygenase-2 in Barrett's esophagus and associated adenocarcinomas. *Cancer Res* 1998; **58**: 2929-2934

133 **Hennig R**, Grippo P, Ding XZ, Rao SM, Buchler MW, Friess H, Talamonti MS, Bell RH, Adrian TE. 5-Lipoxygenase, a marker for early pancreatic intraepithelial neoplastic lesions. *Cancer Res* 2005; **65**: 6011-6016

134 **Izzo JG**, Malhotra U, Wu TT, Luthra R, Correa AM, Swisher SG, Hofstetter W, Chao KS, Hung MC, Ajani JA. Clinical biology of esophageal adenocarcinoma after surgery is influenced by nuclear factor-kappaB expression. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 1200-1205

135 **Weichert W**, Boehm M, Gekeler V, Bahra M, Langrehr J, Neuhaus P, Denkert C, Imre G, Weller C, Hofmann HP, Niesporek S, Jacob J, Dietel M, Scheidereit C, Kristiansen G. High expression of RelA/p65 is associated with activation of nuclear factor-kappaB-dependent signaling in pancreatic cancer and marks a patient population with poor prognosis. *Br J Cancer* 2007; **97**: 523-530

136 **Asakawa M**, Kono H, Amemiya H, Matsuda M, Suzuki T, Maki A, Fujii H. Role of interleukin-18 and its receptor in hepatocellular carcinoma associated with hepatitis C virus infection. *Int J Cancer* 2006; **118**: 564-570

137 **Levidou G**, Korkolopoulou P, Nikiteas N, Tzanakis N, Thymara I, Saetta AA, Tsigris C, Rallis G, Vlasis K, Patsouris E. Expression of nuclear factor kappaB in human gastric carcinoma: relationship with I kappaB a and prognostic significance. *Virchows Arch* 2007; **450**: 519-527

138 **Wu L**, Pu Z, Feng J, Li G, Zheng Z, Shen W. The ubiquitin-proteasome pathway and enhanced activity of NF-kappaB in gastric carcinoma. *J Surg Oncol* 2008; **97**: 439-444

139 **Yamanaka N**, Sasaki N, Tasaki A, Nakashima H, Kubo M, Morisaki T, Noshiro H, Yao T, Tsuneyoshi M, Tanaka M, Katano M. Nuclear factor-kappaB p65 is a prognostic indicator in gastric carcinoma. *Anticancer Res* 2004; **24**: 1071-1075

140 **Voboril R**, Voborilova J, Rychterova V, Jirasek T, Dvorak J. Dissociated invasively growing cancer cells with NF-kappaB/p65 positivity after radiotherapy: a new marker for worse clinical outcome in rectal cancer? Preliminary data. *Clin Exp Metastasis* 2008; **25**: 491-496

141 **Chang BW**, Kim DH, Kowalski DP, Burleson JA, Son YH, Wilson LD, Haffty BG. Prognostic significance of cyclooxygenase-2 in oropharyngeal squamous cell carcinoma. *Clin Cancer Res* 2004; **10**: 1678-1684

142 **Alici S**, Ugras S, Bayram I, Izmirli M. Prognostic factors and COX-2 expression in advanced stage esophageal squamous cell carcinoma. *Adv Ther* 2006; **23**: 672-679

143 **France M**, Drew PA, Dodd T, Watson DI. Cyclo-oxygenase-2 expression in esophageal adenocarcinoma as a determinant of clinical outcome following esophagectomy. *Dis Esophagus* 2004; **17**: 136-140

144 **Liu B**, Ren Z, Shi Y, Guan C, Pan Z, Zong Z. Activation of signal transducers and activators of transcription 3 and overexpression of its target gene CyclinD1 in laryngeal carcinomas. *Laryngoscope* 2008; **118**: 1976-1980

145 **Yang GZ**, Li L, Ding HY, Zhou JS. Cyclooxygenase-2 is overexpressed in Chinese esophageal squamous cell carcinoma, and correlated with NF-kappaB: an immunohistochemical study. *Exp Mol Pathol* 2005; **79**: 214-218

146 **Yoshikawa R**, Fujiwara Y, Koishi K, Kojima S, Matsumoto T, Yanagi H, Yamamura T, Hashimoto-Tamaoki T, Nishigami T, Tsujimura T. Cyclooxygenase-2 expression after preoperative chemoradiotherapy correlates with more frequent esophageal cancer recurrence. *World J Gastroenterol* 2007; **13**: 2283-2288

147 **Santini D**, Vincenzi B, Tonini G, Scarpa S, Vasaturo F, Malacrino C, Vecchio F, Borzomati D, Valeri S, Coppola R, Magistrelli P, Nuzzo G, Picciocchi A. Cyclooxygenase-2 overexpression is associated with a poor outcome in resected ampullary cancer patients. *Clin Cancer Res* 2005; **11**: 3784-3789

148 **Konno H**, Baba M, Shoji T, Ohta M, Suzuki S, Nakamura S. Cyclooxygenase-2 expression correlates with uPAR levels and is responsible for poor prognosis of colorectal cancer. *Clin Exp Metastasis* 2002; **19**: 527-534

149 **Masunaga R**, Kohno H, Dhar DK, Ohno S, Shibakita M, Kinugasa S, Yoshimura H, Tachibana M, Kubota H, Nagasue N. Cyclooxygenase-2 expression correlates with tumor neovascularization and prognosis in human colorectal carcinoma patients. *Clin Cancer Res* 2000; **6**: 4064-4068

150 **Nakamoto RH**, Uetake H, Iida S, Kolev YV, Soumaoro LT, Takagi Y, Yasuno M, Sugihara K. Correlations between cyclooxygenase-2 expression and angiogenic factors in primary tumors and liver metastases in colorectal cancer. *Jpn J Clin Oncol* 2007; **37**: 679-685

151 **Ogino S**, Kirkner GJ, Nosho K, Irahara N, Kure S, Shima K, Hazra A, Chan AT, Dehari R, Giovannucci EL, Fuchs CS. Cyclooxygenase-2 expression is an independent predictor of poor prognosis in colon cancer. *Clin Cancer Res* 2008; **14**: 8221-8227

152 **Soumaoro LT**, Uetake H, Higuchi T, Takagi Y, Enomoto M, Sugihara K. Cyclooxygenase-2 expression: a significant prognostic indicator for patients with colorectal cancer. *Clin Cancer Res* 2004; **10**: 8465-8471

153 **Shi H**, Xu JM, Hu NZ, Xie HJ. Prognostic significance of expression of cyclooxygenase-2 and vascular endothelial growth factor in human gastric carcinoma. *World J Gastroenterol* 2003; **9**: 1421-1426

154 **Petersen S**, Haroske G, Hellmich G, Ludwig K, Petersen C, Eicheler W. COX-2 expression in rectal carcinoma: immunohistochemical pattern and clinical outcome. *Anticancer Res* 2002; **22**: 1225-1230

155 **Kaifi JT**, Yekebas EF, Schurr P, Obonyo D, Wachowiak R, Busch P, Heinecke A, Pantel K, Izbicki JR. Tumor-cell homing to lymph nodes and bone marrow and CXCR4 expression in esophageal cancer. *J Natl Cancer Inst* 2005; **97**: 1840-1847

156 **Ottaiano A**, Franco R, Aiello Talamanca A, Liguori G, Tatangelo F, Delrio P, Nasti G, Barletta E, Facchini G, Daniele B, Di Blasi A, Napolitano M, Ieranò C, Calemma R, Leonardi E, Albino V, De Angelis V, Falanga M, Boccia V, Capuozzo M, Parisi V, Botti G, Castello G, Vincenzo Iaffaioli R, Scala S. Overexpression of both CXC chemokine receptor 4 and vascular endothelial growth factor proteins predicts early distant relapse in stage II-III colorectal cancer patients. *Clin Cancer Res* 2006; **12**: 2795-2803

157 **Yoshitake N**, Fukui H, Yamagishi H, Sekikawa A, Fujii S, Tomita S, Ichikawa K, Imura J, Hiraishi H, Fujimori T. Expression of SDF-1 alpha and nuclear CXCR4 predicts lymph node metastasis in colorectal cancer. *Br J Cancer* 2008; **98**: 1682-1689

158 **Li YH**, Hu CF, Shao Q, Huang MY, Hou JH, Xie D, Zeng YX, Shao JY. Elevated expressions of survivin and VEGF protein are strong independent predictors of survival in advanced nasopharyngeal carcinoma. *J Transl Med* 2008; **6**: 1

159 **Kimura S**, Kitadai Y, Tanaka S, Kuwai T, Hihara J, Yoshida K, Toge T, Chayama K. Expression of hypoxia-inducible factor (HIF)-1alpha is associated with vascular endothelial growth factor expression and tumour angiogenesis in human oesophageal squamous cell carcinoma. *Eur J Cancer* 2004; **40**: 1904-1912

160 **Zhang B**, Zhao WH, Zhou WY, Yu WS, Yu JM, Li S. Expression of vascular endothelial growth factors-C and -D correlate with evidence of lymphangiogenesis and angiogenesis in pancreatic adenocarcinoma. *Cancer Detect Prev* 2007; **31**: 436-442

161   **Jia JB**, Zhuang PY, Sun HC, Zhang JB, Zhang W, Zhu XD, Xiong YQ, Xu HX, Tang ZY. Protein expression profiling of vascular endothelial growth factor and its receptors identifies subclasses of hepatocellular carcinoma and predicts survival. *J Cancer Res Clin Oncol* 2009; **135**: 847-854

162   **Dassoulas K**, Gazouli M, Rizos S, Theodoropoulos G, Christoni Z, Nikiteas N, Karakitsos P. Common polymorphisms in the vascular endothelial growth factor gene and colorectal cancer development, prognosis, and survival. *Mol Carcinog* 2009; **48**: 563-569

163   **Kim JG**, Chae YS, Sohn SK, Cho YY, Moon JH, Park JY, Jeon SW, Lee IT, Choi GS, Jun SH. Vascular endothelial growth factor gene polymorphisms associated with prognosis for patients with colorectal cancer. *Clin Cancer Res* 2008; **14**: 62-66

164   **Tang H**, Wang J, Bai F, Zhai H, Gao J, Hong L, Xie H, Zhang F, Lan M, Yao W, Liu J, Wu K, Fan D. Positive correlation of osteopontin, cyclooxygenase-2 and vascular endothelial growth factor in gastric cancer. *Cancer Invest* 2008; **26**: 60-67

165   **Chen XL**, Wang LC, Zhang WG, Chen XY, Sun ZM. [Correlations of S100A4 and MMP9 expressions to infiltration, metastasis and prognosis of non-small cell lung cancer]. *Nan Fang Yi Ke Da Xue Xue Bao* 2008; **28**: 1254-1258

166   **Kai H**, Kitadai Y, Kodama M, Cho S, Kuroda T, Ito M, Tanaka S, Ohmoto Y, Chayama K. Involvement of proinflammatory cytokines IL-1beta and IL-6 in progression of human gastric carcinoma. *Anticancer Res* 2005; **25**: 709-713

167   **Chung YC**, Chaen YL, Hsu CP. Clinical significance of tissue expression of interleukin-6 in colorectal carcinoma. *Anticancer Res* 2006; **26**: 3905-3911

168   **Ito H**, Miki C. Profile of circulating levels of interleukin-1 receptor antagonist and interleukin-6 in colorectal cancer patients. *Scand J Gastroenterol* 1999; **34**: 1139-1143

169   **Haraguchi M**, Komuta K, Akashi A, Matsuzaki S, Furui J, Kanematsu T. Elevated IL-8 levels in the drainage vein of resectable Dukes' C colorectal cancer indicate high risk for developing hepatic metastasis. *Oncol Rep* 2002; **9**: 159-165

170   **Rubie C**, Frick VO, Pfeil S, Wagner M, Kollmar O, Kopp B, Graber S, Rau BM, Schilling MK. Correlation of IL-8 with induction, progression and metastatic potential of colorectal cancer. *World J Gastroenterol* 2007; **13**: 4996-5002

171   **Terada H**, Urano T, Konno H. Association of interleukin-8 and plasminogen activator system in the progression of colorectal cancer. *Eur Surg Res* 2005; **37**: 166-172

172   **Kubo F**, Ueno S, Hiwatashi K, Sakoda M, Kawaida K, Nuruki K, Aikou T. Interleukin 8 in human hepatocellular carcinoma correlates with cancer cell invasion of vessels but not with tumor angiogenesis. *Ann Surg Oncol* 2005; **12**: 800-807

173   **Kido S**, Kitadai Y, Hattori N, Haruma K, Kido T, Ohta M, Tanaka S, Yoshihara M, Sumii K, Ohmoto Y, Chayama K. Interleukin 8 and vascular endothelial growth factor -- prognostic factors in human gastric carcinomas? *Eur J Cancer* 2001; **37**: 1482-1487

174   **Hu ZL**, Wen JF, Shen M, Liu Y. [Expressions of TGIF, MMP9 and VEGF proteins and their clinicopathological relationship in gastric cancer]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2006; **31**: 70-74

175   **Gu ZD**, Li JY, Li M, Gu J, Shi XT, Ke Y, Chen KN. Matrix metalloproteinases expression correlates with survival in patients with esophageal squamous cell carcinoma. *Am J Gastroenterol* 2005; **100**: 1835-1843

176   **Wang L**, Tang Z, Sun H. [Nitric oxide synthase and vascular endothelial growth factor expression in hepatocellular carcinoma and their relation to angiogenesis]. *Zhonghua Zhong Liu Za Zhi* 2000; **22**: 301-303

177   **Rajnakova A**, Moochhala S, Goh PM, Ngoi S. Expression of nitric oxide synthase, cyclooxygenase, and p53 in different stages of human gastric cancer. *Cancer Lett* 2001; **172**: 177-185

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