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Mini Review

The roles of angiopoietin-like protein ANGPTL2 in inflammatory carcinogenesis and tumor metastasis

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We recently identified angiopoietin-like protein ANGPTL2 as a key mediator of chronic inflammation and its-associated diseases, such as obesity-related metabolic syndrome, cardiovascular disease, and some autoimmune diseases. Inflammation is receiving much attention for the role it plays at different stages of cancer development, including carcinogenesis, tumor invasion, and metastasis. More recently, we demonstrated that ANGPTL2 functions in the pathogenesis of cancer development, particular in inflammatory carcinogenesis and tumor metastasis. In this review, we focus on ANGPTL2 and its-associated chronic inflammation in carcinogenesis and tumor metastasis and propose that ANGPTL2 could serve a molecular target to prevent and treat pathologies associated with cancer.

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Introduction

Cancer is an increasingly prevalent medical and social problem and remains a major cause of mortality[1]. Therefore, the identification of molecular and cellular mechanisms underlying its pathogenesis is essential to develop new therapeutic and preventive approaches. Recently, the concept that chronic inflammation plays an important role at different stages of cancer development, including carcinogenesis, invasion, and metastasis, has emerged[2]: it is well established that inflammation induced by bacterial and viral infections increases cancer risk, as does chronic inflammation induced by environmental exposure, including tobacco smoking and inhalation of pollutants, such as silica and asbestos[3-5]. Interestingly, it is also commonly accepted that continuous low levels of inflammation, which have no association with either infection or environmental inflammatory exposure, also increase cancer risk. For example, obesity promotes chronic inflammation, and obesity-associated inflammation increases risk of liver and pancreatic cancer[6-8].

The angiopoietin-like protein (ANGPTL) family

In 1996, angiopoietin-1 and -2 were reported as Tie2 ligands[9, 10], and at present, members of the angiopoietin family functioning as Tie2 ligands include Angiopoietin-1, -2, -3 and -4[11]. In particular, Angiopoietin-1 signaling through Tie2 plays an essential role in regulating angiogenesis and maintaining hematopoietic stem cells (HSCs)[11, 12]. In addition, we demonstrated that angiopoietin-1 signaling through Tie2 also functions in lymphangiogenesis[13-15].

About a decade ago, a family of proteins structurally similar to angiopoietins was identified and designated "angiopoietin-like proteins"(ANGPTLs). Seven genes, ANGPTL1-7, all encode proteins exhibiting an N-terminal coiled-coil domain and a C-terminal fibrinogen-like domain, both also characteristic of angiopoietins[16]. ANGPTLs do not bind to either the angiopoietin receptor Tie2 or the related Tie1 receptor, indicating that these ligands function differently from angiopoietins. To date, several studies show that most ANGPTLs potently regulate angiogenesis, yet a subset of these proteins also functions in glucose, lipid, and energy metabolism. For example, ANGPTL3 and ANGPTL4 regulate lipid metabolism by inhibiting lipoprotein lipase activity[17, 18]. ANGPTL6/angiopoietin-like growth factor (AGF) reportedly counteracts obesity by increasing systemic energy expenditure and thus antagonizing related metabolic diseases[19].

ANGPTL2 and inflammatory pathological conditions

We reported that *Angptl2* is induced during fin regeneration in adult zebrafish[20]. This finding suggested a function for ANGPTL2 in inflammation, because inflammation functions in pathological condition tissue regeneration[21]. In studies of mice and humans, we have also reported that ANGPTL2 mediates persistent low-grade inflammation and various its-associated diseases such as obesity-associated metabolic diseases[22]. In obesity, increased adipose tissue-derived ANGPTL2 promotes inflammation in those tissues by activating NF-κB inflammatory signaling through the $\alpha 5\beta 1$ integrin receptor expressed on targeted cells, promoting the onset of obesity-associated insulin resistance[22]. More recently, we demonstrated that infiltrating macrophage-derived ANGPTL2 accelerates abdominal aortic aneurysm (AAA) progression by inducing chronic inflammation and extracellular matrix (ECM) degradation in the aneurysmal vessel wall[23]. Overall, we have shown that ANGPTL2 and its-associated inflammation play important roles in the pathogenesis of various non-infectious diseases.

ANGPTL2 promotes carcinogenesis

Chronic inflammation functions at different stages of cancer development including carcinogenesis, tumor invasion, and metastasis, but molecular mechanisms linking inflammation to cancer development have not been fully clarified. Using a chemically-induced skin squamous cell carcinoma (SCC) mouse model, we reported that ANGPTL2 expression in skin tissues is highly correlated with the frequency of carcinogenesis[24]. An initiating oncogenic mutation within a normal cell is essential for "pre-neoplastic change", and cells harboring that mutation must acquire proliferation and survival capacity to allow accumulation of additional mutations[25-27]. In brief, in this model, a single application of the initiator mutagen 7,12-dimethylbenzanthracene (DMBA) is followed by repeated applications of phorbol 12-myristate 13-acetate (PMA)[28], resulting in cutaneous tumors[28-30]. In this SCC model, papilloma formation seen as epidermal dysplasia, which represents a "pre-neoplastic change" in skin epidermal cells, is caused by DMBA-induced mutations in the *H-ras* gene[31], and the degree of "pre-neoplastic change" can be estimated by papilloma number and size, both stimulated by repeated PMA applications. "Malignant conversion" is accelerated by *p53* mutations brought on by serial PMA treatment and is reflected by the rate of conversion of large papillomas to SCC[32]. When an oncogenic mutation occurs within a normal cell, DNA repair mechanisms often prevent carcinogenesis. However, accumulation of reactive oxygen species (ROS) due to chronic inflammation can inactivate DNA repair enzymes[33]. In this regard, both chronic inflammatory status and ROS levels in mouse skin tissues are positively correlated with ANGPTL2 expression levels, suggesting that ANGPTL2-associated inflammation creates a microenvironment promoting genomic instability. Overall, we found that ANGPTL2-associated chronic inflammation in tissues increases the risk of carcinogenesis by enhancing susceptibility to "pre-neoplastic change" and "malignant conversion" and creating a microenvironment conducive to maintaining oncogenic DNA mutations and accumulating additional ones (Fig.1). More recently, we found that ANGPTL2-associated inflammation inactivates various anti-cancer genes, including tumor suppressors by promot-

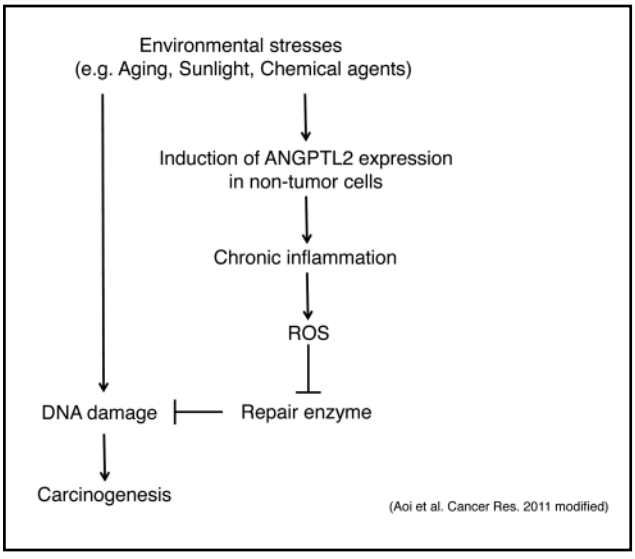

Fig.1 ANGPTL2 facilitates inflammatory carcinogenesis

Environmental stress induced by aging, sunlight or chemical agents causes DNA damage, which is critical to promote carcinogenesis. Environmental stress-induced ANGPTL2 induces chronic inflammation in non-tumor tissues. Chronic inflammation causes overproduction of reactive oxygen species (ROS), which inactivates and decreases levels of DNA repair enzymes, resulting in increased susceptibility to carcinogenesis.

ing DNA methylation (unpublished data). The roles of epigenetic modification accompanying ANGPTL2-associated inflammation in carcinogenesis requires further investigation.

Tumor cell-derived ANGPTL2 promotes metastasis

Using the SCC mouse model also found ANGPTL2 expression in SCC is highly correlated with the frequency of tumor cell metastasis to distant secondary organs and lymph nodes[24]. In brief, epithelial-to-mesenchymal transitions (EMT) in SCC as well as tumor angiogenesis and lymphangiogenesis were significantly increased in SCC and peripheral non-tumor skin tissues of K14-*Angptl2* mice, promoting metastasis and shortening survival periods compared to wild-type mice. Conversely, tumor metastasis was markedly attenuated in *Angptl2* KO mice, resulting in extended survival. These findings led us to ask whether and how tumor cell-derived ANGPTL2 affects metastasis. Interestingly, we observed variation in ANGPTL2 expression levels in cells of the primary tumor, but high, uniform ANGPTL2 expression in cells within metastasized tumor regions[34], suggesting that ANGPTL2-positive tumor cells exhibit high metastatic capacity. We also observed a shortened period of disease-free survival after surgery in lung cancer patients showing high ANGPTL2 expression in tumor cells within primary tumor sites. Using tumor cell-implanted mouse models, we demonstrated that tumor cell-derived ANGPTL2 accelerated metastasis and shortened survival periods but that decreasing ANGPTL2 expression in tumor cells significantly attenuated metastasis and extended survival periods[34]. Interestingly, our experiments indicated that tumor cell-derived ANGPTL2 increase tumor cell motility and invasive capacity through binding the integrin $\alpha 5\beta 1$ receptor and by activating Rac in an autocrine/paracrine manner, resulting in acquisition of aggressive, metastatic phenotypes[34]. Two types of tumor cell movements have been described: a Rac-dependent mesenchymal mode and a Rho-dependent amoeboid mode[35]. Our findings suggest that ANGPTL2-induced cell motility occurs via the mesenchymal mode. Relevant to this, we found that ANGPTL2-expressing human lung cancer cells and chemically-induced mouse SCC tumor cells positive for ANGPTL2 expression show phenotypes indicating that they are undergoing the EMT[24, 34].

ANGPTL2 induction in tumor cells

Activation of ATF/CREB family proteins and/or the calcineurin/NFATc pathway occurs in aggressively advanced tumors[36-39]. Interestingly, NFATc, ATF2 and c-Jun also induce *Angptl2* expression, providing a mechanism for *Angptl2* induction in tumor cells[34]. In adipocytes ER stress also increases ANGPTL2 expression or secretion[22]. ER stress is easily induced by hypoxia, oxidative stress, hypoglycemia, and viral infection, all commonly observed in primary tumor microenvironment[40]. *Angptl2* mRNA levels in tumor cells are significantly increased under hypoxia and undernutrition[34]. In addition, increased ANGPTL2 expression was detected in tumor cells in hypoxic regions[34], suggesting that hypoxia and/or undernutrition in the tumor microenvironment induce tumor cell ANGPTL2 expression. Cytoplasmic calcium concentrations increase due to ER stress-dependent calcium release from the ER[41] and activate the serine/threonine phosphatase calcineurin, which in turn dephosphorylates NFATc proteins and triggers their nuclear accumulation[42]. NFATc function has been extensively studied in the immune system, but there is increased interest in NFATc activity in cancer[36]. Tumor cell-autonomous responses to the microenvironment, such as activa-

tion of the ER stress/calcineurin/NFATc pathway and/or ATF/CREB family proteins, may induce *Angptl2* expression in tumor cells, promoting aggressively metastatic phenotypes.

ANGPTL2 expression in the primary tumor microenvironment

Metastatic phenotypes are influenced by the primary tumor microenvironment[43, 44]. For example, recent studies reveal that metastasis from a primary tumor site is highly regulated by signals emanating from tumor- or cancer-associated fibroblasts (TAFs or CAFs, respectively) within the primary tumor microenvironment[27, 45]. Loss of oxygen or nutrients such as glucose or amino acids occurs in tumor cells during expansion of the primary tumor tissue mass, creating a microenvironment unfavorable to cell growth and to survival of tumor cells at the primary site[46, 47] and "educating" tumor cells to acquire aggressive cell phenotypes by activating metastasis-associated genes[27, 43, 44, 48]. It is reported that CAFs in cancer tissues refractory to anti-VEGF therapy, which when combined with chemotherapy is efficacious in treating several human cancers, express increased levels of ANGPTL2[49]. ANGPTL2 is also expressed in monocytes/macrophages[23, 50] as well as in various tumor cells with agrresive phenotypes[24, 34]. It is well identified that infiltrated monocytes/macrophages in the primary tumor site also mediate tumor development including metastasis[27, 45]. These findings suggets that it is important to clarify molecular mechanisms underlying crosstalk between cancer cells and stromal cells in the primary tumor microenvironment as those interactions may enhance *Angptl2* expression in these cells. Integrins, which act as functional receptors for ANGPTL2 in endothelial cells and monocytes/macrophages[22, 50], are also expressed on several cancer cells where they regulate tumor cell growth, survival and invasion[51, 52]. Thus, in the primary tumor microenvironment, both CAF- and monocytes/macrophages-derived ANGPTL2 as well as cancer cell-derived ANGPTL2 might play critical roles in cancer development by educating tumor cells to acquire aggressive cell phenotypes and creating a microenvironment favorable for tumor cells in an autocrine or paracrine manner. Interestingly, during the preparation of this manuscript, Zhang *et al.* demonstrated that the human leukocyte immunoglobulin-like receptor B2 (LILRB2) and its mouse orthologue paired immunoglobulin-like receptor (PIRB) are receptors for ANGPTL2 and ANGPTL5, and that the binding of these ANGPTLs to receptors supported *ex vivo* expansion of HSCs[53]. Our preliminary study reveals that LILRB2 is abundantly expressed in monocytes/macrophages as well as HSCs. In contrast, many kinds of cancer cells show few expression of LILRB2 (data not shown), whereas Integrins are abundantly expressed on cancer cells. These findings suggest that ANGPTL2 may function through a different receptor system dependent on cell types.

Conclusion and Perspective

We have shown that ANGPTL2-associated chronic inflammation in non-tumor tissues increases risk of carcinogenesis in mice[24]. It is well-established that sunburn in humans increases the risk of skin carcinogenesis due to DNA damage and inflammation[54]. Relevant to this, human subjects show increased *Angptl2* mRNA expression in skin tissues exposed to sunlight compared to unexposed tissues[24]. Most solid malignancies appear in older subjects, and aging or cell senescence is postulated to function as a cancer promoter that acts through inflammatory mechanisms. Accordingly, *Angptl2* levels increase in unexposed skin as an individual ages[24]. These findings suggest that *Angptl2* induction in skin cells promoted by sunburn or aging increases cancer susceptibility in humans. On the other hand, tumor cell-derived ANGPTL2 increases tumor metastasis by enhancing aggressive, metastatic tumor phenotypes, such as cell motility and invasive capacity in an autocrine/paracrine manner (Fig.2)[24, 34].

Interestingly, we recently found that DNA methylation of CpG sites of the mammalian genome, the most well-characterized epigenetic modification, is important for transcriptional regulation of *Angptl2* expression in some cancer cells (unpublished data). It will be of interest to investigate the function of epigenetic modification of *Angptl2* gene in acquisition of aggressively metastatic tumor phenotypes.

In conclusion, we propose here that ANGPTL2 could be targeted in development of new therapeutic strategies to antagonize inflammatory carcinogenesis and tumor metastasis.

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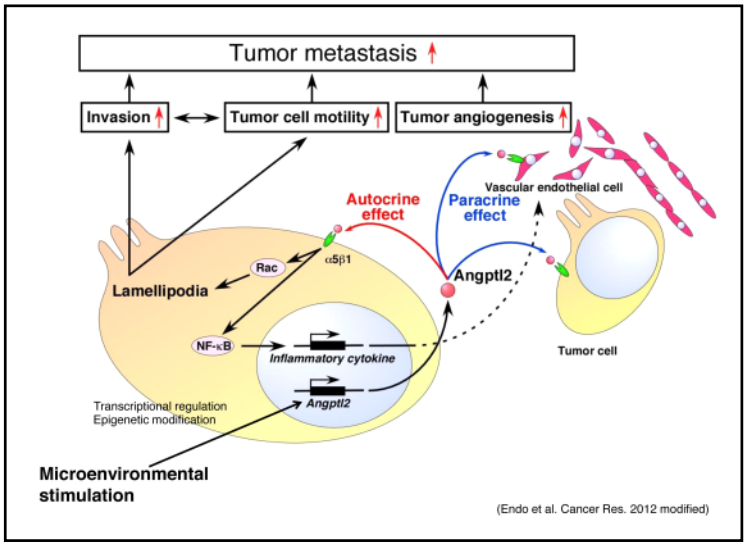

Fig.2 Proposed model of tumor metastasis promoted by ANGPTL2

At a primary tumor site, microenvironmental stimuli, such as hypoxia, undernutrition, or ER stress, promote *Angptl2* transcription through genetic and epigenetic modifications. Tumor cell-derived ANGPTL2 increases tumor angiogenesis and migratory activity of tumor cells in an autocrine/paracrine manner, promoting metastasis.

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Disclosure

Authors declare no conflict of interest.

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