Cyclooxygenase-2, Epidermal Growth Factor Receptor, and Aromatase Signaling in Inflammation and Mesothelioma

Barbara Nuvoli and Rossella Galati

Abstract

Malignant mesothelioma or mesothelioma is a rare form of cancer that develops from transformed cells originating in the mesothelium, the protective lining that covers many of the internal organs of the body. It is directly linked to asbestos exposure, which acts as a carcinogen by initiating the carcinogenic process. Because of their shape, asbestos fibers can cross the membrane barriers inside the body and cause inflammatory and fibrotic reactions. Such reactions are believed to be the mechanism by which asbestos fibers may trigger malignant mesothelioma in the pleural membrane around the lungs. Carcinogens are known to modulate the transcription factors, antiapoptotic proteins, proapoptotic proteins, protein kinases, cell-cycle proteins, cell adhesion molecules, COX-2, and growth factor signaling pathways. This article reviews recent studies regarding some malignant mesothelioma molecular targets not only for cancer prevention but also for cancer therapy. Mol Cancer Ther; 12(6); 844–52. ©2013 AACR.

Introduction

Malignant mesothelioma is a rare form of malignant disease that arises primarily from neoplastic mesothelial cells. The mesothelial cells consist of serous membranes of the pleura, peritoneum, pericardium, or testis. Mesothelioma fails to respond effectively to chemo and radiotherapy and is associated with poor prognosis. Its incidence is on the rise and it is expected to peak in the year 2020 (1). Thus, to improve the clinical outcome in the pharmacologic treatment of this refractory tumor, drugs directed against novel and/or characterized tumor-specific cellular targets are needed. The development of malignant mesothelioma is associated in most patients with a history of asbestos exposure (2). In addition, some investigations have implicated simian virus 40 (SV40), in the pathogenesis of a subset of mesotheliomas (3). Human mesothelial cells are highly susceptible to SV40-mediated transformation in vitro, and SV40 DNA sequences and large T antigen (Tag) have been detected in human malignant mesothelioma cells. However, an analysis of human malignant mesothelioma biopsies revealed that SV40 sequences were present in about half of them. In human malignant mesothelioma biopsies, SV40 has been shown to bind and inactivate p53 and pRb, and to activate c-met, insulin growth factor (IGF)-I, and other oncogenes.

Data unequivocally show that the SV40 virus acts as a cofactor for asbestos carcinogenesis, whereas the role of SV40 in causing human malignant mesothelioma remains controversial (4). Malignant pleural mesothelioma (MPM) originates from the pleural layers. Pleura is not just a limiting protective layer of the lung, but a dynamic cellular structure regulating serial responses to injury, infection, and disease. Mesothelial cells are biologically active because they can sense and respond to signals within their microenvironment. Exposure to asbestos typically occurs during mining and milling of these fibers or during industrial application of asbestos in textiles, insulation, shipbuilding, brake lining mechanics, and other areas. Nonoccupational exposure is usually related to asbestos fibers inadvertently released into the environment and transported by asbestos-contaminated clothing or other materials. After asbestos inhalation, fibers deposited in the lungs typically remain in close contact with lung epithelial cells. Given that this fiber–cell interaction could potentially initiate or inhibit cellular functions, asbestos acts as a carcinogen by initiating the carcinogenic process. Carcinogens are known to modulate the transcription factors, antiapoptotic proteins, proapoptotic proteins, protein kinases, cell-cycle proteins, cell adhesion molecules, COX-2, and growth factor signaling pathways. Research has shown that asbestos exposure generates reactive oxygen species and activates macrophages and other cell types to produce these compounds as well as cytokines and growth factors (5). Furthermore, the deposition of insoluble amphibole fibers results in a chronic inflammatory state and increased rates of malignant mesothelioma in exposed individuals (6). This article reviews recent studies regarding some malignant mesothelioma molecular targets involved in
inflammation not only regarding prevention but also cancer therapies.

**Malignant Mesothelioma Molecular Targets Involved in Inflammation**

The origin and pathogenesis of malignant mesothelioma are closely associated with inflammation (7). Inflammatory cells and mediators are critical components of the tumor microenvironment. Many cancer cells have adapted inflammatory signaling molecules as autocrine and/or paracrine survival factors. Arachidonic acid-derived lipid mediators are very potent signaling molecules that are important in the inflammatory process and implicated in tumorigenesis. Conversion of arachidonic acid by the COX enzymes gives rise to the production of prostaglandins and thromboxane. A large body of evidence has shown that COX-2 is often highly expressed in adult cancers of epithelial origin and has been implicated in resistance to apoptosis, promotion of proliferation, decreased immunosurveillance, as well as increased tumor invasiveness and angiogenesis. Angiogenesis is required for tumors to grow beyond a certain size and to metastasize. To develop a stable blood supply for tumor growth, many cells in the tumor microenvironment, including tumor epithelial cells, stromal cells, and immune cells, secrete various proangiogenic factors that stimulate endothelial cell recruitment, proliferation, migration, and tubule formation. Proinflammatory COX-2–derived prostaglandin E2 (PGE2) can directly act on epithelial, endothelial, and/or immune cells to induce angiogenic factors (8). VEGF is regarded as the most important player in angiogenesis (9). VEGF has been identified as an important mediator of angiogenesis in malignant mesothelioma. The significant higher levels of VEGF found in the pleural exudates of patients with malignant mesothelioma compared with patients with nonmalignant pleural disease and the detection of a significant inverse correlation between serum VEGF and malignant mesothelioma patient survival confirm VEGF as an important mediator of angiogenesis in this disease and support targeting angiogenesis by VEGF inhibitor in malignant mesothelioma (10). Consequently, there have been several attempts to therapeutically implicate this finding. Despite the strong preclinical rationale for targeting VEGF malignant mesothelioma, a multicenter single-arm phase II study, it failed to show a significant improvement in progression-free survival with the addition of VEGF inhibitor (bevacizumab) to cisplatin and pemetrexed in advanced, untreated malignant mesothelioma (11).

A considerable amount of evidence indicates that COX-2–derived PGE2 can activate EGFR receptor (EGFR) signaling and thereby stimulate cell proliferation (12). The mechanism(s) by which this occurs seem to be complex and context specific (13). Exposure to COX-2–derived PGE2 can initiate a positive feedback loop whereby the activation of EGFR results in enhanced expression of COX-2 and increased synthesis of prostaglandins (14). Although there is a crosstalk between EGFR and COX-2 in carcinogenesis, it is important to stress that EGFR and its downstream effectors can be activated independently of COX-2/PGE2. For example, in malignant mesothelioma, asbestos fibers activate the EGFR causing the activation of extracellular signal–regulated kinases (ERK) downstream (15). Similarly, COX-2/PGE2 and its downstream effectors can be regulated independently of EGFR signaling. For example, PGE2 is able to rapidly stimulate Erk phosphorylation in a subset of non–small cell lung cancer (NSCLC) cell lines via intracellular activation of kinase cascades independently of the proteolytic release of EGFR ligands via Src (16, 17). These findings have provided the basis for developing agents targeting EGFR or COX-2 and a recent study has further been conducted with COX-2 and EGFR inhibitors (18, 19). PGE2, as well as the EGF, upregulate aromatase (CYP19) expression, the enzyme that plays a key role in estrogen (E2) biosynthesis (20–21). The biologically active E2 aggravates pathologic processes including inflammation and influences the risk of cancer through an inflammation-related mechanism (22–24). Lately, the aromatase (CYP19A1) has been identified in malignant mesothelioma (25). This new discovery has highlighted the possibility that there may be a relationship between inflammation, COX-2, EGFR, and CYP19A1 in malignant mesothelioma as well as in breast cancer.

The molecular complexity of cancer and therapy-associated side effects often limit effectiveness of many anticancer modalities, and require identification of novel cancer cell growth inhibitory target/pathways for potential exploitation in devising efficacious therapeutic strategies. This review provides a rationale for a further in-depth analysis of COX-2 EGFR CYP19A1 axis in malignant mesothelioma growth suppression and their possible future exploitation in effective management of malignant mesothelioma.

**Cyclooxygenases**

Cyclooxygenases, also known as prostaglandin–endothelium-derived factors, are key regulatory enzymes in the biosynthesis of prostanoids, a class of hormones including prostaglandins, prostacyclins, and thromboxanes responsible for multiple inflammatory diseases/states. Increasing interest shown toward COXs is due to the extensive amount of evidence showing the involvement of these enzymes not only in physiologic processes but also in pathophysiologic ones such as the development and progression of cancer. Two COX isomers have been identified as COX-1 and COX-2. COX-1 is expressed constitutively in several cell types of normal mammalian tissues, where it is involved in the maintenance of tissue homeostasis. In contrast, COX-2 is an inducible enzyme responsible for PGE2 production at sites of inflammation (26). The mechanism through which COX-2 exerts its tumorigenic action can be directly mediated by the enzyme or due to the effects of its products. COX-2 is an oxygenase where its intermediates are highly reactive. It is possible
that these compounds may cause free radical damage, for instance, against DNA molecules (27). There is considerable evidence suggesting that prostaglandins, participate both in normal growth responses and in aberrant growth, including carcinogenesis (28). PGE2 promotes tumor growth by stimulating PGE receptor (EP) signaling with subsequent enhancement of cellular proliferation, promotion, and angiogenesis, stimulation of invasion/mobility, suppression of immune responses, and inhibition of programmed cell death by inducing expression of the Bcl-2 proto-oncogene (which can suppress apoptosis; ref. 27). For several types of cancers, the real risk factor seems to be chronic inflammation (29) that maintains high level of COX-2 and increases events that promote tumor formation. A clear but tragic example of this mechanism is malignant mesothelioma. Although the molecular mechanisms of asbestos tumorigenicity have not yet been elucidated, research has shown that the deposition of insoluble amphibole fibers results in a chronic inflammatory state (6). This state generates reactive oxygen and nitrogen species, as well as cytokines and growth factors, through the activation of macrophages and other cell types (5).

As expected, prolonged inflammation causes the level of COX-2 to increase, which is actually recognized as an important malignant mesothelioma prognostic factor (30, 31). A recent study has clearly shown that COX-2 expression is a strong prognostic factor in human mesothelioma, which contributes independently to other clinical and histopathologic factors in determining short survival (31). Although the regulation of mRNA stability seems to be the most important regulatory step for COX-2 expression, several studies have reported that other mechanisms, such as transcriptional control or hypermethylation (32), are also involved in regulating COX-2 expression in cancer cells. It was previously shown that altered posttranscriptional regulation of COX-2 is mediated by increased cytoplasmic mRNA binding of the mRNA stability factor HuR (33). In malignant mesothelioma, the cytoplasmic expression of HuR was significantly correlated with high COX-2 expression and with poor survival (34). Finally, COX-2 has been proposed to exert its influence on mesangial cell proliferation in vitro by a novel mechanism involving the tumor suppressor p53 and the cell-cycle inhibitors p21 and p27 (35). Interestingly, several recent studies have investigated the potential prognostic value of p53, p21, and p27 in malignant mesotheliomas. Thus, reinforcing the evidence of COX-2 primary role in the pathogenesis and progression of malignant mesothelioma (36, 37). Because of the lack of reliable treatment capable of achieving long-term control in patients with mesothelioma, these enzymes are becoming more and more credible as potential therapeutic targets (19, 38, 39). Celecoxib, a nonsteroidal anti-inflammatory drug (NSAID) and selective COX-2 inhibitor, in association with other drugs, is used in malignant mesothelioma clinical trials (Table 1).

Epidermal Growth Factor Receptor

The EGFR is the cell-surface receptor for members of the EGF family of extracellular protein ligands (40). Upon activation by its growth factor ligands, EGFR undergoes a transition from an inactive monomeric form to an active homodimer. In addition, EGFR may pair with another member of the ErbB receptor family, such as ErbB2/Her2/neu, to create an activated heterodimer. EGFR dimerization stimulates its intrinsic intracellular protein-tyrosine kinase activity. As a result, autophosphorylation of several tyrosine residues in the C-terminal domain of EGFR (P-EGFR) occurs. This autophosphorylation leads to the activation of downstream signaling cascades including the RAS/ERK pathway, the phosphoinositide 3-kinase pathway, and the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway (Fig. 1). These pathways act in a coordinated manner to promote cell survival (41). Such proteins modulate phenotypes such as cell migration, adhesion, and proliferation. EGFR is reportedly overexpressed in a wide variety of malignancies. Various studies suggest that receptor tyrosine kinase activation participates in the oncogenic progression of nonneoplastic mesothelial progenitor cells to malignant mesothelioma. Asbestos fibers interact with the external domain of the EGFR to trigger dimerization, activation, and increased EGFR mRNA and protein levels in rat and human SV40 immortalized mesothelial cells (15). Upregulated EGFR and resulting tyrosine phosphorylation leads to the activation of downstream mitogen-activated protein kinase (MAPK) signaling pathway associated with proliferation (42) and to the involvement of EGFR activation in mitogenicity and carcinogenesis induced by asbestos (43). In addition, malignant mesothelioma cell lines are reported to express EGFR and transforming growth factor-α (TGF-α), suggesting that EGFR has an autocrine role in malignant mesothelioma (44, 45). EGFR immunopositivity has been indicated as a poor prognostic factor in many solid tumors in the past (46). The EGFR expression in malignant mesothelioma has previously been reported with controversial results, possibly due to the lack of a standardized method of EGFR detection and quantification (47–51). Until now, the role of immunohistochemistry (IHC) EGFR-positive staining in influencing prognosis of malignant mesothelioma is not clear. Some authors did not find any differences in survival when immunohistochemical EGFR-positive or EGFR-negative stainings were compared (48, 52). This is because only few reports analyzed the effect of IHC EGFR-positive status and cell subtype in patients with malignant mesothelioma. Recently, EGFR overexpression has been identified by IHC in 52% of epithelial malignant mesothelioma and is shown to be a factor negatively affecting prognosis (53). In view of these studies, EGFR was targeted for malignant mesothelioma therapy, but despite the high expression of EGFR, not all cells are sensitive to EGFR inhibitors (54). Much focus is now directed toward understanding the lack of sensitivity of malignant mesothelioma to EGFR inhibitors. EGFR mutations were found...
in 31% (9/29) of malignant mesothelioma cases. Seven of these mutations were novel, and one was the L858R mutation described in NSCLC (55). Activating EGFR mutations in malignant mesothelioma associated with optimal resectability and prolonged survival. Clinically, these mutations may ultimately be useful in selecting patients for surgery, systemic therapy, and for EGFR-TKI selection. The clinical course of patients with malignant mesothelioma with EGFR-mutant tumors seems to share the same “relative” improved clinical outcome like mutant EGFR–NSCLC (56). Studies show the ineffectiveness of the EGFR inhibitors due to coactivation of multiple receptor tyrosine kinases (EGFR, ERBB3, MET, and AXL) and ERβ expression in individual mesothelioma cell lines (57, 58). Thus, a combination therapy could be the winning strategy in treating mesothelioma. The synergistic effect of gefitinib (EGFR tyrosine kinase inhibitor) and rofecoxib (COX-2 inhibitor) on malignant mesothelioma cell death was observed (19). There is ongoing recruitment for the study of cetuximab (EGFR inhibitor) combined with cisplatin or carboplatin/pemetrexed as first-line treatment in patients with MPM (Table 1).

### Table 1. Summary of studies with COX-2, EGFR, and CYP19A1 inhibitors

<table>
<thead>
<tr>
<th>Status</th>
<th>Study</th>
<th>Conditions</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruiting</td>
<td>Pilot study of allogeneic tumor cell vaccine with metronomic oral cyclophosphamide and celecoxib in patients undergoing resection of lung and esophageal cancers, thymic neoplasms, and malignant pleural mesotheliomas</td>
<td>Lung cancer; esophageal cancer; malignant pleural mesothelioma; thymoma; thymic carcinoma</td>
<td>Drug: celecoxibDrug: cyclophosphamide Biologic: Allogeneic tumor cell vaccine (K562)</td>
</tr>
<tr>
<td>Recruiting</td>
<td>Tumor cell vaccines with ISCOMATRIX (Trademark) adjuvant and celecoxib in patients undergoing resection of lung and esophageal cancers and malignant pleural mesotheliomas</td>
<td>Mesothelioma; esophageal cancer; lung cancer</td>
<td>Drug: celecoxibDrug: ISCOMATRIX (TM) Adjuvant; Biologic: autologous tumor cell vaccine</td>
</tr>
<tr>
<td>Completed</td>
<td>Phase I study of gene induction mediated by sequential decitabine/depsipeptide infusion with or without concurrent celecoxib in subjects with pulmonary and pleural malignancies</td>
<td>Small cell carcinoma; mesothelioma:non–small cell lung carcinoma</td>
<td>Drug: decitabineDrug: depsipeptide</td>
</tr>
<tr>
<td>Completed</td>
<td>An open-label, phase II trial of ZD1839 (IRESSA) in patients with malignant mesothelioma</td>
<td>Mesothelioma</td>
<td>Drug: ZD1839</td>
</tr>
<tr>
<td>Completed</td>
<td>Gefitinib in treating patients with malignant mesothelioma</td>
<td>Malignant mesothelioma</td>
<td>Drug: gefitinib</td>
</tr>
<tr>
<td>Recruiting</td>
<td>A study of cetuximab combined with cisplatin or carboplatin/pemetrexed as first line treatment in patients with malignant pleural mesothelioma</td>
<td>Cancer</td>
<td>Drug: cetuximab (Erbitux)</td>
</tr>
<tr>
<td>Terminated</td>
<td>Fulvestrant and anastrozole as consolidation therapy in postmenopausal women with advanced non–small cell lung cancer</td>
<td>NSCLC; postmenopausal women</td>
<td>Drug: fulvestrant (Faslodex) Drug: anastrozole (Arimidex) Drug: bevacizumab (Avastin) Drug: best supportivecare</td>
</tr>
<tr>
<td>Not yet recruiting</td>
<td>Exemestane, pemetrexed disodium, and carboplatin in treating postmenopausal women with stage IV NSCLC</td>
<td>Stage IV NSCLC</td>
<td>Drug: exemestaneDrug: pemetrexed disodiumDrug: carboplatin</td>
</tr>
</tbody>
</table>
suggest the importance of EGFR (or similar receptors) in
ments for some EGFR actions (67, 68). Recent findings
EGFRs (66). Work in this area has established ER require-
past decade describes a cross-talk between ERs and
plasma membrane to initiate signaling pathways in the
mRNA levels, the production of associated proteins, and
er. This consequently leads to an increase or decrease in
tory proteins (coactivators or corepressors) to the promot-
ERE sequences in the promoter region of estrogen-
ERE homodimers, and the subsequent binding of this nuclear
homo- or heterodimers, and the subsequent binding of this nuclear
expression element (ERE) sequences in the promoter region of estrogen-
requirement of nuclear estrogen receptor (ER) homo- or heterodimers, and the subsequent binding of this nuclear
estrogen-responsive genes, triggering the recruitment of coregula-
proteins (coactivators or corepressors) to the promoter.
Aromatase
A novel marker of malignant mesothelioma that has
recently been identified is the CYP19A1 (25). CYP19A1 is
the cytochrome P450 enzyme complex that converts C19
androgens to C18 estrogens. The human CYP19A1 gene,
located in the 21.2 region on the long arm of chromosome
15 (15q21.2), spans a region that consists of a 30 kb coding
region and a 93 kb regulatory region. Its regulatory region
contains at least 10 distinct promoters regulated in a
tissue- or signaling pathway-specific manner. Each pro-
mitter is regulated by a distinct set of regulatory sequences
in DNA and transcription factors that bind to these spe-
cific sequences. These partially tissue-specific promoters
are used in the gonads, bone, brain, vascular tissue, adipose
tissue, skin, fetal liver, and placenta for estrogen
biosynthesis necessary for human physiology (59). Estro-
gens contribute to differentiation and maturation in nor-
mal lungs (60) and also stimulate growth and progression
of lung tumors (61, 62). Estrogen influences the cellular
events through 2 main pathways, genomic and nonge-
nomic (Fig. 2; ref. 63). In the genomic pathway, estrogen
exerts its function via ERα and ERβ. In general, this
classical pathway of estrogen involves estrogen-depen-
dent formation of nuclear estrogen receptor (ER) homo-
or heterodimers, and the subsequent binding of this nuclear
estrogen–ER complex binds to estrogen response element
(ERE) sequences in the promoter region of estrogen-
responsive genes, triggering the recruitment of coregula-
tory proteins (coactivators or corepressors) to the promot-
ernuclear androgen receptor). In the nongenomic pathway,
estrogen signaling from the membrane in breast cancer. It
has been shown that a pool of ERα resides in or associates
with the plasma membrane and uses the membrane EGFR
to rapidly signal through various kinase cascades that
influence both transcriptional and nontranscriptional
actions of estrogen in breast cancer cells (66, 69). The
interaction between EGFR and ERβ has been shown in
malignant mesothelioma cells. In cells that express high
levels of ERs, ERβ but not ERα constitutively colocalize
with EGFR in caveolin 1–enriched regions. This clustering
interferes with EGFR phosphorylation in response to its
ligand, and also results in delayed internalization of the
receptor and activation of coupled signaling cascades
following stimulation (58). PGE2 increased CYP19A1 activity level in malignant
mesothelioma cell lines (25). During the last decade, many
studies have been carried out to identify potential
CYP19A1 stimulatory factors: interleukin (IL)-6 was the
most potent factor found to stimulate CYP19A1 activity
(70). The malignant mesothelioma cell lines were capable
of releasing a constitutively high amount of IL-6 (>1,100
pg/mL supernatant-1 of confluent cultures; ref. 71). This
may explain the presence of CYP19A1 in malignant meso-
thelioma cells. Furthermore, ERs were also detected in
malignant mesothelioma cell lines. The classic 67 kDa and
a variant 46 kDa of ERα and 59 kDa of ERβ were expressed
in malignant mesothelioma cell lines. Recent data pub-
lished in literature support our findings on gender role
orientation in malignant mesothelioma pathogenesis (72).
Metintas and colleagues compared the relative risk of
malignant mesothelioma in men versus women following
environmental exposure to asbestos in a rural area of
Anatolia in Turkey, where MPM is a frequent cause of
cancer death. The risk was found to be higher in women
than in men (73). The same data were obtained in a
previous study covering another area of Turkey rich in
erionite, a naturally occurring fibrous mineral that
belongs to the family of zeolites (74). Conversely, in North
America, Australia, and European countries, the risk is always very low in women (75). This seeming discrepancy may be due to different types of exposure to the carcinogen. Recently, sex steroid receptors have been found in peritoneal mesothelioma (76).

CYP19A1 is expressed in the majority of samples from patients with malignant mesothelioma. Cytoplasmic expression of CYP19A1 significantly correlated with poor survival (25). The World Health Organization classifies malignant mesothelioma into epithelial, sarcomatoid, and biphasic types, each of which can be subdivided even further (77). This classification has implications for both diagnosis and prognosis. Prognosis is poor for all types of malignant mesotheliomas, but sarcomatoid malignant mesotheliomas have a particularly poor response rate to treatment (78). A significant association between high expression of CYP19A1 and sarcomatoid malignant mesotheliomas was found. These observations strongly suggest that CYP19A1 plays a role in tumor progression in malignant mesothelioma. Treatment of malignant mesothelioma cells with exemestane, an aromatase inhibitor, led to significant reduction of tumor cell growth, perturbation of cell cycle, caspase activation, PARP cleavage, and downregulation of p-AKT and Bcl-xL. Because the Akt pathway as well as the Bcl-xL are implicated in conferring resistance to conventional chemotherapy, exemestane could possibly open new treatment strategies in association with standard therapy for patients afflicted with malignant mesothelioma (25). At present, there are no clinical trials being conducted on CYP19A1 inhibitors in malignant mesothelioma. This may be due to the recently identifying CYP19A1 in malignant mesothelioma. In lung cancer, where studies of CYP19A1 are at a more advanced stage, some clinical studies consider the inhibitors of CYP19A1 and antiestrogen (Table 1).

Conclusion

COX-2, EGFR, and CYP19A1 are still under investigation at the present time. The cross-talk between markers that have been described and their value as prognostic indicators will need to be validated in prospective studies in larger patient populations. Their role at present is to direct us toward developing newer therapies in this extremely resistant tumor. The current form of standard care for malignant mesothelioma does not involve checking these markers or making patient care decisions based on them. But we do hope that in the near future, this approach will be adopted toward treatment and prognosis. Malignant mesothelioma is caused by exposure to asbestos and by inhaling asbestos particles. In most cases, malignant mesothelioma symptoms will not appear in an individual exposed to asbestos until many years after the exposure has occurred. Those with a history of past asbestos exposure experiencing symptoms should undergo chemoprevention. Inflammation is involved in the progression of malignant mesothelioma. A possible relation between inflammation COX-2, EGFR, and CYP19A1 is shown.
in Fig. 3. Arachidonic acid metabolic pathway can be activated by inflammation (stimulus). Arachidonic acid is released from membrane phospholipids by a phospholipase A2 (PLA-2) enzyme and converted to bioactive PGE-2 by COX-2. PGE2 induces transactivation of the EGFR by triggering Src and PGE2, an important regulator of CYP19A1 gene expression, stimulates CYP19A1 activity to increase localized estrogen 17β-estradiol (E2). The E2 binds to the classical ERα to promote its dimerization and translocation to the nucleus where it modulates the expression of estrogen target genes (COX-2). The interaction of E2 with ER-α also activates signaling cascades that promote cell proliferation, such as the activation of c-Src tyrosine kinase (Src). Src activation stimulates a matrix metalloproteinase cascade that culminates in liberating the EGF. The free EGF ligand binds to EGFR family receptors that activates ERK signaling cascade. Cytosolic phospholipase A2 (cPLA2) is a substrate for ERK and phosphorylation of cPLA2 (cPLA2p), promoting its association with intracellular membranes such as those of the endoplasmic reticulum and mitochondria releasing lysophospholipids and arachidonic acid from these membranes. COX-2 catalyzes the conversion of arachidonic acid into PGE2. These key molecules and pathways that connect chronic inflammation with inflammation-associated oncogenic transformation could be targeted by drugs or natural products for novel preventive and therapeutic strategies for malignant mesothelioma.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: B. Nuvoli, R. Galati
Development of methodology: B. Nuvoli
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B. Nuvoli
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B. Nuvoli
Writing, review, and/or revision of the manuscript: R. Galati

Received November 21, 2012; revised February 19, 2013; accepted February 25, 2013; published OnlineFirst May 31, 2013.

References

20. Zhao Y, Agarwal VR, Mendelson CR, Simpson ER. Estrogen biosynthesis proximal to a breast tumor is stimulated by PGE2 via cyclic AMP, leading to activation of promoter II of the CYP19 (aromatase) gene. Endocrinology 1996;137:3–42.

Mol Cancer Ther; 12(6) June 2013


Molecular Cancer Therapeutics

Cyclooxygenase-2, Epidermal Growth Factor Receptor, and Aromatase Signaling in Inflammation and Mesothelioma

Barbara Nuvoli and Rossella Galati


Updated version
Access the most recent version of this article at:
doi:10.1158/1535-7163.MCT-12-1103

Cited articles
This article cites 76 articles, 14 of which you can access for free at:
http://mct.aacrjournals.org/content/12/6/844.full#ref-list-1

Citing articles
This article has been cited by 1 HighWire-hosted articles. Access the articles at:
http://mct.aacrjournals.org/content/12/6/844.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.