OncoTargets and Therapy

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REVIEW

Chemotherapy-enhanced inflammation may lead to the failure of therapy and metastasis

This article was published in the following Dove Press journal:
OncoTargets and Therapy
12 June 2014
Number of times this article has been viewed

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Abstract: The lack of therapy and the failure of existing therapy has been a challenge for clinicians in treating various cancers. Doxorubicin, 5-fluorouracil, cisplatin, and paclitaxel are the first-line therapy in various cancers; however, toxicity, resistance, and treatment failure limit their clinical use. Their status leads us to discover and investigate more targeted therapy with more efficacy. In this article, we dissect literature from the patient perspective, the tumor biology perspective, therapy-induced metastasis, and cell data generated in the laboratory.

Keywords: chemotherapy, cancer, inflammation

Introduction

Drug resistance and failure remains a major challenge in cancer therapy. Two broad categories have been identified that classify cancer resistance on the basis of response to chemotherapy: primary and acquired.[1] Although primary resistance precedes initial chemotherapy, acquired resistance involves an accumulation of genetic changes after clinical intervention until tumor cells develop resistance phenotypes. A form of acquired resistance is mediated by the interaction of tumor cells with their microenvironment.[1] Here, tumor cells circumvent the apoptotic effects of chemotherapy through cell adhesion-mediated resistance, in which tumor cell integrins adhere to fibroblast or the extracellular matrix;[2] and soluble factor-mediated resistance, which induces the stroma to produce cytokines, chemokines, and growth factors.[3–5]

One developing theme is that not only do chemotherapies induce signaling events that eliminate and control tumor cells but also they stimulate signals that could minimize their clinical efficacy and promote metastatic development.[6] Advances in our understanding of the molecular mechanisms that elucidate cancer progression and the etiology of drug resistance have identified various crucial targets. Unsurprisingly, some of these targets promote inflammation events and seem to play a role in tumor proliferation, angiogenesis, and metastasis. In this review, we explore four common chemotherapy drugs (cisplatin, paclitaxel, 5-fluorouracil, and doxorubicin) and discuss how each drug induces inflammatory events that may lead to metastasis.

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Cisplatin and inflammation

Cisplatin is one of the most effective anticancer drugs used to treat a variety of solid tumors.[7] Cisplatin-DNA crosslinks cause cytotoxic lesions in dividing tumor cells; however, the drug's effect on quiescent renal tubular cells is problematic. Many studies indicate that cisplatin-induced renal injury is mediated by oxidative stress, apoptosis, and inflammation.[7]

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http://dx.doi.org/10.2147/OTT.S60114

The inflammatory changes play an important role, in particular nuclear factor kappa B (NFkB) and tumor necrosis factor alpha (TNF-α) signaling pathways. Ohta et al assessed the effects of cisplatin treatment on ovarian cancer cells on NFkB activation and found that cisplatin enhanced its phosphorylation significantly, mediated by the PI3/Akt signaling cascade.[8] This finding is consistent with the coexpression of NFkB transcription factors p65 and p50 in ovarian cancer patients who received a chemotherapy regimen that included cisplatin.[9]

NFkB signaling is a converging point for controlling downstream signaling cascades that include TNF-α, interleukin 1 (IL-1), IL-6, IL-8, and transcription of other inflammatory genes.[10–12] IL-6 is an important cytokine that regulates angiogenesis, cell proliferation, and invasion.[13–16] The IL-6 receptor system involves STAT-3- and extracellular signal regulated kinase (ERK)-mediated pathways.[17] STAT-3 plays multiple roles in cell survival and proliferation through activation of *c-myc*, *cyclin-D*, and *bcl-2*,[17] and persistent activation of STAT-3 is involved in tumorigenesis in a variety of leukemias.[18,19] Activation of ERK induces cell proliferation through phosphorylation of transcription factors such as c-FOS and ELK1.[20] IL-8 has been implicated in cancer progression, particularly in mediating angiogenesis in various cancer types including melanoma,[21] pancreatic,[22] colon,[23] and non-small-cell lung carcinoma.[24]

TNF-α is also increased after cisplatin treatment, and a variety of pharmacological inhibitors attenuate cisplatin nephrotoxicity mediated by TNF-α.[25–27] Salicylate treatment on mouse kidneys attenuated cisplatin-induced increase in TNF-α mRNA and also reduced serum TNF-α levels. Rutin treatment on Wistar rats has a beneficial effect on cisplatin's deteriorative effects through inhibition of TNF-α and NFkB pathway-mediated inflammation. Likewise, administration of luteolin in kidneys of mice significantly reduced TNF-α and NFkB, as well as COX-2 expression.

The role of poly (ADP-ribose) polymerase (PARP) proteins has been a target for anticancer therapy. PARP-1 has been implicated in DNA base excision repair, and many studies on PARP inhibitors have explored its antineoplastic profile. Mukhopadhyay et al found that its genetic deletion and pharmacological inhibition attenuates cisplatin-induced

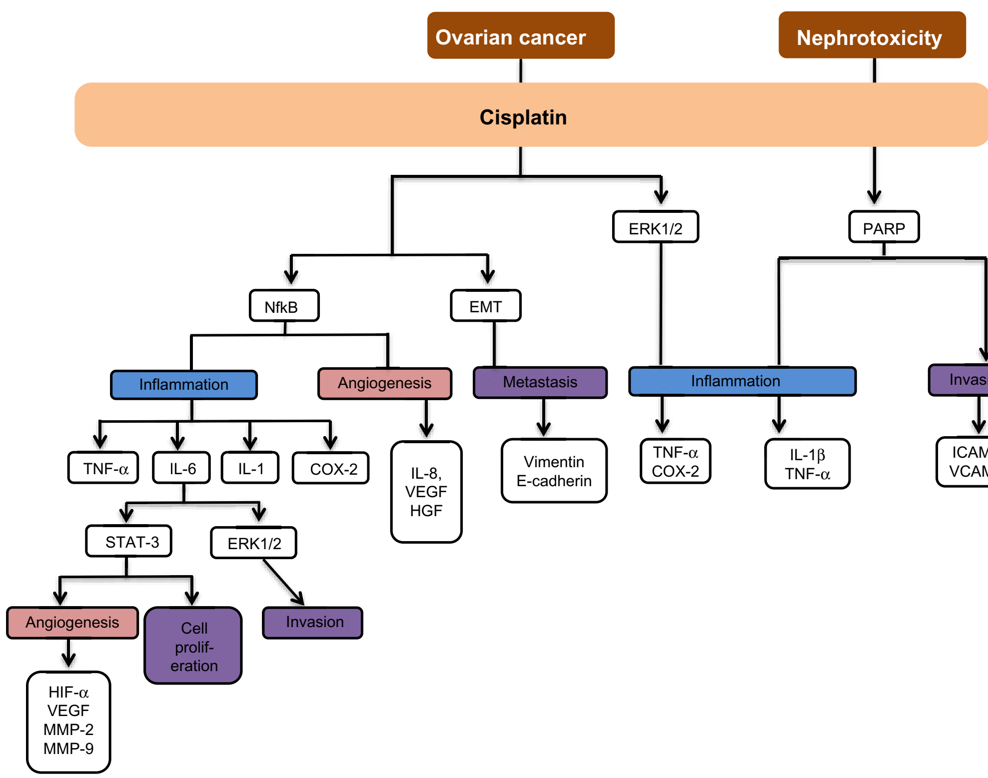

Figure 1 Cisplatin-induced inflammation is mediated through multiple effectors including activation of NFkB, TNF-α, and PARP. NFkB is a focal point for downstream cell survival and proliferation signaling that involves IL-6 and IL-8 upregulation. Cisplatin also induces the MAPK/ERK pathway and EMT acquisition. The ERK signaling cascade is suggested as an upstream signal for TNF-α activation.

Abbreviations: ADP-ribose, poly; COX-2, cyclooxygenase; EMT, epithelial–mesenchymal transition; ERK, mitogen-activated protein kinase; HGF, hepatocyte growth factor; HIF-α, hypoxia-inducible factor; ICAM-1, intercellular adhesion molecule; IL, interleukin; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NFκB, nuclear factor kappa B; PARP, polymerase; STAT-3, signal transducer and activator of transcription; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

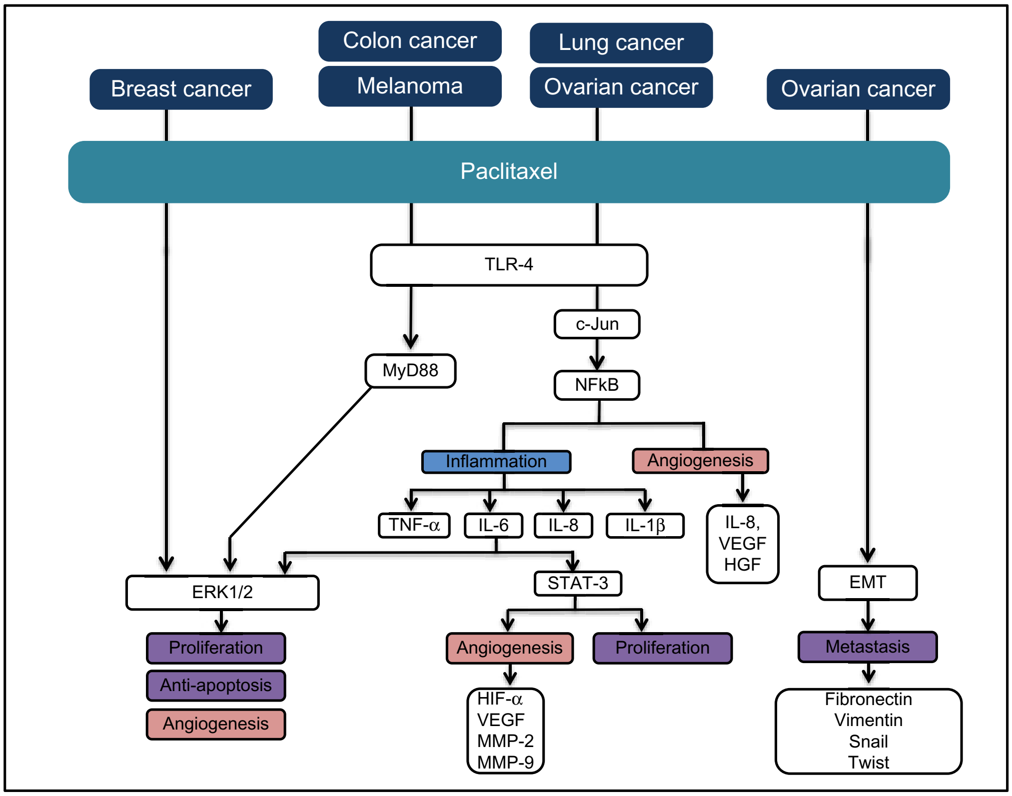

Figure 2 Paclitaxel-induced inflammation is mediated by upregulation of IL-8 via NFκB signaling. In some cancers, paclitaxel has been shown to activate ERK through Toll-like receptor 4 (TLR4)-myeloid differentiation gene 88 (MyD88) signaling. TLR-4 phosphorylates c-Jun (component of activator protein 1 transcription complex), thereby inducing NFκB activation and upregulation of IL-6, IL-8 and VEGF. Paclitaxel also upregulates metastatic markers consistent with EMT acquisition, including fibronectin, vimentin, Snail, and Twist.

Abbreviations: COX-2, cyclooxygenase; EMT, epithelial–mesenchymal transition; ERK, mitogen-activated protein kinase; HGF, hepatocyte growth factor; HIF-α, hypoxia-inducible factor; IL, interleukin; MMP, matrix metalloproteinase; NFκB, nuclear factor kappa B; STAT-3, signal transducer and activator of transcription; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

renal damage and inflammatory response. In this study, cisplatin triggers PARP activation, renal oxidative stress, and inflammatory response. Conversely, administration of PARP inhibitors and PARP-1 knockout mice showed reduced expression of mRNA TNF-α and IL-1β, as well as adhesion molecules intracellular adhesion molecule (ICAM)-1 and vascular cellular adhesion molecule (VCAM)-1, and also reduced leukocyte infiltration.[28]

Cisplatin and metastasis

Several studies have associated cisplatin in inducing prosurvival signaling pathways and markers for invasion, such as the mitogen-activated protein kinase (MAPK), ERK, and acquisition of epithelial–mesenchymal transition (EMT) in cancer.

Genotoxic stress in response to cisplatin causes activation of multiple signal transduction pathways,[29,30] among which are members of the MAPK pathways.[31] The MAPK pathway is also implicated in Twist suppression, which sensitizes alveolar cancer cells to cisplatin.[32] In addition, cisplatin-induced c-Jun N-terminal protein kinase (JNK) and ERK1/2 activation has been demonstrated in ovarian cancer cell lines.[33] Lee et al showed that cisplatin-resistant ovarian cancer cell lines have high basal levels of nuclear ERK2.[34] Moreover, inhibition of ERK1/2 has also been shown to sensitize ovarian cancer cells to cisplatin,[35] implicating a role of ERK1/2 as a mediator in prosurvival signaling in cisplatin-resistant cell lines. Finally, in a recent study, Latifi et al[36] assessed the role of EMT in ovarian cancer cells in response to cisplatin.[36] In this study, cisplatin-induced acquisition of EMT correlated with reduced E-cadherin and increased Vimentin, Snail, Twist, and matrix metalloproteinase (MMP)-2, as well cell surface expression of a variety of cancer stem cell-like markers.[36]

Relationship between cisplatin-induced increase in inflammation and metastasis

(Figure 1). Although there is evidence of the association between inflammation and metastasis as a result of cisplatin treatment,[37] the underlying mechanism remains to be elucidated. Several reports suggest that ERK is an upstream signal for the expression of TNF-α, prostaglandin, interleukin, and

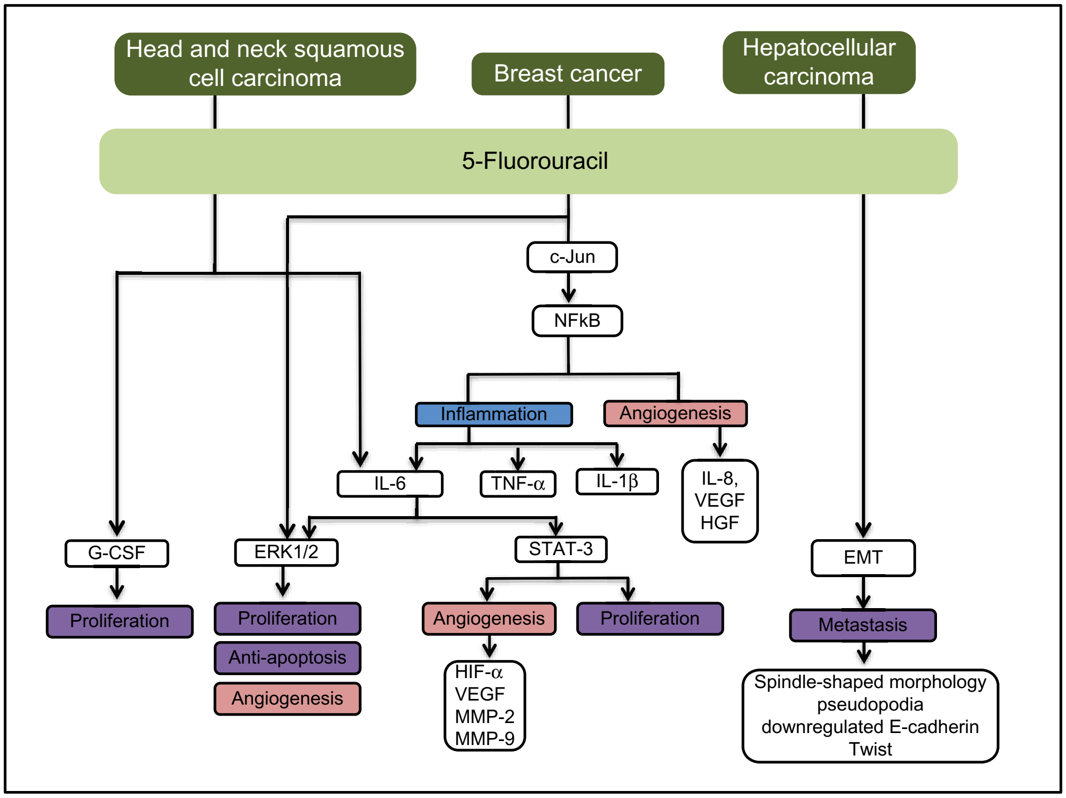

Figure 3 In HNSCC, 5-FU activates G-CSF and IL-6. In breast cancer, 5-FU induces NFκB as well as the mitogen activated protein kinase (MAPK)/extracellular signal regulated kinase (ERK) pathway. Hepatocellular carcinoma cells treated with 5-FU have phenotypes consistent with epithelial-to-mesenchymal transition (EMT) acquisition, including down-regulation of E-cadherin, spindle-shaped morphology, increased pseudopodia formation and upregulation of Twist.

Abbreviations: 5-FU, 5-Fluorouracil, c-Jun, component of the activator protein 1 transcription complex; EMT, epithelial–mesenchymal transition; ERK, mitogen-activated protein kinase; G-CSF, granulocyte colony-stimulating-factor; HGF, hepatocyte growth factor; HIF-α, hypoxia-inducible factor; HNSCC, Head and Neck Squamous Cell Carcinoma; IL, interleukin; MMP, matrix metalloproteinase; NFκB, nuclear factor kappa B; STAT-3, signal transducer and activator of transcription; TNF-α, tumor necrosis factor alpha; TWIST, oncogene protein TWIST; VEGF, vascular endothelial growth factor.

COX-2. Inhibition of ERK pathway reduces gene expression of TNF-α in mouse kidney tissue.[38] In sertoli cells, an ERK inhibitor reduced the cisplatin induction of prostaglandin, interleukin, and COX-2.[39]

Paclitaxel and inflammation

Paclitaxel, another major drug used to treat solid tumors,[40] causes apoptosis by overstabilizing microtubules,[41] leading to cell arrest.[42] Overall low response to this therapy, especially in breast cancer patients, limits its clinical use, primarily because of recurrence after cessation therapy.[43] Pathways associated with cell death induced by paclitaxel include phosphorylation of Bcl-2, activation of p53 and cyclin dependent kinases, and activation of the component of the activator protein 1 transcription complex (c-jun) NH2-terminal kinase/stress-activated protein kinase signaling pathway.[44,45]

A variety of inflammatory mediators and signaling pathways are upregulated in response to paclitaxel administration such as IL-1β,[46] IL-8,[47] IL-6,[48] and vascular endothelial growth factor (VEGF)-A.[49,50] IL-8 expression, in particular, is activated by paclitaxel in ovarian and lung carcinoma cells via activator protein 1 and NFkB promoter sites.[47–51] Paclitaxel activates Toll-like-receptor 4[52] and other prooncogenic signaling, including NFκB.[53] These effects are evident in a variety of cancer systems.[53–56] Rajput et al showed that paclitaxel upregulated cytokine production via Toll-Like-Receptor-4 (TLR-4) in breast cancer cells and that overexpression of TLR-4 is correlated with resistance to the drug by promoting anti-apoptopic proteins.[57] In addition, many studies show that paclitaxel can induce inflammatory cytokine production in murine macrophages cell lines and in human PBMCs, which is most likely related to its ability to mimic bacterial lipopolysaccharide.[58,59]

Paclitaxel and metastasis

Several studies also report the induction of markers for invasion and metastasis as a result of paclitaxel administration. Paclitaxel induces activation of the MEK/ERK pathway in human breast cancer[60] and lymphoma.[61]

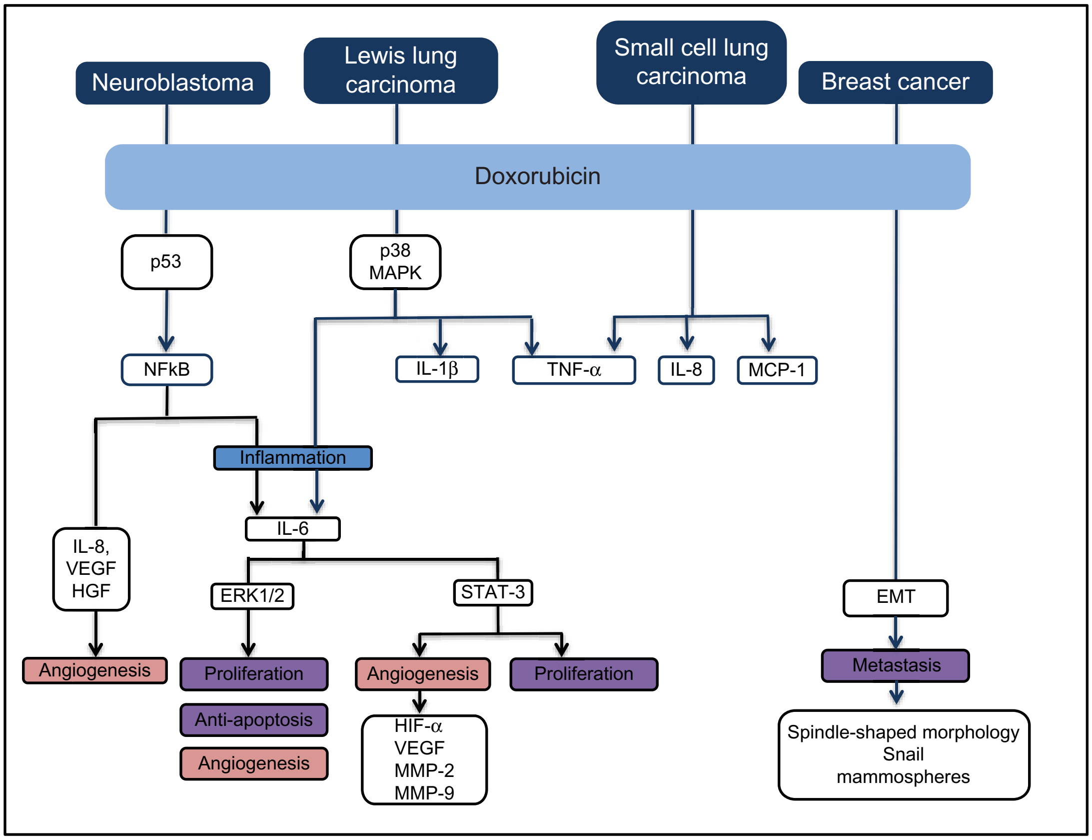

Figure 4 Doxorubicin-induced inflammation in a variety of cancers includes upregulation of NFκB, IL-1β, IL-6, IL-8, TNF-α and monocyte chemoattractant protein 1 (MCP-1). In neuroblastoma cells, p533 is required for doxorubicin to activate NFκB. In Lewis lung carcinoma, IL-1β and IL-6 are upregulated by the p38/MAPK pathway. Doxorubicin induces EMT acquisition in breast cancer.

Abbreviations: EMT, epithelial–mesenchymal transition; ERK, mitogen-activated protein kinase; HGF, hepatocyte growth factor; HIF-α, hypoxia-inducible factor; IL, interleukin; MAPK, mitogen activated protein kinase; MMP, matrix metalloproteinase; NFκB, nuclear factor kappa B; STAT-3, signal transducer and activator of transcription; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

Taxman et al showed that paclitaxel increases the expression of multiple genes that are important in proliferation, adhesion, and metastasis, such as chemokine IL-8 and EGF-like growth factors.[6] In particular, the melanoma growth stimulating activity/growth-related oncogene 1 (MGSA/Gro1), a gene linked to melanoma growth and transformation and that is a marker for melanoma metastasis, is increased by paclitaxel and is reduced by an MEK inhibitor. These findings provide evidence that paclitaxel coordinately targets a group of genes with crucial global effects on the tumor cell.

Kajiyama et al[62] also investigated the effects of paclitaxel treatment of epithelial ovarian carcinoma on cellular functions such as cell motility, invasive ability, and proliferative potential. Consistent with EMT acquisition, *epithelial-ovarian cancer cell line* (NOS2-PR) cells showed spindle-shaped morphology and enhanced pseudopodia formation. In addition, a decreased expression of E-cadherin and an increased expression in mesenchymal markers such as fibronectin, vimentin, smooth muscle actin, and EMT regulatory factors Snail and Twist were observed. A marked enhancement of migratory potential in wound assay and metastatic potential to the peritoneum of mice was also evident.[62]

Connection between paclitaxel-induced increase in inflammation and metastasis

(Figure 2). Recent studies indicate that the expression of TLR-4, its adaptor protein MyD88, and the activation of ERK signaling pathways are inextricably linked with tumor growth, progression, invasion, and chemoresistance. Wu et al showed that paclitaxel activated the TLR-4-MyD88-ERK signaling pathway.[63] Another study demonstrated that the inhibition of ERK signaling potentiates paclitaxel-induced apoptosis in human colon cancer cells. In ovarian cancer cell lines, paclitaxel binding to TLR-4 induced cJun phosphorylation, activated the NFκB pathway, and induced the production of IL-8, IL-6, VEGF, and monocyte chemotactic protein 1.[64] Conversely, silencing of TLR-4 with siRNA resulted in down-regulation of cJun phosphorylation and chemoresistance.[65]

5-Fluorouracil and inflammation

5-Fluorouracil (5-FU), another commonly used antineoplastic drug, leads to the misincorporation of fluoronucleotides into RNA and DNA and to the inhibition of the nucleotide synthetic enzyme thymidylate synthase. It is used to treat a variety of cancers, including colorectal cancers and breast cancers.[66] However, its clinical use is hampered because of drug resistance[67] and induction of intestinal damage, referred to as intestinal mucositis, the most significant dose-limiting toxicity.[68,69]

Studies in animal and human models have established evidence of changes in proinflammatory cytokine levels after administration of 5-FU. Logan et al showed that tissue and serum levels of NFκB, TNF-α, IL-1β, and IL-6 in rats were elevated after 5-FU administration before histological evidence of tissue damage.[70]

Another recent study by Reers et al demonstrated complex cytokine changes in the tumor microenvironment in eight different cell lines of patients with squamous cell cancer of the head and neck.[71] In this study, although no evidence of changes in IL-8 secretion was observed, low doses of 5-FU stimulated the secretions of IL-6 and granulocyte colony-stimulating-factor (G-CSF) on all screened squamous cell cancer of the head and neck cell lines. However, sublethal concentrations of 5-FU revealed a dose-dependent decrease in IL-1β. Concerning G-CSF and TNF-α secretion in primary tumors versus metastatic cell lines, G-CSF and TNF-α were increased in primary tumors at low doses of 5-FU, whereas a sharp decrease in secretion was evident in the metastases. Another recent study has investigated the inflammatory effects of 5-FU chemotherapy in bone, which can result in osteopenia and osteoporosis. Supplementation with Emu oil, a substance known to have a potent anti-inflammatory effect, demonstrated suppression of 5-FU-induced expression of TNF-α and an osteoclast activator of NFκB.[72]

5-FU and metastasis

Several reports have shown that 5-FU treatment results in activation of markers for invasion and metastasis. Elsea et al demonstrated that clinically relevant doses of cytotoxic chemotherapy drugs, including 5-FU, activate the p38 MAPK pathway in murine macrophages.[73] A recent study has implicated a mechanistic role for EMT in elucidating 5-FU chemoresistance in human hepatocellular carcinoma cell lines (HLF-R). Uchibori et al found that after treatment with 5-FU, HLF-R cell lines showed a decreased number of apoptotic cells and had morphologic phenotypes consistent with EMT acquisition, such as spindle-shaped morphology, increased pseudopodia formation, and loss of cell–cell adhesion.[74] In addition, 5-FU treatment also downregulated E-cadherin gene expression and induced Twist gene expression in HLF-R cells. Genes associated with 5-FU metabolism such as ribonucleotide reductases and multidrug resistance protein 5 were also downregulated and upregulated, respectively, providing further evidence that 5-FU metabolism plays a role in 5-FU-induced EMT acquisition.

Connection between 5-FU-induced inflammation and metastasis

(Figure 3). Several reports have explored the interplay between the induction of markers for invasion and inflammation as a result of 5-FU administration. As stated earlier, findings from Elsea et al showed that 5-FU treatment activated the MAPK pathway in murine macrophages.[73] In this study, 5-FU-induced activation of MAPK activity was associated with increased production of IL-1β, IL-6, and TNF-α. Addition of an inhibitor of p38 MAPK blocked the accumulation of IL-1β, IL-6, and TNF-α, demonstrating that 5-FU-induced inflammatory cytokine production is dependent on p38 MAPK.[73] A recent study by Vinod et al also showed that 5-FU treatment upregulates NFκB, MAPK pathway, and thymidylate synthase in breast cancer cell lines and demonstrated that there is cross-talk between NFκB, MAPK pathway, and thymidylate synthase as a result of 5-FU-induced signaling events.[75]

Doxorubicin and inflammation

Doxorubicin is used for hematologic and solid tumors;[76,77] however, its major limitation is cardiotoxicity,[78] cardiomyopathy, and congestive heart failure[79,80] through partially understood mechanisms.

Doxorubicin treatment induces inflammation in various cancer cell lines (eg, urothelial cells on exposure to doxorubicin show an increase in prostaglandin E2 and IL-1β).[81] Similarly, studies have shown that high IL-8,[82,83] NFκB, TNF-α,[82,84] monocyte chemotactic protein-1 (MCP-1),[83] and G-CSF[84]-expressing mice have better outcomes from doxorubicin-induced mortality and cardiac damage if they are pretreated with an IL-1 receptor antagonist.[85]

Doxorubicin-mediated activation of NFκB and inflammatory cytokines has been shown with doxorubicin effect on adipose tissue, thereby increasing serum total cholesterol, triglyceride, and low-density lipoprotein levels.[86–88] This can be explained by doxorubicin induced downregulation of peroxisome proliferator activated receptor gamma, which is present in white adipose tissue.[89–93] The sequence of events can be summarized as a reduction in circulating free fatty acid clearance,[94–96] macrophage recruitment,[97] and activation of NFκB and inflammatory cytokines.[98,99]

Doxorubicin and metastasis

Doxorubicin induces production of transforming growth factor beta, leading to EMT acquisition in human MDA-MB-231.[100] Doxorubicin-induced transforming growth factor beta production enhances Smad2 and Smad3 phosphorylation, causing tumor cell migration and invasion, suggesting a role in EMT-associated signaling. Doxorubicin also induced spindle-shaped morphology and increased nuclear translocation of Snail, suggestive of EMT phenotypic characteristics in breast cancer cells.

Connection between doxorubicin-induced increase in inflammation and metastasis

(Figure 4). In neuroblastoma cell lines, doxorubicin-induced p53 activation is essential for subsequent NFκB activation.[101] In murine macrophages, exposure to doxorubicin resulted in significant increase in IL-1β and IL-6 mRNA expression and this pathway is mediated by p38 MAPK, suggesting a role for p38 MAPK in the induction of inflammatory cytokines.[73]

Disclosure

The authors report no conflicts of interest in this work.

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