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REVIEWS

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GENES CONTROLLING SPREAD OF BREAST CANCER TO LUNG "GANG OF 4"

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Cancer-related mortality is caused in a large part by the metastasis of primary tumor. Each cancer has a particular way of spreading cancerous cells. Recently, genetic and pharmacological analysis identified the set of genes, such as epidermal growth factor receptor ligand epiregulin (EREG), cyclooxygenase-2 (COX2) and matrix metalloproteinases 1 and 2 (MMP-1 and MMP-2) that have been found to be associated with metastasis of breast cancer to lung. Inhibition of EGFR and COX2 could minimize lung metastasis of breast cancer in a clinical setting. In this review, we summarized the current knowledge on EREG, COX2, MMP-1 and MMP-2 in tumor development and metastasis.

Key Words: **breast cancer, EPREG, COX2, MMPs, metastasis.**

Breast cancer is the leading cause of female mortality from malignant diseases in the industrialized world. Most breast cancer related deaths are not due to cancer at the primary site, but rather due to the metastasis. Metastasis entails numerous biological functions that collectively enable cancerous cells from a primary site to disseminate and overtake distant organs. Breast cancer metastasis can be undetectable and remain latent for many years following primary tumor removal only to emerge as incurable lesion that are triggered by unknown causes in a variety of organs including bone, lung, lymph nodes, liver and brain.

Due to its paramount clinical significance, much effort was devoted to exploring the molecular mechanism of metastasis. There is a public demand to identify hematogenic metastasis as early as possible in order to help those patients and improve their survival rate.

With knowledge cemented in decades of research into tumor-initiating events, current experimental and conceptual models are beginning to address the genetic basis for cancer cell colonization of distant organs. Identification of a growing number of genes involved in several steps of the metastatic process and the search for molecular targets that are amenable to therapy is a major focus of cancer research.

Recently, scientists have shown that some genes are involved in the development of a new tumor and some — in promoting the dissemination of cancerous cells to other organs. A set of four genes seems to be required for both processes. Gupta *et al.* [1] reported the presence of four genes that promote not only the growth of primary tumors, but also the entry of cancer cells into the vasculature (intravasation), as well as their colonization of the lung, permeation through blood vessels (extravasation) and outgrowth. The products of these genes are epidermal growth factor receptor ligand epiregulin (EREG), the cyclooxygenase COX2, and the matrix metalloproteinases 1 and 2 (MMP-1 and MMP-2) (Figure).

EPIREGULIN. Epiregulin (EREG) is a member of the epidermal growth factor (EGF) family and can function as a ligand of EGFR [2]. There are four types of EGF receptors, including ErbB1 (also EGFR or Her1), ErbB2 (Neu/Her2), ErbB3 (Her3), and ErbB4 (Her4) [3]. The action mode of epiregulin is similar to EGF, transforming growth factor-α (TGF-α), heparin binding EGF-like growth factor (HB-EGF), amphiregulin (AR), betacellulin (BTC); it binds to ErbB1 and ErbB4 [4].

Toyoda *et al.* [2, 5] cloned human epiregulin gene. Epiregulin is essential for several cellular processes, such as cell survival, proliferation, differentiation, adhesion, migration and axon guidance of several types of cancer [6]. For example, epiregulin was reported to act as a mitogen for various cell types and stimulates proliferation of fibroblasts, hepatocytes, smooth muscle cells, and keratinocytes, but it also inhibits growth of several tumor-derived epithelial cell lines [7, 8]. Although other members of the EGF family are ubiquitously expressed in normal tissues, the level of expression of epiregulin was extremely low in normal specimens but clearly detectable in macrophages and placenta and was high in carcinoma cells [9, 10]. Increased expression of epiregulin has been associated with the pathogenesis of colon, pancreatic, and androgen-independent prostate cancer [11, 12].

By *in vivo* selection, transcriptomic analysis, functional verification, and clinical validation, Minn *et al.* [13] identified a set of genes that marks and mediates breast cancer metastasis to the lungs. Some of these genes have dual functions, providing growth advantages both for the primary tumor and in the lung microenvironment [13, 14].

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Abbreviations used: AR – amphiregulin; BTC – betacellulin; CASP8 – caspase-8; CAMs – cell adhesion molecules; COX2 – cyclooxygenase2; EGF – epidermal growth factor; EREG – epidermal growth factor receptor ligand epiregulin; ECM – extracellular matrix; HB-EG – heparin-binding epidermal growth factor; HRGs – heregulins; MMP – matrix metalloproteinases; PTGS2 – prostaglandins synthetase 2; TGF – transforming growth factor; VSMC – vascular smooth muscle cell.

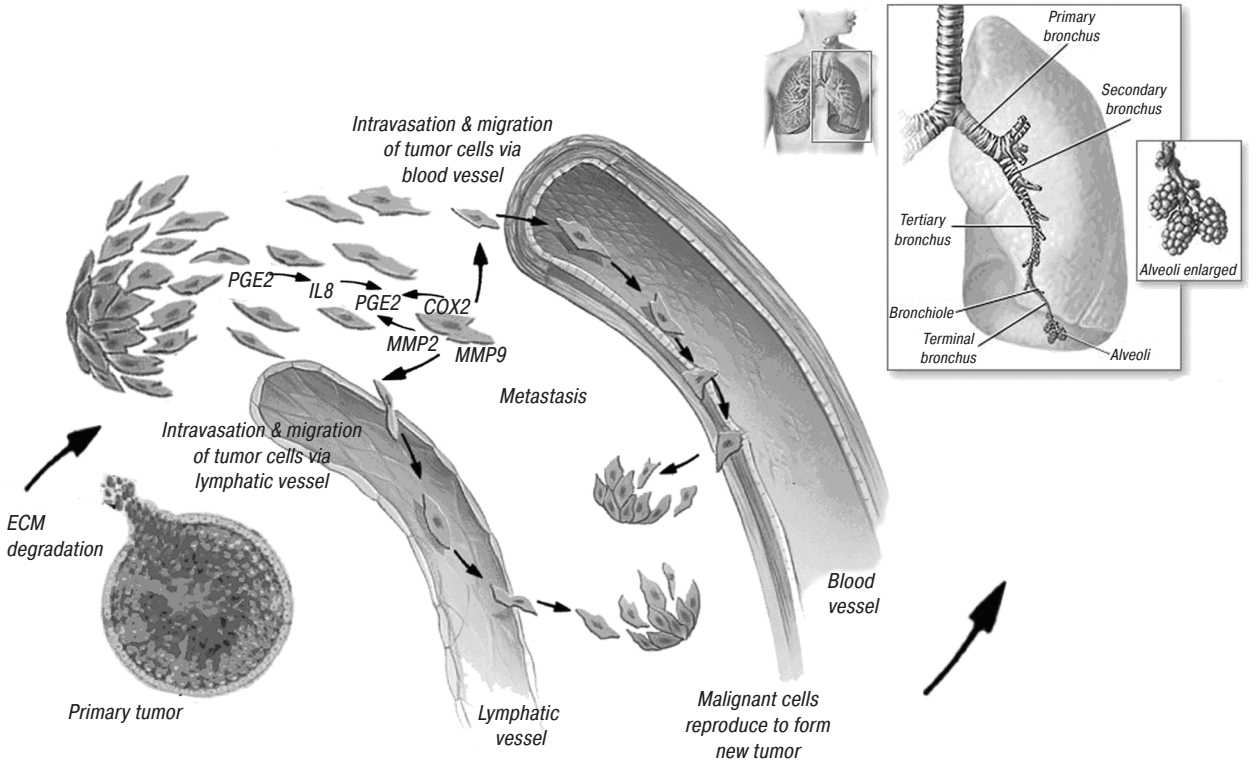

Fig. Genes controlling spread of breast cancer to lung.

Among the identified lung metastasis signature genes, several, including EREG, were functionally validated. Tumors expressing the lung metastasis signatures had a significantly poorer lung-metastasis-free survival but not bone-metastasis-free survival. Cetuximab, a antibody inhibiting the EGFR has been demonstrated to be efficient in the treatment of irinotecan-resistant metastatic colorectal cancer expressing the EGFR [15].

Recently, Gupta *et al.* [1] showed that epiregulin, together with the other three genes could facilitate the assembly of new tumor blood vessels, the release of tumor cells into the circulation, and the breaching of lung capillaries by circulating tumor cells to seed pulmonary metastasis, suggesting that the biological activities may have value for developing specific drug combinations.

MATRIX METALLOPROTEINASES

Family of matrix metalloproteinases (MMPs). The matrix metalloproteinases (MMPs), which are also known as matrixins, are a family of structurally and functionally related proteolytic enzymes containing zinc atom and requiring Ca^{++} for activities. They are secreted as 52 kDa pro-enzymes, which are N-glycosylated (57 kDa form) and can be activated by cleavage of defined peptide sequences *in vitro* by proteinases (e. g., trypsin and plasmin), mercurials (e. g. 4-aminophenylmercuric acetate) and *in vivo* by plasmin and MMP-3 [16]. Physiologically, these enzymes play a role in normal tissue remodelling events, such as embryonic development, angiogenesis, ovulation, mammary gland involution, and wound healing [17]. Abnormal expression appears to contribute to various pathological processes including rheumatoid arthritis and osteoarthritis, pulmonary emphysema, and tumor growth, invasion and metastasis [16–17]. There are at least 23 distinct members in this family. There are four major groups according to substrate specificity: the collagenases, gelatinases, stromelysins, and the epithelial cell membrane-bound MMPs, referred to as membrane-type MMPs (MTMMPs).

MMPs are known to degrade extracellular matrix (ECM) components, many other cell membrane and peri-cellular proteins, including cell membrane precursor forms of growth factors, growth factor binding proteins, growth factor receptors, cell adhesion molecules, clotting factors, and proteinase inhibitors as well as their own inactive zymogen forms [19]. They have either positive or negative effects on cellular growth, migration, angiogenesis, and invasion [20].

MMPs have the ability to cleave collagen helixes. After initial cleavage by collagenases, fibrillar collagens are denatured into gelatin and further are degraded by gelatinases [21].

MMPs are believed to play an important role in tumor invasion and metastasis. MMPs have been identified as pre-forms of tumor-associated enzymes, such as procollagenase, which participate in the angiogenesis, as well as in tumor-cell migration and invasion. Structural changes in the ECM are necessary for cell migration during normal and pathologic tissue remodelling and neoplastic cell invasion [22]. MMPs and their inhibitors have been identified to be critical modulators of ECM composition.

MMP-1 is a member of a family of MMPs that degrades collagens I, II, and III [23]. Overexpression of MMP-1 has been demonstrated to be associated with poor prognosis in various cancers and to be related to hematogenous metastasis [23]. A close correlation between lymph node metastasis and the expression

of MMP-1 in primary tumors was found [24]. Promoter polymorphisms in MMP-1 and their inhibitors were associated with breast cancer susceptibility and progression [25].

MMP-2 (gelatinase A) plays a critical role in basement membrane degradation [26]. It is able to hydrolyze elastin, laminin, fibronectin, proteoglycans, fibrillin, and most notably collagen type IV, which is a major structural component of basement membranes [27]. Additional MMP-2 substrates include Fas ligand, TNF, fibroblast growth factor receptor 1, HB-EGF, interleukin 8, interleukin 1, insulin-like growth factor binding proteins, fibrinogen, factor XII, the CC chemokine MCP-3, and the CXC chemokines SDF-1 [28]. Strong association was reported between MMP-2, invasiveness, and metastasis in a variety of cancers, including lung, prostate, breast, colon tumors, and neuroblastoma [29, 30]. For breast cancer, MMP-2 plays a role in the development of brain and lung metastases [1, 31].

Matrix metalloproteinases as prognostic markers in breast cancer. The early data on implication of MMPs in metastasis were based on correlations between the levels of specific MMPs and metastatic potential in model systems [32]. Over 10 years ago, Duffy *et al.* [33] proposed that proteinases causally involved in experimental metastasis might serve as the markers of metastatic potential or prognosis in human cancers.

High levels of two MMPs (ie MMP-2 and stromelysin-3) have been found to correlate with poor outcome in patients with breast cancer [34]. However, none of these MMPs was shown to be of prognostic significance in axillary node-negative breast cancer patients. However, recently, it was shown that MMP-1 and MMP-2 in cooperation with COX2 and EREG can mediate primary tumor growth and promote breast cancer metastasis to lung. The metastasis-promoting activities can be pharmacologically inhibited using combined drugs against the products of those genes [1].

Matrix metalloproteinase inhibitors. The tissue inhibitors of metalloproteinases (TIMPs) comprise a four-member family of homologous MMP inhibitors (TIMP1, 2, 3, and 4) [35]. TIMP concentrations generally far exceed the concentration of MMPs in tissue and extracellular fluids, thereby limiting their proteolytic activity to focal pericellular sites. In contrast to the inhibitory function, low concentrations of TIMP2 enhanced MMP-14 induced activation of MMP-2 by forming a triplex with these proteins on the cell surface [36]. In addition, TIMPs have been shown to have growth promoting activities, which are independent of their inhibitory function and apoptosis-inducing properties (TIMP3). The transcription of TIMPs is regulated by similar cytokines and growth factors that control MMP expression (i. e. TGF, TNF, IL-1, IL-6), although often in distinct ways [37].

The important role of the MMPs in tumor progression and metastasis has prompted the development of therapeutic agents that block the enzyme activity. One approach has been the development of pseudopeptides that copy structural components of MMP substrates and thus act as competitive, reversible inhibitors. Another approach has used insight from x-ray crystallographic determination of three-dimensional structures of MMPs to generate nonpeptide molecules that selectively bind to the zinc-binding of MMP. The resultant synthetic MMPIs can be either broad-spectrum or selective inhibitors. Broad-spectrum inhibitors effectively block multiple MMPs that may be involved in a wide range of processes that affect tumor growth, invasion, angiogenesis, and metastasis, whereas selective inhibitors have been designed to block the activity of particular MMPs [38].

The MMP inhibitors represent a new class of potential anticancer agents that are currently undergoing intensive clinical evaluation in a variety of malignant diseases. Many of these compounds were successfully studied in clinical trials and are currently being assessed in definitive randomized clinical trials. The results of these studies, which should be available in the near future, will determine whether currently available compounds result in clinically meaningful anti-tumor effects. The research is directed to develop more specific inhibitors, to refine the clinical trial design, and to create optimal treatment strategies that combine MMP inhibitors with standard cytotoxic agents or other biologic agents [38].

COX2. Cyclooxygenase-2 (COX2/PTGS2) is a key rate-limiting enzyme that converts arachidonic acid into pro-inflammatory prostaglandins, induced in inflammation and cancer. It is not expressed constitutively like COX-1, and is not normally present or is present at very low amounts, but is rapidly induced by growth factors, cytokines, tumor promoters, hypoxia, ionizing radiation and carcinogens [39, 40].

COX2 expression is strongly correlated with increased tumor microvasculature density. It also plays an important role in inhibiting apoptosis, stimulating angiogenesis and promoting tumor cell metastasis and invasion [41]. COX2 is overexpressed in most human epithelial cancers and has been linked to various aspects of tumor progression. Epidemiological studies have reported a significant reduction in the incidence of human gastrointestinal cancers with COX2 inhibition by non steroidal anti inflammatory drugs [42].

There is an evidence that COX2 is implicated in breast cancer tumorigenesis. It was shown that 56% of infiltrating mammary carcinoma and intraductal carcinomas express significant level of COX2 whereas normal breast tissues do not express COX2 [43].

Ristimaki *et al.* [44] analysed the expression of COX2 protein by immunohistochemistry in tissue array specimen of invasive breast cancers. Moderate to strong expression of COX2 protein was observed in 37.4% of the tumors. COX2 expression was associated with unfavourable distant disease-free survival. Elevated COX2 expression was correlated with larger tumor size, higher grade, negative hormone receptor status, higher proliferation rate, higher p53 expression and the presence of human epidermal growth factor receptor 2 oncogene amplification, along with axillary node metastasis and a ductal histological type [44].

Also Singh *et al.* [45] demonstrate that COX2 produced in breast cancer cells is important for bone metastases. They also found that COX2 levels were directly associated with the levels of a VEGF growth factor. In the cells missing the *COX2* gene, VEGF levels were substantially lower. With an active COX2 gene, VEGF levels dropped after treatment with COX2 inhibitors [45].

INTERPLAY OF COX2, EREG, MMP-1 AND MMP-2 IN LUNG METASTASIS DEVELOPMENT. Gupta *et al.* [1] examined the function of *COX2, EREG, MMP1* and *MMP2* genes in tumor cells based on the genetic and pharmacological manipulation and confirmed that breast cancer spread might be stopped by switching off the genes. The expression of these genes was stably reduced using short hairpin RNA interference (shRNA) in LM2 cells. Reduction of each gene expression (EREG, COX2, MMP-1 or MMP-2) had statistically significant effects on tumor growth. But when combinations of these genes were inactivated, additive or synergistic effects are apparent, with an almost complete abrogation of both primary-tumor growth and lung metastasis when all four genes are inactived [1].

So, these data indicate that epiregulin, COX2 and MMP1/2 have a crucial role in both the intravasation of tumor cells and extravasation. By contrast, combinatorial ablation of signature genes that exclusively affect lung metastasis, such as full names *IL13Ra2*, *SPARC* and *VCAM1*, did not affect primary-tumor growth [46].

Cetixumab, a neutralizing antibody against EGFR, and celecoxib, a specific inhibitor of COX2, are in clinical use, and GM6001 — a broadspectrum MMP inhibitor — has been tested in preclinical trials [47]. Combinatorial treatment of mice transplanted with the lung-metastasing variant of the MDA-MB-231 cells repeated the results of the genetic ablation studies. The authors observed efficient repression of primary tumor growth, as well as tumor-cell intravasation, extravasation and lung metastasis. This treatment also inhibited lung metastasis in mice intravenously injected with primary breast cancer cells and their variants that express high levels of epiregulin, COX2 and MMP-1. Cessation of treatment resulted in the release of tumor cells trapped within the lung capillaries into the lung parenchymal tissue.

In conclusion, current findings identify *EREG*, *COX2*, *MMP-1* and *MMP-2* as a subset of LMS genes that promote metastasis of breast cancer. In orthotropic primary tumor assays, these factors collectively mediate neoangiogenesis with an ensuing increase in vascular Although the individual targeting of these mediators was insufficient, their combined inhibition resulted in profound reduction in sequential steps of metastatic progression.

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ГЕНЫ, КОНТРОЛИРУЮЩИЕ МЕТАСТАЗИРОВАНИЕ ОПУХОЛИ МОЛОЧНОЙ ЖЕЛЕЗЫ В ЛЕГКИЕ

Очень часто опухолевые заболевания приводят к смерти не в результате прогрессирования первичной опухоли, а из-за метастазирования. Недавно в результате генетического и фармакологического анализа идентифицирован набор генов, а именно кодирующих лиганд рецептора эпидермального фактора роста эпирегулин (EREG), циклооксигеназу-2 (COX2) и матриксные металлопротеиназы 1 и 2 (MMP-1/MMP-2). Продукты этих генов ассоциированы с метастазированием опухоли молочной железы в легкие. Ингибирование EREG и COX2 может минимизировать риск метастастазирования рака молочной железы в легкие. В обзоре рассмотрены последние данные о EREG, COX2, MMP-1 и MMP-2 и их участии в развитии опухоли и метастазировании.

Ключевые слова: **рак молочной железы, EPREG, COX2, MMPs, метастазирование.**