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Inflammation and Cancer: How Friendly Is the Relationship For Cancer Patients?

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Abstract

Evidence has emerged in the last two decades that at the molecular level most chronic diseases, including cancer, are caused by a dysregulated inflammatory response. The identification of transcription factors such as NF-kB, AP-1 and STAT3 and their gene products such as tumor necrosis factor, interleukin-1, interleukin-6, chemokines, cyclooxygenase-2, 5 lipooxygenase, matrix metalloproteases, and vascular endothelial growth factor, adhesion molecules and others have provided the molecular basis for the role of inflammation in cancer. These inflammatory pathways are activated by tobacco, stress, dietary agents, obesity, alcohol, infectious agents, irradiation, and environmental stimuli, which together account for as much as 95% of all cancers. These pathways have been implicated in transformation, survival, proliferation, invasion, angiogenesis, metastasis, chemoresistance, and radioresistance of cancer, so much so that survival and proliferation of most types of cancer stem cells themselves appear to be dependent on the activation of these inflammatory pathways. Most of this evidence, however, is from preclinical studies. Whether these pathways have any role in prevention, progression, diagnosis, prognosis, recurrence or treatment of cancer in patients, is the topic of discussion of this review. We present evidence that inhibitors of inflammatory biomarkers may have a role in both prevention and treatment of cancer.

2. Introduction

Cancer is one disease that fits the paradigm that “more we know, less we understand its intricacies”. That continuous irritation over long periods of time can lead to cancer (called arbuda), has been described in Ayurveda (means the science of long life), written as far back as 5000 years ago. Whether this irritation is the same as that Rudolf Virchow referred to as inflammation in the nineteenth century is uncertain. The observable consequences of irritation were first described by Aulus Cornelius Celsus, a Roman medical writer and possibly a physician in the first century (ca 25BC-50 AD), who characterized inflammation as “redness (rubor) and swelling (tumor) with heat (calor) and pain (dolor)”. Virchow postulated that microinflammation that results from irritation leads to the development of most chronic diseases including cancer. This inflammation is now regarded as a “secret killer” for diseases such as atherosclerosis, rheumatoid arthritis, multiple sclerosis, asthma, Alzheimer's, depression, fatigue, neuropathic pain, lack of appetite, and cancer (1). With the recent advent of molecular biology, cell signaling, recombinant DNA, and genomics, there has been

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reawakening and tremendous interest in the role of inflammation in cancer and other diseases. This review will focus primarily on the role of inflammation in cancer.

3. Inflammatory network in cancer

In the last two decades numerous molecules have been identified that play a critical role in inflammation. These include tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6), chemokines, cyclooxygenase (COX)-2, 5 lipooxygenase (LOX), matrix metalloproteases (MMP), vascular endothelial growth factor (VEGF), TWIST and cell surface adhesion molecules. What is common to all these molecules is that they are regulated by the transcription factor NF-κB (Fig. 1). Although initially discovered in the kappa chain of immunoglobulin and in nucleus of B cells, NF-κB is now known to be a transcription factor that is ubiquitous to all cell types and present in the cytoplasm in its resting stage. Soon after its discovery, certain NF-κB proteins were shown to exhibit oncogenic activity e.g; v-rel. The activity of NF-κB itself is regulated by other transcription factors such Notch-1 (2), PPAR-g (3), STAT3 (4), beta-catenin (5) and p53 (6). NF-κB has been shown to regulate AP-1 through ELK-1-mediated expression of c-fos (7) (Fig. 2).

For many reasons NF-κB and gene products regulated by it play a critical role in tumorigenesis (8). First, almost all gene products linked with inflammation are regulated by the activation of NF-κB (e.g; TNF, IL-1, IL-6, chemokines, COX2, 5LOX, CRP). Second, NF-κB is activated in response to tobacco, stress, dietary agents, obesity, alcohol, infectious agents, irradiation and environmental stimuli, which together account for as much as 95% of all cancers. Third, NF-κB has been linked with transformation of cells (8). Fourth, NF-κB is constitutively active in most tumor cells. Fifth, NF-κB has also been linked with the survival of cancer stem cells, an early progenitor cells that have acquired self-renewal potential (9-14). Sixth, NF-κB regulates the expression of most antiapoptotic gene products (bcl-2, bcl-xl, c-FLIP, XIAP, IAP-1, IAP-2, and survivin) associated with the survival of the tumor. Seventh, NF-κB also regulates the gene products linked with proliferation of tumors such as c-myc, cyclin D1, and COX2. Additionally most growth factors (e.g; EGF, TNF, IL-6) linked with proliferation of tumors either activate NF-κB or are regulated by this transcription factor. Eighth, NF-κB controls the expression of gene products linked with invasion, angiogenesis and metastasis of cancer (e.g; MMP, adhesion molecules, VEGF, TWIST, CXCR4). Ninth, while most carcinogens activate NF-κB, most chemopreventive agents have been shown to suppress NF-κB activation (Fig. 1). Thus based on cell culture and animal models, the role of NF-κB and the gene products regulated by it are very well established. Because very rarely discoveries in cell culture or animals models translate directly into treatments or preventive for patients (8), we decided to focus in this review on the role of the NF-κB-regulated inflammatory network in progression, diagnosis, prognosis, recurrence, and treatment of cancer in the patients.

4. Evidence that inflammatory genes/products are overexpressed in cancer patients

Both TNF and NF-κB, two major mediators of inflammation (isolated around 1984 and 1986, respectively) are now the subjects of around 73,000 and 27,000 citations. The Pubmed database also shows 2300 citation for NF-κB in patients in general and around 800 in cancer patients alone. Thus it is not possible to cover all this information. Both NF-κB and NF-κB gene products have been, however, linked with prognosis and response to therapy in patients with different cancers (see Tables 1-3 (18-270).

4A. Role of NF-κB in cancer patients

The presence of constitutively active NF-κB has now been identified in tissue of most cancers including leukemia, lymphoma, and cancers of the prostate, breast, oral cavity, liver, pancreas, colon, and ovary (Table 1;). The role of NF-κB in cancer patients has also been examined. Activation of NF-κB has been linked with metastasis of prostate cancer to the lymph nodes (15) and it predicts patient outcomes in prostate cancer (16). Similarly, it is associated with high recurrence and poor survival in squamous cell carcinoma of the tonsil (17) and with oral tumor progression (18); it is a prognostic indicator in esophageal cancer (19), and is associated with chemoradiation resistance in patients with this tumor (20). Progression of lung cancer (21) reduced survival in ovarian cancer (22), aggressiveness of breast cancer (23,24)and response to chemotherapy in breast cancer (25) have all been linked to NF-κB activation. Why NF-κB is expressed constitutively in these tissues is not clear. Whole-genome structure analysis revealed that the kinase needed for NF-κB activation (IKKe) is amplified and overexpressed in patient -derived breast cancer tissue (7 of 20) (26). In multiple myeloma, high-density oligonucleotide array CGH and gene expression profiling data revealed ten genes causing the inactivation of TRAF2, TRAF3, CYLD, and IAP1/cIAP2, and activation of NFKB1, NFKB2, CD40, LTBR, TACI, and NIK was linked to constitutive activation of the noncanonical NF-κB pathway (27). Constitutive activation of NF-κB in multiple myeloma patients has also been ascribed to elevated expression of NIK due to genomic alterations or protein stabilization ((28). All these studies suggest that NF-κB plays important in most human cancers and thus that suppression of NF-κB should have therapeutic potential.

4B. Role of STAT3 in cancer patients

Unlike NF-κB, very little is known about the status of STAT3 in cancer patients. Various growth factors for cancer cells can activate STAT3, including IL-6 and EGF. Constitutively active STAT3 has been reported in multiple myeloma (29), chronic lymphocytic leukemia (30), gastric cancer (31), lung cancer (32), and laryngeal carcinoma (33). Its constitutive activity has been correlated with unfavorable treatment outcome in acute myelogenous leukemia (34): constitutive STAT3 activity was detected in samples from 44% of patients. Disease-free survival (DFS) was significantly shorter in patients with constitutive STAT3 activity (median 8.7 vs 20.6 months), although overall survival did not differ significantly. The subgroup of patients with constitutive STAT3 activity and the STAT3 beta isoform had the shortest DFS and overall survival of all the patients.

4C. Role of COX2 in cancer patients

COX2 has emerged as another major mediator of inflammation, accounting for over 15,000 citations in the medical literature. Overexpression of COX2 has been shown in patients with various cancers (Table 2). Its overexpression has been linked with poor survival in prostate cancer (35), with a high probability of recurrence of this cancer (36), with shorter survival of lung cancer patients (37), with pathogenesis and progression of oral cancer (38) and progression of esophageal cancer (39). Angiogenesis in Hodgkin's disease (40), shorter progression-free survival in multiple myeloma (41), and lymphoangiogenesis and poor prognosis in invasive breast cancer (42) likewise have been linked to COX overexpression. Levels of COX-2 expression were significant prognostic factors for patients with multiple myeloma (43): overall survival of those patients with negative or weak-moderate COX-2 expression was significantly better than that of patients with strong COX-2 immunoreactivity. Overexpression of COX-2 is also associated with a poor prognosis in patients with SCC of the uterine cervix treated with radiation and concurrent chemotherapy (44). COX-2 expression was also found to be related to nuclear grade in ductal carcinoma in situ, and it was increased in its normal adjacent epithelium (45).

4D. Role of TNF in cancer patients

Although TNF is the most potent activator of NF-kB, elevated levels of TNF in tissue or serum are not very common in cancer patients. One of the first reports of a possible role for TNF in cancer was presented by (46). TNF was detected in 50% of 226 freshly obtained serum samples from cancer patients with active disease. In contrast, only 3% of 32 samples from normal subjects and 18% of 39 samples from cancer patients with no clinically evident disease were positive for this factor, with low activity. Greater proportions of serum samples from patients with ovarian or oat-cell carcinoma were positive (69% and 63%) than those from patients with lymphoma (26%). TNF mRNA was found in 8 of 11 samples of PBMC from cancer patients, but only 1 of 8 normal subjects, and in 2 of 6 colorectal tumors. The similarity in production of TNF both in patients with ovarian tumors (47) and in patients with benign tumors supports the conclusion that the production of these cytokines is more a nonspecific indicator of an inflammatory process than a specific response to a malignant process. In contrast to these studies, the clinical significance of TNF plasma level in patients with chronic lymphocytic leukemia has been reported (48); and acts as an autocrine and paracrine growth factor in this disease. In CLL patients TNF was significantly higher than in the healthy control population (16.4 versus 8.7 pg/mL). The TNF-alpha level was a predictor of survival, and in fact patients with a TNF level above the mean value of14 pg/mL had significantly shorter survival duration.

4E. Role of IL-1 in cancer patients

IL-1β is another cytokine that is regulated by NF-κB. This cytokine has been associated with growth and progression of human gastric carcinoma (49), colorectal cancer (50), esophageal cancer (51) and ovarian cancer (47). In one study, surgical removal of the ovarian tumor and resolution of ascites was followed by declines in serum levels of IL-1beta (52).

4F. Role of IL-6 in cancer patients

IL-6 is another cytokine that is regulated by NF-κB and serves as a growth factor for various tumors through the upregulation of STAT3., An overproduction of IL-6, indicated by increased plasma C-reactive protein levels, is found in 37% of multiple myeloma patients at diagnosis and is associated with disease aggressiveness, myeloma-cell proliferation, and poor prognosis (53). A systemic inflammatory response predicts prognosis in patients with advanced-stage colorectal cancer. (54). Inflammatory markers were measured at baseline in 52 patients with stage IV colorectal cancer. Significantly elevated levels of IL-6 and sgp130 were observed in patients with colon cancer, and inflammatory markers paralleled clinical outcome. Use of these markers could improve prognostication and allow for intervention strategies to reduce tumor-associated inflammation. Malignant ascites of epithelial ovarian cancer patients contains high levels of IL-6 (55).

4G. Role of chemokines in cancer patients

Among the chemokines, IL-8 has been linked with progression of colorectal cancer (CRC) (56), metastasis of CRC to liver (57,58), metastasis of hepatocellular carcinoma (HCC) (59), progression of prostate cancer (60), poor prognosis of nasopharyngeal carcinoma (61), prognotc maker for gastric cancer (62), and tumor progression and time to relapse of lung cancer (63), ovarian cancer (64) and malignant melanoma (65). The expression of the chemokine receptor CXCR4, which binds to stem cell-derived factor (SDF)-1, has also been linked with metastasis, poor prognsis, and short survival of patients with a wide variety of cancers (Table 3). These include breast (66), prostate (67), esophagus (68), CRC (69), lung (70), thyroid (71), astrocytoma (72) and neuroblastoma (73). In addition, the metastatic potential of a cancer stem cell is determined by the expression of CXCR4 (74,75). The SDF-1 and the G-protein-coupled seven-span transmembrane receptor CXCR4 axis regulates the trafficking of both normal and cancer stem cells. Moreover, functional CXCR4 is also

expressed on nonhematopoietic tissue-committed stem/progenitor cells (TCSCs); hence, the SDF-1-CXCR4 axis emerges as a pivotal regulator of trafficking of various types of stem cells in the body. Furthermore, because most if not all malignancies originate in the stem/progenitor cell compartment, cancer stem cells also express CXCR4 on their surface and, as a result, the SDF-1-CXCR4 axis is also involved in directing their trafficking/metastasis to organs that highly express SDF-1 (e.g., lymph nodes, lungs, liver, and bones). Consequently, strategies aimed at modulating the SDF-1-CXCR4 axis could have important clinical applications both in regenerative medicine to deliver normal stem cells to the tissues/organs and in clinical hematology/oncology to inhibit metastasis of cancer stem cells.

4H. Role of 5LOX in cancer patients

The expression of 5-lipooxygenase is also regulated by NF-κB and it has been linked with progression and development of cancer of the kidney ((76), breast (77) and pancreas (78). Besides 5-LOX, 12 –LOX, has also been linked with progression of breast (79) and prostate cancer (80).

4I. Role of VEGF in cancer patients

VEGF is another cytokine that plays an essential role in proliferation of endothelial cells and angiogenesis. The expression of VEGF has been linked with metastasis, poor prognosis and relapse of numerous cancers in pts including those of the lung (81,82), liver (83), CRC (84), ovary (85), papillary thyroid (86), stomach (87), nasopharyngeal space (88) and pancreas (89) and melanoma (90). Four most common organs of tumor metastasis are lung, bone, lymph node, and brain. Whether VEGF expression in the tumor tissue or the surrounding normal tissue can selectively regulate metastasis to any of these organs is a subjeect of investigation. VEGF has also been found to activate NF-κB in hematopoietic progenitor cells and mediate their survival (91).

4J. Role of iNOS in cancer patients

iNOS, whoseexpression is regulated by NF-κB, mediates the production of NO. Overexpression of iNOS has been linked with gastric cancer progression (92), brain tumor (93), Barrett's associated neoplastic progression (94), poor survival for stage III melanoma patients (95) and progression of transitional cell carcinoma (96). Some of the effects of iNOS are mediated through the suppression of apoptosis.

4K. Role of CRP in cancer patients

C-reactive protein (CRP), an NF-κB-regulated gene product first linked to cardiovascular diseases, has recently been linked with prognosis of cancers of the breast (97), colon (98), kidney (99), ovary (100)lung (101) and stomach (51), and multiple myeloma (102), melanoma (103), and non-Hodgkin's lymphoma (104). Thus CRP is emerging as an important prognostic marker in a wide variety of cancers.

4L. Role of MMP-9 and UPA in cancer patients

The invasion of vital organs by a tumor is regulated by matrix metalloproteases (MMP) and urinary plasminogen activator (UPA). Both of these proteins are regulated by NF-κB. Expression of MMP-9 has been correlated with prognosis, aggressiveness, and survival in cancer of the lung (105,106), stomach (107), and esophagus (108), and in non-Hodgkin's lmphoma NHL (109), renal cell carcinoma (110), and liposarcoma (111). The role of UPA under these conditions is less well understood.

4M. Role of cyclin D1 in cancer patients

Cyclin D1, whose expression is regulated by NF-κB, is involved in the transition of cells from G1 to S phase. Mantle cell lymphoma (MCL), which accounts for 5-10% of all non-Hodgkin lymphomas and has the worst prognosis among all lymphomas, The hallmark of MCL is a t (11;14) translocation that results in overexpression of cyclin D1 by tumor cells of virtually all patients (5). Cyclin D1 is also a prognostic marker for other type of cancers but the relationship is highly variable. Approximately 30% of myeloma patients express cyclin D1. The low incidence of translocation t(11;14) detected by conventional cytogenetics suggests that the up-regulation of cyclin D1 protein might result from other mechanisms as well as from gene amplification(112).

5. Inhibitors of inflammation in the clinic for treatment of cancer patients

From these studies, it is clear that various inflammatory markers are expressed in various cancers and they mediate progression of the diseases. Thus agents which suppress these inflammatory markers or the pathways activated by them have a potential for prevention and treatment of cancer (Fig. 3). Some of the agents that have potential to suppress these pathways and are being tested include steroids (such as dexamethasone and predensilon), proteasome inhibitors (such as velcade), TNF inhibitors (such as thalidomide, enbrel, humira and remicade), NF-κB inhibitors (such as curcumin), and COX2 inhibitors (such as aspirin and celecoxib). In addition most nutraceuticals derived from fruits, vegetables, legumes, and spices have been shown to suppress both constitutive and inducible NF-κB activation pathways, thus leading to suppression of various inflammatory biomarkers.

A model for regulation of inflammatory biomarkers is proposed (Fig. 3). Disease is normally due to dysregulation of numerous inflammatory biomarkers (represented by each bulb). Complete inhibition of a single biomarker (such as COX2) is more likely to be toxic and unlikely to cure the disease. However, downregulation of several biomarkers "*partially*" is more likely to inhibit the dysregulated inflammation and be less toxic and more efficient in treating the disease.

6. Conclusion

All the studies described above provide conclusive proof that inflammation is a critical mediator of cancer. Thus antinflammatory agents should be explored for both prevention and treatment of cancer. Although numerous cell culture and animal studies have identified several natural anti-inflammatory agents, their true potential will be recognized only through well-controlled clinical trials. Such studies are urgently needed. Curcumin, a component of turmeric, is one such agent that has been shown to suppress all the pathways indicated above. But its full clinical potential remains to be recognized.

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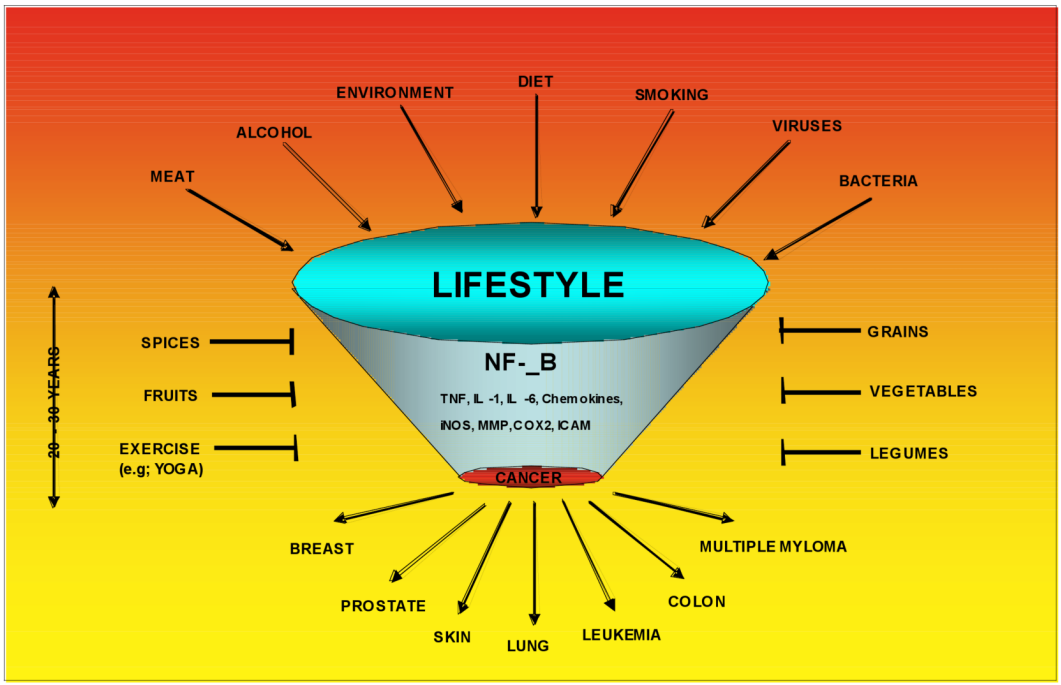

Fig.1.

Activation of inflammatory pathway mediated through NF-κB by life-style related factors such as tobacco, stress, dietary agents, obesity, alcohol, infectious agents, irradiation and environmental stimuli that account for as much as 95% of all cancers. Suppression of inflammatory pathway by life style –related agents such as vegetables, fruits, legumes, grains, spices and exercise (such as Yoga), is indicated.

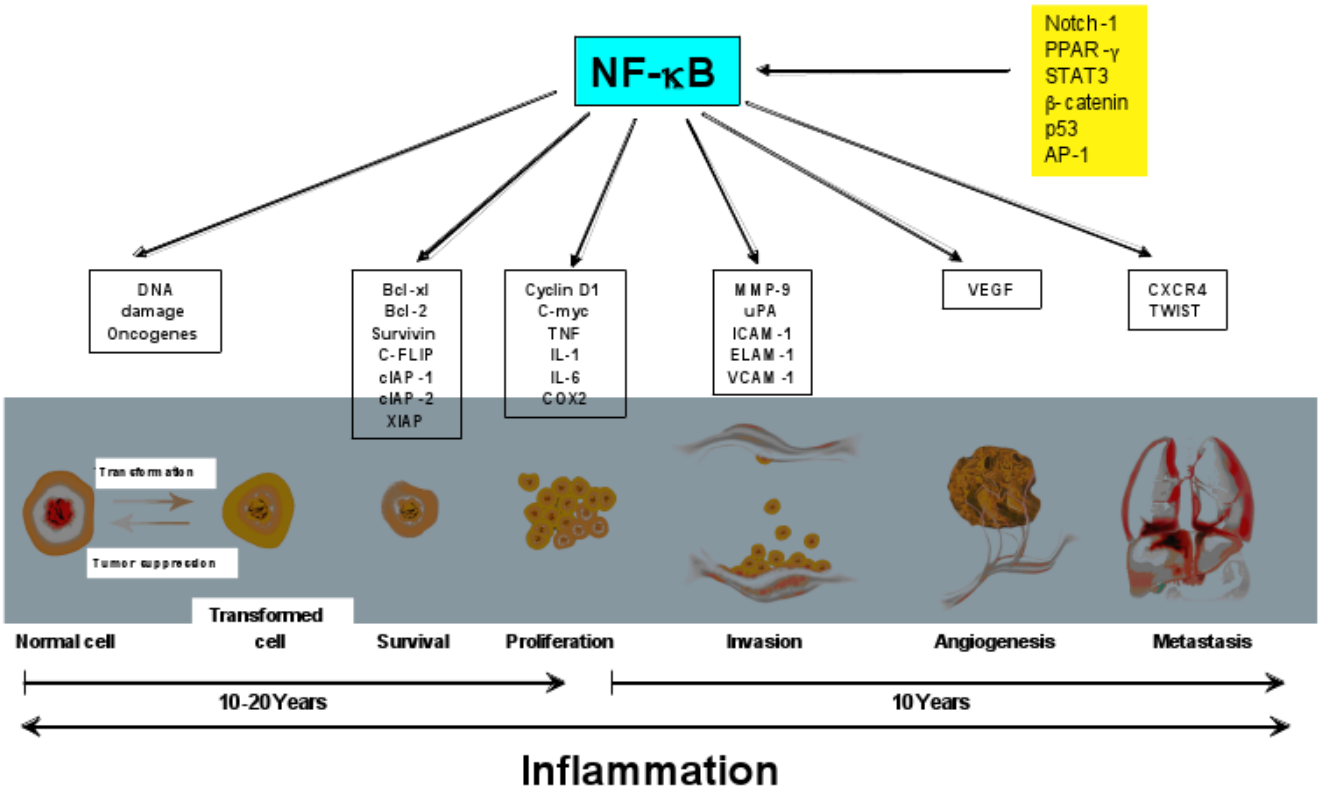

Fig. 2.

Activation of various inflammatory pathways that lead to expression of gene products linked to cellular transformation, survival, proliferation, invasion, angiogenesis and metastasis of cancer.

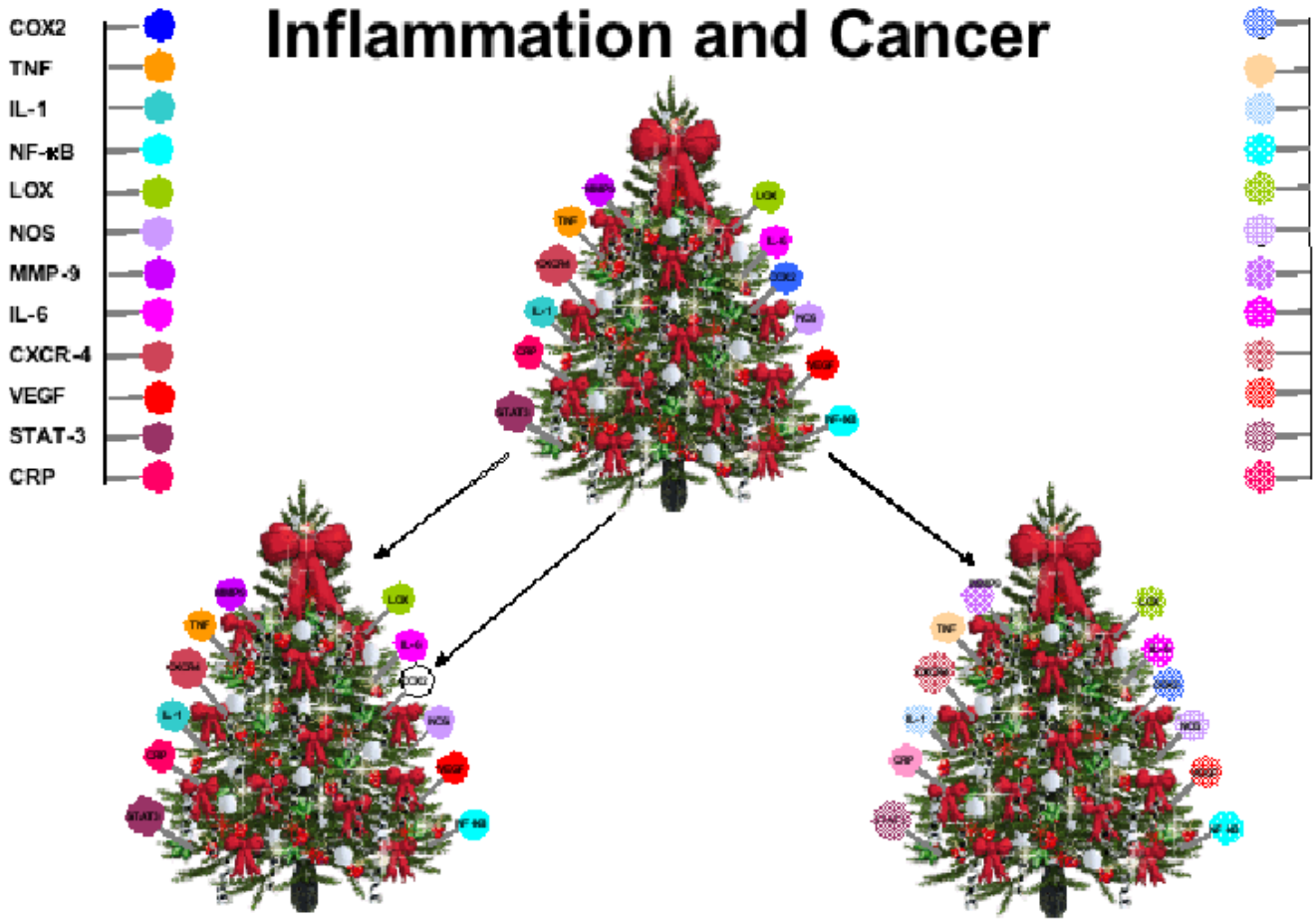

Fig. 3.

A model for regulation of inflammatory biomarkers. Disease is normally due to dysregulation of numerous inflammatory biomarkers (represented by each bulb). Complete inhibition of a single biomarker (such as COX2) is more likely to be toxic and unlikely to cure the disease. However, downregulation of several biomarkers ***partially*** is more likely to inhibit the dysregulated inflammation, be less toxic and more efficient in treating the disease.

Table 1

Overexpression of constitutive active NF-kB is linked to the progression of cancer in patients

Leukemia:

- Constitutive NF-kB/Rel activation was a common finding in Philadelphia chromosome positive (Ph+) ***acute lymphoblastic leukemia*** (113)
- B-***Chronic lymphocytic leukemia*** (CLL) patients had constitutive high NF-kB activity (114)
- NF-kB in ***Chronic lymphocytic leukemia*** (CLL) was linked with fludarabine resistance (115)
- Rel A is an independent prognostic marker of survival in ***Chronic lymphocytic leukemia*** (CLL) and predicted the duration of response to therapy ((116)
- NF-kB genes were significantly associated with shorter survival of patients and seemed to be an independent prognostic factor in a multivariate analysis in ***T-cell lymphomas*** (117)
- NF-kB was highly predictive of *Helicobacter pylori*-independent status in high-grade gastric ***MALT lymphoma*** (118)
- NF-kB was predictive of *Helicobacter pylori* -independent status of low-grade gastric ***MALT lymphoma*** (119)
- NF-kB transcription pathway was found to be linked to overall survival of ***Burkitt's lymphomas*** patients (120)
- Shorter survival was associated with the expression of NF-kB-regulated genes (TRAF5, REL, and PKCA) in pts with ***Splenic marginal zone lymphoma*** **(SMZL)** (121)
- NF-kB activation was linked with the clinical and pathologic manifestations of ***Hodgkin's disease*** (122)
- NF-kB activity was involved in the pathogenesis of ***Hodgkin's disease*** patients (123)
- NF-kB pathway activation displayed the most chemoresistant response in B-cell ***non-Hodgkin's lymphoma*** (124)
- Constitutive activation of the noncanonical NF-kB pathway mediated the pathogenesis of ***multiple myeloma*** (27)

Gastrointestinal Cancers:

- Constitutive activation and differential expression of NF-kB proteins was associated with severity of oral lesions during development of ***oral cancer*** (18)
- NF-kB was associated with ***oral tumor*** progression and with minimal residual disease (125)
- NF-kB following cytotoxic chemotherapy was associated with the pathogenesis of mucositis (126)
- Elevated NF-kB-regulated cytokines were found in ***oral lichen planus patients*** (127)
- Elevated NF-kB-regulated cytokines were discovered in the saliva of patients with ***oral squamous cell carcinoma*** (128)
- Activated NF-kB was associated with the lack of complete pathologic response, metastases and survival in patients with ***esophageal carcinoma*** (129)
- NF-kB was an independent prognostic indicator of poor outcome in patients with ***esophageal adenocarcinoma*** (19)
- NF-kB was a major factor in the pathogenesis of ***ulcerative colitis*** (130)
- NF-kB overexpression was associated with the **hepatocarcinogenesis** induced by HBV or HCV infection (131)
- High expression of activated NF-kB indicates poor patient survival in ***pancreatic cancer*** (132)
- Nuclear colocalization of NF-kB (p50/p52) and Bcl-3, interactions mediate ***HCC pathogenesis*** (133)
- NF-kB activation in ***HCC*** was implicated in a poor patient outcome (134)
- Strong expression of NF-kB was found in patients with ***pancreatic cancer*** *(*135*)*
- The high NF-kB group demonstrated a shorter overall survival rate in ***gastric cancer*** (136)
- Nuclear expression of NF kB (1/p50) in ***gastric carcinoma*** was a prognosis biomarker (137,138)
- NF-kB positivity after radiotherapy was linked with worse clinical outcome in ***rectal cancer*** (139)

Genitourinary Cancers:

- Nuclear expression of NF-kB was correlated with histologic grade and T category in ***bladder urothelial carcinoma*** (140)
- NF-KB1 promoter polymorphism is a useful marker for the identification of patients with superficial ***bladder cancer*** where the risk of recurrence is high (141)
- Nuclear NF-kB was linked with poor outcome in patients with ***prostate cancer*** (16)
- Activation of NF-kB was linked with metastasis of ***prostate cancer*** to lymph node (15)

- Nuclear NF-kB was strongly predictive of biochemical recurrence in patients with positive surgical margins after radical prostatectomy in ***prostate cancer*** (142)
- Nuclear localisation of NF-kB is an independent prognostic factor of biochemical relapse in ***prostate cancer*** (143)

Brain Cancers:

- Nuclear NF-kB1/p50 expression in ***astrocytoma***s was associated with tumor grade and angiogenic factors (144)
- Constitutive activation of NF-kB in malignant ***astrocytomas***, especially in glioblastoma, was associated with resistance to TNF-α immunotherapy (145)
- Upregulation of NF-kB in ***human gliomas*** was related to tumor grade (146)

Breast Cancers:

- NF-kB linked gene products contributed to unusual phenotype and aggressiveness of ***inflammatory breast cancer*** (23)
- Increased NF-kB activity was noted in the HER-2/neu overexpressing ***breast cancer*** (147)
- Increased NF-kB p50 DNA-binding was prognostic biomarker in high-risk ER-positive ***breast cancer*** (148)
- Activated NF-kB was detected in ER-negative and ErbB2-positive ***breast tumors*** (149)
- NF-kB activation was a potential prognostic marker for high-risk subset of ER-positive, primary ***breast cancers*** destined for early relapse despite adjuvant endocrine therapy with tamoxifen (24)

Gyneoncologic Cancers:

- NF-kB (p65) expression was a significant prognostic indicator of reduced survival in **ovarian cancer** patients (22)
- Overexpression of NF-kB p65 was involved in the carcinogenesis and metastasis of ***ovarian cancer*** (150)
- The association of NF-kB activation with cytokine upregulation was only evident in patients with **adenocarcinoma** (151)
- The association of NF-kB activation with angiogenesis and apoptosis was evident in ***renal cell carcinoma*** (152)

Head & Neck Cancers:

- High levels of NF-kB (p65) was significantly higher in SCLC compared with ***NSCLC*** (21)
- Upregulation of NF-kB was marked in lesional advance in patients with ***larynx cancer*** (153)
- NF-kB expression was associated with poor prognosis in ***non-small-cell lung cancer patient*****s** (154)
- Elevated expression of NF-kB was correlated with poor clinical outcome in ***lung cancer*** patients (155)
- NF-kB (RelA and pIkB α-positive) was a statistically significant predictor of patient death in early stage ***non-small cell lung cancer*** (156)
- NF-kB was overexpressed in high-grade dysplasia and poor survival in ***squamous cell carcinoma of the tonsil*** (17)
- The activation of NF-kB contributed to the process of ***chronic obstructive pulmonary disease*** in humans (157)

Melanoma:

- NF-kB was associated with poor prognosis of ***human squamous cell carcinoma*** (158)
- Overexpression of NF-kB p65 played an important role in the progression of ***malignant melanoma*** (159)
- NF-kB p105/p50 was correlated with progression and prognosis in human ***melanoma*** patients (160)

ALL-Acute Lymphoblastic Leukemia, ATL-Acute T cell Leukemia, AML-Acute Myelogenous Leukemia, HCC-Hepatocellular Carcinoma, MALT-Mucosa-Associated Lymphoid Tissue, NSCLC- Non-Small-Cell Lung Cancer

Table 2

Effect of Overexpression of Cyclooxygenase-2 in Progression of Cancer in Patients

Leukemia:

- COX-2 was correlated with prognosis of chronic-phase group of chronic myeloid leukemia (CML-CP) and ***chronic lymphocytic leukemia*** (161)
- COX-2 expression was associated with poor treatment response, higher systemic recurrence, and unfavorable prognosis in patients with extra nodal natural killer (NK)/***T-cell lymphoma*** (45)
- COX-2 expression was correlated with cellular proliferation in the gastric ***MALT lymphoma*** (162)
- COX-2 expression was associated with cell proliferation and angiogenesis in ***Hodgkin's lymphoma*** (40)
- COX-2 was correlated with shorter progression-free survival in ***multiple myeloma*** (41)
- COX-2 was associated with reduced estimated survival and poor prognostic factors in ***multiple myeloma*** (43)

Gastrointestinal Cancers:

- COX-2 was the most important predictor of poor survival in patient cohort in ***oropharyngeal squamous cell carcinoma*** (163)
- COX-2 expression was associated with pathogenesis in ***mucositis*** (126)
- COX-2 was associated with pathogenesis and progression of ***oral cancer*** (38)
- COX-2 expression was correlated with tumor progression in ***esophageal SCC*** (39)
- Increased COX-2 expression in ***Barrett's*** metaplasia was associated with a change in the local inflammatory reaction (164)
- COX-2 was associated with tumor growth in ***esophageal squamous cell carcinoma*** (165)
- COX-2 expression was correlated with an unfavorable prognostic factor in ***esophageal squamous cell carcinoma*** (166)
- Expression of COX-2 was elevated in squamous cell carcinoma of the ***esophagus*** and correlated with lymph node metastases and shorter survival (33)
- Increased expression of COX-2 was associated with a poor survival outcome in ***esophageal adenocarcinoma*** (167)
- COX-2 expression was correlated with depth of invasion and survival in ***esophageal squamous cell carcinoma*** (168)
- COX-2 expression played a prognostic factor in frequent tumor recurrence in ***esophageal squamous carcinoma*** patients undergoing neoadjuvant chemoradiotherapy (169)
- COX-2 expression in primary ***mid-gut carcinoids*** was associated with a negative prognostic outlook (170)
- Overexpression of COX-2 was important in the pathogenesis of ***cholangiocarcinomas*** (171)
- COX-2 expression contributed to suppression of local immune responses and enhancement of metastatic potential in ***human hepatocellular carcinoma*** (172)
- COX-2 was a predictive marker in the early stages of ***hepatocarcinogenesis*** (173)
- Elevation of the COX-2 was correlated with the suppression of local immune responses and early tumor recurrence in the residual ***liver*** in patients after resection (174)
- COX-2 was significant in the progression of ***hepatocellularcarcinoma*** (175)
- COX-2 expression was associated with proliferation of cancer in patients with ***pancreaticobiliary duct*** (176)
- COX-2 was involved in inflammatory response and progression in ***chronic pancreatitis*** (177)
- COX-2 expression was related to the histologic grade of intraductal papillary-mucinous tumor of the ***pancreas*** (178)
- COX-2 expression was a significant prognostic factor after surgical resection in patients affected by cancer of ***ampulla of vater*** (179)
- COX-2 expression in primary ***colorectal cancer*** was associated with liver metastasis (180)
- COX-2 expression was associated with poor survival in ***colon cancer*** patients (181)
- COX-2 expression was associated with reduced survival and was recognized as an independent prognostic factor in cohort of ***colorectal cancer*** patients (182)
- COX-2 was involved in lymph node metastasis and tumor vascularization in patients with ***colorectal cancer submucosa*** (183)
- COX-2 expression was observed in ***colorectal cancer*** cells due to the dysfunction of p53 (184)
- COX-2 gene expression was markedly elevated in human ***colorectal cancer*** compared to accompanying normal mucosa (185)
- COX-2 expression was correlated with poor prognosis in patients with ***colorectal cancer*** (186,187)
- COX-2 expression was associated with the carcinogenesis of the ***gastric cancer*** (188)

- COX-2 was associated with prognosis and intestinal pathways in ***gastric carcinogenesis*** (189)
- COX-2 expression was associated with invasion, metastasis and implicated a poor prognosis in ***gastric carcinoma*** (190)
- COX-2 expression mediated ***gastric cancer*** development by promoting angiogenesis and inhibiting apoptosis (191)
- COX-2 was linked to an increased risk of hematogenous metastatic spread in ***rectal carcinoma*** (192)

Genitourinary Cancers:

- COX-2 expression was significance to the development and proliferation of ***bladder transitional cell carcinoma*** (193)
- COX-2 expression was associated with development and invasion of ***transitional cell carcinoma*** (194)
- COX-2 expression was associated with high-grade bladder carcinoma and progression of ***bladder urothelial*** carcinoma (195)
- COX-2 was commonly expressed in patients with ***bladder transitional cell carcinoma*** (196)
- COX-2 expression was associated with poor survival in patients with ***prostate cancer*** who had radiotherapy (197)
- COX-2 expression was associated with proliferation of human ***prostate carcinoma*** cells (198)
- COX-2 expression was an independent predictor of ***prostate cancer*** progression which had the highest probability of recurrence (36)

Breast Cancer:

- COX-2 over-expression promoted lymph node metastasis by a lymphangiogenic pathway and affected the prognosis in patients with ***breast cancer*** (199)
- COX-2 expression was associated with angiogenesis, lymph node metastasis, and apoptosis in human ***breast cancer*** (200)
- COX-2 expression was associated with younger age, larger tumor size, worse local control, distant metastasis, and worse overall survival in ***breast cancer*** patients (201)
- COX-2 was associated with lymphangiogenesis and prognosis in invasive ***breast cancer*** (42)
- COX-2 correlated with poor prognostic markers, large tumor size and high tumor grade in ***breast cancer*** (202)
- COX-2 expression in human ***breast*** epithelial cells will predispose the mammary gland to carcinogenesis (203)
- COX-2 expression was an early event in ***breast carcinogenesis*** (204)

Gyneoncologic Cancers:

- COX-2 expression was associated with poor prognosis in ***cervix cancer*** patients (205)
- COX-2 expression was used in patients with FIGO Stage IIB SCC of the ***uterine cervix*** who are treated with radiotherapy and concurrent chemotherapy (44)
- COX-2 expression was associated with very poor chance of response to neoadjuvant therapy and unfavorable prognosis in ***cervical cancer*** (206)
- COX-2 expression was associated with tumor cell proliferation and clinicopathological factor in patients with ***renal cell carcinoma*** (207)
- COX-2 expression was observed in endometriotic ovarian cyst wall with respect to other extra ***ovarian*** localizations (208)
- COX-2 expression was associated with angiogenesis in ***ovarian cancer*** (209)
- COX-2 expression was correlated with tumor angiogenesis and with survival in ***serous ovarian carcinoma*** patients (210)
- COX-2 expression was an independent prognostic factor in ***ovarian carcinoma*** (211)
- COX-2 expression was associated with poor clinicopathologic prognostic factor in ***ovarian cancer*** (212)
- COX-2 expression was correlated with poor chemotherapy response and prognostic outcome in ***ovarian carcinoma*** (213)

Head & Neck Cancers:

- COX-2 expression was correlated with shorter survival in patients with early stage ***non-small cell lung cancer*** (37)
- COX-2 expression was associated with tumor progression by stimulating lynphangiogenesis in ***NSCLC*** patients (214)
- COX-2 expression was correlated with clinically prognostic indicator of tumor growth and differentiation in ***laryngeal carcinoma*** (215)
- COX-2 expression in ***glottic cancer*** was associated with increased overall mortality and an increased risk of second primary cancer (SPC) (216)
- Cyclooxygenase-2 expression in ***human basal cell carcinoma*** increased antiapoptosis, angiogenesis, and tumorigenesis (217)
- COX-2 expression was associated with poor survival in ***gliomas*** patients (218)

ALL-Acute Lymphoblastic leukemia, ATL-Acute T cell leukemia, AML-Acute myelogenous leukemia, HCC-Hepatocellular carcinoma, MALT-Mucosa-associated lymphoid tissue, NSCLC- non-small-cell lung cancer

Tables 3

Expression of cytokines and chemokines and their receptors is linked to the development of cancer in patients

CXCR-4

Leukemia:

- CXCR-4 expression was associated with extramedullary organ infiltration in childhood ***acute lymphoblastic leukaemia*** (219)
- CXCR-4 was involved in the chemotactic interaction between ***B-lymphoma cells*** and lymph node stromal cells (220)

Gastrointestinal Cancers:

- CXCR-4 expression was associated with tumor aggressiveness, tumor size, extrathyroidal extension (ETE), angiolymphatic invasion (ALI), and lymph node metastasis in ***papillary thyroid carcinoma*** (71)
- CXCR-4 expression was associated with poor clinical outcome in ***esophageal cancer*** patients (68)
- CXCR-4 was associated with lymph node-metastasis in ***colorectal cancer*** (69)
- CXCR-4 expression was associated with a strong and independent predictor of early distant relapse in ***colorectal cancer*** (221)

Genitourinary Cancers:

- CXCR-4 expression was induced a aggressive phenotype in ***prostate cancer*** cells (67)
- CXCR-4 was involved in the process of human ***prostrate cancer*** metastasis by the activation of cancer cell migration (222)
- CXCR-4 expression in ***neuroblastoma*** primary tumors was significantly correlated with the pattern of metastatic spread (73)

Breast Cancers:

- CXCR-4 expression was correlated with lymph node metastasis in ***breast cancer*** (66)
- CXCR-4 expression had a significant impact on disease-free survival in HER-2 negative ***breast cancer*** patients (223)
- CXCR-4 expression was associated with tumor progression in ***breast cancer*** (224)
- CXCR-4 contributed to the homing of ***breast cancer*** cells to the bone (225)
- CXCR-4 expression was associated with lymph node metastasis in ***breast cancer*** patients (226)
- CXCR-4 expression was correlated with a poor overall survival rate in patients with ***breast cancer*** (227)

Gyneoncologic Cancers:

- CXCR-4 expression was involved in poor overall survival rate in patients with ***ovarian cancer*** (228)
- CXCR-4 expression was associated with progression of ***endometrial carcinoma*** (75)
- CXCR-4 expression was associated with lymph node metastasis and poor prognosis in patients with ***cervical cancer*** (229)

Head & Neck Cancers:

- CXCR-4 expression was associated with the metastatic potential of ***NSCLC*** patients (70)
- CXCR-4 was expressed and activated in ***astrocytomas*** and phosphorylation of CXCR-4 can occur through ligand activation or transactivation via the EGF receptor (72)

VEGF

Leukemia:

- VEGF played an important role in the development and evaluation of the severity and the outcome in ***ALL*** (39)
- VEGF expression was linked in malignant cell proliferation and angiogenesis in ***AML*** (230)
- VEGF was associated with poor outcome in ***non-Hodgkin's lymphoma*** (231)

Gastrointestinal Cancers:

- VEGF-C expression was associated with cervical lymph node metastasis in ***papillary thyroid carcinoma*** (86)
- VEGF expression was an independent prognostic factor for the patients with ***Nasopharyngeal carcinoma*** (88)
- VEGF expressions was correlated with pathologically positive lymph node in ***esophageal squamous cell carcinoma*** (232)

- VEGF expression was associated with prognosis in squamous cell carcinoma of the ***esophagus*** (233)
- VEGF expression was associated with prognosis in patients with more advanced ***esophageal squamous cell carcinoma*** (234)
- VEGF-C and VEGF-D expression was associated with lymphatic metastasis and prognosis in patients with ***pancreatic adenocarcinoma*** and induced lymphangiogenesis (89)
- VEGF expression was associated with prognosis in patients with ***hepatocellular carcinoma*** (83)
- VEGF expression was associated with prognosis in Greek ***colorectal cancer*** patients (235)
- VEGF was involved in tumor vascularization and lymph node metastasis in patients with ***colorectal cancers*** with submucosal invasion (183)
- VEGF expression was associated with angiogenesis and metastasis in ***gastric cancer*** (87)
- VEGF expression was associated with prognosis in ***colorectal cancer*** patients (84)
- VEGF expression was associated with the pathogenesis of ***ileal pouch-anal anastomosis*** (236)
- VEGF expression was associated with lymph node metastasis and progression of ***ampullary carcinoma*** (105)

Breast Cancers:

- VEGF-C expression was associated with lymphangiogenesis and prognosis in invasive ***breast cancer*** (42)
- VEGF-C expression was associated with lymphatic metastasis of ***breast cancer*** (82)
- VEGF expression was correlated with pathogenesis, angiogenesis and cell survival in ***breast cancer*** (237)

Gyneoncologic Cancers:

- VEGF expression was correlated with poor prognosis in ***ovarian cancer*** patients (85)

Head & Neck Cancers:

- VEGF-C expression was associated with lymph node metastasis in ***NSCLC*** (82)
- VEGF-D was associated with lymph node metastasis and poor prognosis in ***NSCLC*** (81)
- VEGF expression was associated with poor prognosis and survival in patients with early stage ***non-small cell lung cancer*** (238)

Melanoma:

- VEGF-C expression was associated with shorter overall and disease-free survival in ***melanoma*** (90)

STAT-3

- STAT-3 was constitutively present in all (CLL) ***chronic lymphocytic leukemia*** (30)
- STAT-3 expression was associated with shortest disease free-survival and shorter overall survival in patients with ***acute myeloid leukemia*** **(AML)** (34)
- STAT-3 expression was associated with pathogenesis ***offollicular lymphoma*** (239)
- STAT-3 expression was associated with the tumorigenesis of ***colorectal carcinoma*** (240)
- STAT-3 expression was associated with activation of ***laryngeal carcinomas*** (33)
- STAT-3 expression was associated with cell survival in ***gastric cancer*** (31)
- STAT-3 expression was associated with the development and proliferation of ***colorectal cancer*** (241)
- STAT-3 expression was correlated with vascular emboli and perineural invasion in ***colorectal cancer*** (242)
- STAT-3 expression was constitutively activated in ***prostate cancer*** (243)
- STAT-3 expression was associated with adenocarcinomas and was critical for the growth and survival of ***prostate cancer*** cells (244)
- STAT-3 expression was associated with distant metastasis in ***prostrate cancer*** (245)
- STAT-3 expression was associated with tumor cell survival in early-stage ***NSCLC*** (32)

IL-1 and 6

- IL-6 expression was associated with the growth in high-grade ***B lymphomas*** (246)
- IL-6 expression was associated with poor prognosis in patients with diffuse large-cell ***lymphoma*** (247)
- IL-6 expression was correlated with the independent prognostic factor for complete response and failure-free survival in patients with ***diffuse large-cell lymphoma*** (248)

- IL-6 expression was associated with pathogenesis of ***anaplastic large-cell lymphoma*** (249)
- IL-6 expression was correlated with neoplastic lymphoid cells in patients with B-cell **non-Hodgkin's lymphoma** (250)
- IL-1and IL-6 associated with cell proliferation in ***non-Hodgkin's lymphoma*** (251)
- IL-6 expression was associated with clinical aggressiveness in ***non-Hodgkin's lymphoma*** (252)
- IL-6 was associated with adverse prognostic feature in ***non-Hodgkin's lymphoma*** (253)
- IL-6 expression was associated with a prognostic factor in ***multiple myeloma*** (254)
- IL-6 expression was associated with the progression of ***multiple myeloma*** (255)
- IL-6 expression was associated with the development of apoptosis resistance ***Barrett's esophagus*** (256)
- IL-1β expression was associated with a potential independent factor influencing systemic inflammation in ***gastric cancer*** patients (51)
- IL-1β and IL-6 expression was associated with the growth and progression of human ***gastric carcinoma*** (49)
- IL-1and IL-6 expression was associated with the survival and proliferation of remnant cancer cells after tumor resection in ***colorectal carcinoma*** (50)
- IL-6 expression was associated with the growth in human ***colorectal cancer*** (257)
- IL-6 expression was associated with the proliferation in ***colorectal carcinoma*** (258)
- IL-6 expression was associated with progression of ***colorectal carcinoma*** (259)
- IL-1B expression was correlated with distal ***gastric cancer*** in Mexican population (260)
- IL-6 expression was associated with invasion, lymph node, hepatic metastasis and prognosis in ***gastric cancer*** patients (261)
- IL-6 expression was associated with poor prognosis in ***colorectal cancer*** (262)
- IL-6 expression was associated with the malignant phenotype of Egyptian ***bladder cancer*** patients (263)
- IL-6 expression was correlated with metastatic ***breast cancer*** patients (264)
- IL-6 expression was associated with tumor angiogenesis and the development of ***cervical cancer*** (265)

IL-8

- IL-8 expression was associated with the poor prognosis in ***nasopharyngeal carcinoma*** (61)
- IL-8 expression was associated with hepatic metastasis in patients with ***colorectal cancer*** (58)
- IL-8 expression was correlated with the tumor progression and liver metastasis of ***colorectal carcinoma*** (57)
- IL-8 expression was associated with metastatic potential, angiogenesis and cell proliferation in human ***HCC*** (59)
- IL-8 expression was associated with induction, progression liver metastases in ***colorectal carcinoma*** (56)
- IL-8 expression was associated with prognosis in human ***gastric carcinoma*** (62)
- IL-8 expression was associated with cell proliferation and angiogenesis in ***prostate cancer*** (60)
- IL-8 mRNA expression was associated with tumor progression, tumor angiogenesis and time to relapse suggesting its use as a prognostic indicator in ***NSCLC*** (63)
- IL-8 expression was associated with a angiogenic switch in myometrial invasion in stageI ***uterine endometrial*** cancer (209)
- IL-8 expression was associated with poor prognosis in epithelial ***ovarian cancer*** patients (64)
- IL-8 expression served as a significant prognostic factor for tumor progression in human ***malignant melanoma*** (65)

MMP-9

- MMP9 expression was associated with poor overall survival in patients with aggressive ***non-Hodgkin's lymphoma*** (109)
- MMP9 expression was associated with tumor cell differentiation, vessel permeation, lymph node metastasis in ***esophageal squamous cell carcinoma*** (108)
- MMP9 expressions was correlated with the metastasis of lymph node in ***gastric cancer*** (107)
- MMP9 expression was correlated with poor prognostic variables including shortened patient survival in ***renal cell carcinoma*** (110)
- MMP9 expression was correlated with metastasis and grade in ***liposarcoma*** (111)
- MMP9 expression was associated with the clinical and biological behavior in ***NSCLC*** (105)
- MMP9 expression was associated with progression, metastasis and survival in ***lung cancer*** (106)

NOS

- NOS expression was correlated with ***Barrett's***-associated neoplastic progression (94)
- NOS expression was correlated with the progression in ***gastric cancer*** patients (92)
- NOS expression was associated with angiogenesis of ***hepatocellular carcinoma*** (266)
- NOS expression was associated with angiogenesis and tumor-induced immunosuppression in ***human bladder cancer*** (267)
- NOS expression was associated with adenocarcinoma, metabolism and behavior in ***lung cancer*** (268)
- NOS expression was associated with carcinogenesis of ***transitional cell carcinoma*** (96)

LOX

- 5-LOX expression was associated the development of ***pancreatic cancer*** (78)
- LOX expression was associated with prognosis in patients with ***breast cancer*** (79)
- 12-LOX expression was associated with basal and EGF-induced ***breast cancer*** cell growth (269)
- 5-LOX expression was associated with prognosis in ***breast cancer*** patients (77)
- 12-LOX expression was associated with progression and prognosis of ***prostate cancer*** (80)
- 5-LOX expression was associated with the progression in ***renal cancer*** (76)
- 5-LOX expression was associated with idiopathic pulmonary fibrosis in ***lung*** patients (270)

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