Review

Cancer Research

Inflammation Amplifier, a New Paradigm in Cancer Biology

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Abstract

Tumor-associated inflammation can induce various molecules expressed from the tumors themselves or surrounding cells to create a microenvironment that potentially promotes cancer development. Inflammation, particularly chronic inflammation, is often linked to cancer development, even though its evolutionary role should impair nonself objects including tumors. The inflammation amplifier, a hyperinducer of chemokines in nonimmune cells, is the principal machinery for inflammation and is activated by the simultaneous stimulation of NF-κB and STAT3. We have redefined inflammation as local activation of the inflammation amplifier, which causes an accumulation of various immune cells followed by dysregulation of local homeostasis. Genes related to the inflammation amplifier have been genetically associated with various human inflammatory diseases. Here, we describe how cancer-associated genes, including interleukin (IL)-6, Ptgs2, ErbB1, Gas1, Serpine1, cMyc, and Vegf-α, are strongly enriched in genes related to the amplifier. The inflammation amplifier is activated by the stimulation of cytokines, such as TNF-α, IL-17, and IL-6, resulting in the subsequent expression of various target genes for chemokines and tumor-related genes like BCL2L11, CPNE7, FAS, HIF1-α, IL-1RAP, and SOD2. Thus, we conclude that inflammation does indeed associate with the development of cancer. The identified genes associated with the inflammation amplifier may thus make potential therapeutic targets of cancers. *Cancer Res; 74(1); 8–14. ©2013 AACR.*

Background and Summary of Key Findings

Inflammation has the paradoxical property of both enabling and suppressing tumor development. For example, infiltrated immune cells, including T cells and natural killer cells, as well as chemotherapeutic agents induce inflammation that can exterminate tumors. However, at the same time, tumor-associated inflammation may enhance tumorigenesis by inducing genome instability, tumor cell growth, angiogenesis, etc. In other words, inflammation can lead to more virulent forms of tumor clones by compromising tissue homeostasis via the accumulation of various immune cells. In addition, various molecules from immune cells and tumors themselves might promote tumor development. Consistent with this notion, neoplastic lesions are infiltrated by immune cells from the beginning of tumor development (1). Therefore, there is a need for investigation on how inflammation is specifically associated with tumor development, including the relevant molecular mechanisms.

Our discovery of the inflammation amplifier [formerly, the interleukin (IL)-6 amplifier] has redefined inflammation as the accumulation of immune cells, particularly activated ones, and subsequent dysregulation of local homeostasis (Fig. 1A; ref. 2). The inflammation amplifier, which is a chemokine inducer in type I collagen$^+$ nonimmune cells, including endothelial cells, fibroblasts, glia cells, and epithelial cells, is activated by the simultaneous activation of NF-κB and STAT and locally infiltrates various immune cells (2–5). In fact, the inflammation amplifier is activated by various soluble molecules, including IL-17, TNF-α, ErbB1 ligands, and norepinephrine, which act as NF-κB stimulators, and IL-6 and IFN-γ, which act as STAT stimulators (Fig. 1A; refs. 6, 7). The main signal of the amplifier is NF-κB activation, whereas STAT activation, particularly that mediated by IL-6, likely acts more as a fuel via its positive feedback to enhance the NF-κB pathway (Fig. 1A). We have shown that the inflammation amplifier is associated with various human diseases and disorders by using a new method, the reverse-direction method, which consists of data from the genome-wide screenings of animal models and data from human genome-wide association studies. This method shows concrete correlations between the results of animal models and human diseases. We have applied this method to studying the fundamental molecular mechanism of the inflammation amplifier, demonstrating our mass screening data corresponds with many human diseases and disorders, including not only

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autoimmune diseases but also metabolic syndromes, neurodegenerative diseases, and other inflammatory diseases (2). However, we have not investigated the link between the inflammation amplifier and tumor development, although we have shown that a tumor-related axis, which is established by ErbB1 and its ligand epiregulin, is involved in the development of chronic inflammation in animal models and patients (2).

Here, we reinvestigated our data of genome-wide screenings and performed several additional statistical analyses to show whether the inflammation amplifier genetically links to cancer development. A total of 147 genes related to inflammation amplifier activation were found to also associate with cancer development. The expected association rates of those genes identified as candidate-positive regulators, mouse targets, and human targets of the inflammation amplifier were higher, particularly those genes that overlapped all groups, than the rates of randomly selected control genes. Moreover, some of these genes, such as IL-6, Ptgs2, ErbB1, Gas1, Serpine1, cMyc, and Vegf-α, which are tumor-related genes as well as listed as positive regulators and targets of the amplifier, were found to regulate the inflammation amplifier (2). Furthermore, genes specifically associated with various cancer types were enriched in the gene lists related to the inflammation amplifier. Thus, inflammation related to the inflammation amplifier associates with the development of cancers, suggesting the identified genes here may make for potential therapeutic targets.

Relationship between Regulators of the Inflammation Amplifier and Tumor Development

We performed genome-wide screenings using a mouse short hairpin RNA (shRNA) library (about 65,500 clones which cover about 16,000 genes) to identify positive regulators of the inflammation amplifier (2). Mouse endothelial cells were stimulated with IL-17, an NF-κB stimulator, and human IL-6 plus soluble IL-6 receptor, a STAT3 stimulator. The expression level of mouse IL-6, a target of the amplifier, and cell viability was measured and 1,289 mouse genes were identified as candidate-positive regulators of the inflammation amplifier. We then applied these genes to single-nucleotide polymorphism analysis to identify the associations between them and human tumor development using the Genetic Association Database (GAD) as described previously (detailed methods are shown in Supplementary Materials and Methods; ref. 2).

We found that 63 genes are also associated with tumor development (Supplementary Fig. S1 and Supplementary Table S1). The ratio of expected associations for tumors per gene in the candidates was higher than that of the control genes (0.049 vs. 0.047; first column from left in Supplementary Table S1).

We performed a second screen using the same shRNA and found that more than 90% of shRNA were significantly reduced (2). This result supports the majority of the 63 tumor-related genes contributing to the activation of the inflammation amplifier. Furthermore, Ingenuity Pathways Analysis (IPA) demonstrated that genes related to cell development, transport, signal transduction, cell cycle, and adhesion and cell movement were significantly enriched, as too were genes related to extracellular space, plasma membrane, receptor activity, and receptor binding (Supplementary Table S1). Thus, genes that are both positive regulators of the inflammation amplifier and tumor related seem to be affected by multiple biologic processes and translate more of the extracellular molecules that fall into categories like extracellular space, plasma membrane, receptor activity, and receptor binding.

Relationship between Targets of the Inflammation Amplifier and Tumor Development

Target genes expressed after activation of the amplifier can also associate with tumor development, because the candidate-positive regulators contain various tumor-related genes, as described above. Therefore, we used microarray analysis to study these genes (detailed methods are shown in Supplementary Material and Methods; ref. 2). We selected 576 target genes by DNA microarray analysis using a mouse fibroblast line with or without IL-17 and IL-6 stimulation (2). GAD identified 28 genes to have positive associations with tumor development (see mouse DNA array in Supplementary Fig. S1 and Supplementary Table S1). The number of expected associations per gene in the candidates was 0.049, which is higher than that in the control list (0.047).

Similar to the analysis of the positive regulators, IPA-based analysis demonstrated that the target genes related to immune response, development, apoptosis, adhesion and cell movement, metabolic process, extracellular space, plasma membrane, and receptor binding were significantly enriched (Supplementary Table S1). Thus, genes that are both targets of the inflammation amplifier in mice and tumor related seem to be affected by multiple biologic processes and contain an unusually high number of extracellular molecules.

We used human microarray analysis to study the target genes directly in a human fibroblast line with or without IL-17 and IL-6 stimulation. We selected 885 target gene candidates (2). GAD identified 54 as having positive associations with tumor development (Supplementary Fig. S1 and Supplementary Table S1). The number of expected associations per gene in the candidate list was 0.061, which again is higher than the 0.047 seen for the control list, a difference that this time was statistically significant ($P = 0.031$).

IPA-based analysis demonstrated that genes related to immune response, development, cell cycle, apoptosis, adhesion and cell movement, extracellular space, plasma membrane, receptor activity, and receptor binding were significantly enriched in these 54 genes (Supplementary Table S1). Thus, genes that are both targets of the inflammation amplifier in humans and tumor related seem to be affected by multiple biologic processes and express an unusually high number of the extracellular molecules that fall into categories like extracellular space, plasma membrane, receptor activity, and receptor binding.

Investigation of Overlapping Genes

Only the *IL-6* and *Ptgs2* genes were seen in all three lists, whereas three genes, ErbB1, Gas1, and Serpine1, were found in

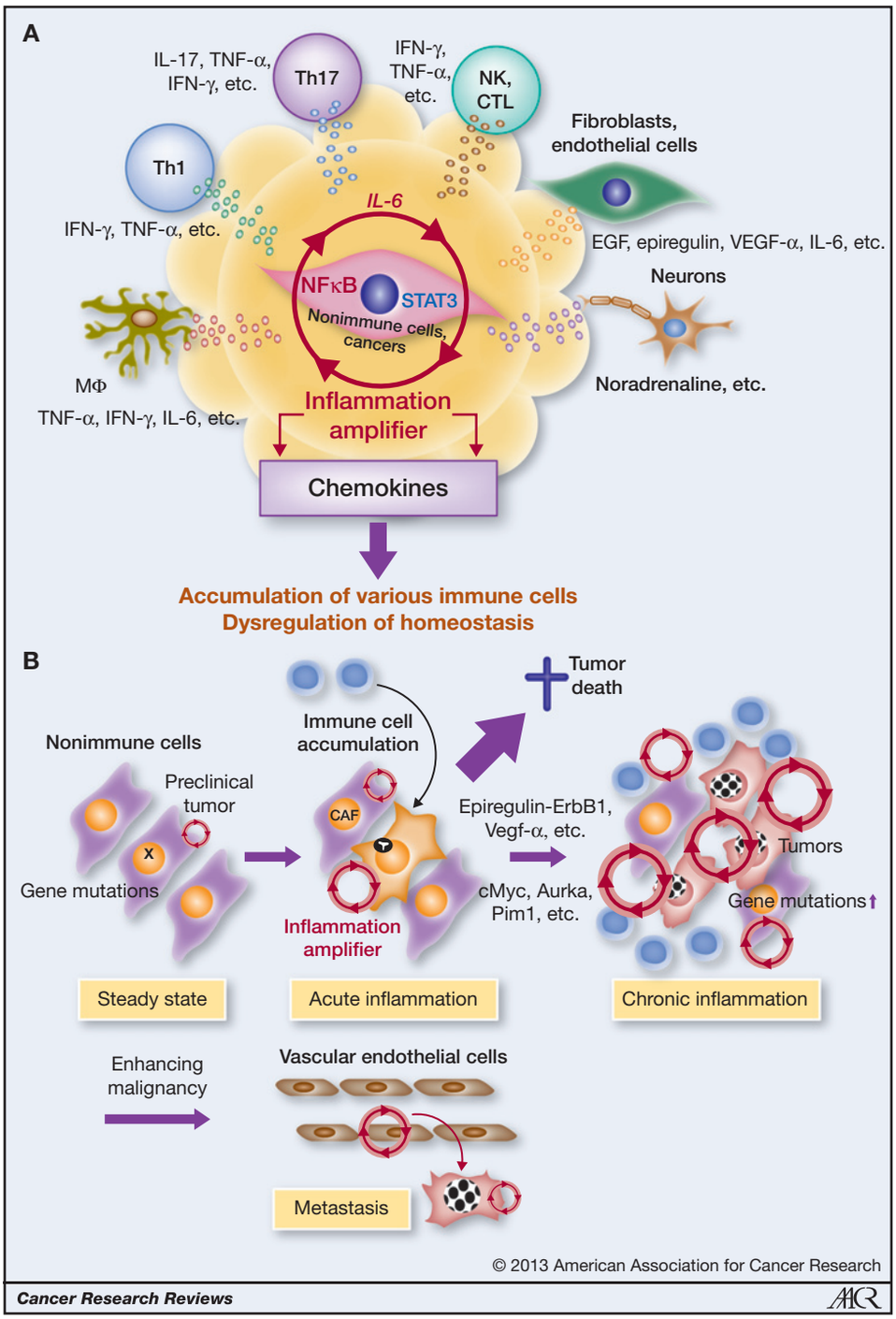

Figure 1. A, the inflammation amplifier, which is a chemokine inducer via an enhanced NF-κB pathway, is activated by various stimulators, resulting in the simultaneous activation of NF-κB and STAT3 in nonimmune cells, including cancers. The inflammation amplifier is activated by the simultaneous activation of NF-κB and STAT3, which can be triggered by various factors derived from immune cells, fibroblasts, neural cells, etc. The inflammation amplifier is activated in normal and cancerous type I collagen$^+$ nonimmune cells, including fibroblasts, endothelial cells, and epithelial cells. Its activation amplifies the expression of chemokines and IL-6 followed by an accumulation of immune cells, which induces inflammation and dysregulation of local homeostasis. At the same time, its activation correlates with the expression of various tumor-associated genes (see Supplementary Fig. S1). Chemokines act as functional molecules to locally accumulate in various cell populations, whereas IL-6 acts like fuel for the amplifier via its positive feedback loop. B, activation of the inflammation amplifier during the development of cancers. Gene mutations in type I collagen$^+$ nonimmune cells, including fibroblasts, epithelial cells, glia cells, and endothelial cells, in the steady state might induce preclinical tumors and activation of the inflammation amplifier followed by an accumulation of immune cells. Cytokines derived from immune cells enhance the activation of the amplifier in tumor cells as well as surrounding CAF. (*Continued on the following page*.)

the lists of positive regulators and targets of the mouse inflammation amplifier, and two genes, cMyc, and Vegf-α, in the lists of positive regulators and targets of the human inflammation amplifier (Supplementary Fig. S1). Genes that were targets of the inflammation amplifier in mouse and human cells included Bcl2l11, Cpne7, Fas, Hif1-α, IL-1rap, and Sod2.

The numbers of expected associations per gene in the candidate lists were 0.091, 0.065, 0.092, and 0.222, respectively, all higher than the 0.047 seen for the control list (see rows 5–8 in the first column of Supplementary Table S1). The differences were statistically significant except for those genes that are positive regulators and targets of the human inflammation amplifier. Importantly, the numbers of expected associations per gene increased in all overlapping genes compared with nonoverlapping ones, suggesting that the overlapping genes related to the inflammation amplifier show more associations with cancers.

IPA-based analysis revealed that those overlapping genes related to immune response, cell cycle, apoptosis, adhesion and cell movement, extracellular space, and receptor binding were significantly enriched in the overlapping targets (Supplementary Table S1). Thus, the overlapping genes related to both the inflammation amplifier and tumors seem to be affected by multiple biologic processes and express an unusually high number of extracellular receptor–associated molecules that fall into categories like extracellular space and receptor binding.

With regard to the function of these overlapping genes, IL-6 and ErbB1 are both critical for activation of the inflammation amplifier (3, 4). Two soluble factors, Vegf-α and PGE2, which are established by Ptgs2, are known to induce the expression of chemokines as well as NF-κB activation in tumor cells (8–12). In addition, chemokine expression is reported to be positively regulated by cMyc in tumor cells (13). Thus, the overlapping genes might be important therapeutic targets for the regulation of tumor-associated inflammation.

The Inflammation Amplifier in Relation to Cancer Types

We performed statistical comparison analysis using the identified 131 tumor-associated genes that are also related to inflammation amplifier activation (positive regulators and/or targets = 56+18+44+2+2+3+6) and 1,403 tumor-associated genes that are listed in GAD (see the row 1. "Gene numbers in 1,403 tumor-associated genes" in Supplementary Table S2). The numbers of associations to specific tumors are shown in the columns of Supplementary Table S2. Genes related to four cancer types (hematologic malignancies, tumors in lung, colorectal/intestinal, and urinary/bladder/vulvar) were enriched in all three primary lists (shRNA screening, mouse DNA array, and human DNA array) compared with the control 1,403-gene list (Supplementary Table S2). The genes associated with seven other cancer types, including tumors in the brain, breast, esophagus, stomach, liver, kidney, and thyroid, were significantly higher in at least two of the lists (Supplementary Table S2). Nine cancer types out of these 11 were also higher in at least two overlapped gene lists (Supplementary Table S2). No significant gene enrichment was found in genes related to tumors in prostatic and pancreatic cancer (Supplementary Table S2). These results strongly suggest that the inflammation amplifier is involved in various cancer types.

Future Directions

We had previously believed that any effects by inflammation on the development of tumors would be limited because inflammation is listed as just one of the many factors for cancer development such that its effects are expected not to be primary (14). At the same time, it was shown that gene expression patterns in tumor cells, including metastatic breast cancer cells in the lung, are sometimes similar to the gene expression patterns of the the inflammation amplifier (2, 15), and cancer-related inflammation contributes to the tumor microenvironment, affecting various characteristics of tumor malignancies (16). We observed that a large number of genes related to the inflammation amplifier, which includes 63 candidates from 1,289 positive regulators, 29 from 576 mouse targets, and 54 from 885 human targets, are associated with human cancer development. To our surprise, more than 9% of tumor-associated genes are present in our gene lists and relate to the amplifier (131 out of 1,403 genes). The ratios of the expected associations for tumors per candidate gene were higher, particularly among those genes found in all three lists, than the ratios of randomly selected control genes (see red numbers in first column of Supplementary Table S1). Functional analyses indeed showed that some tumor-associated genes play a role in activation of the inflammation amplifier (2). These results strongly suggest that inflammation is indispensable for the development of various tumors. Therefore, it would appear that inflammation affects multiple tumor-inducing factors during tumor development. Consistent with this notion, it has been reported that inflamed regions, as indicated by the accumulation of immune cells, are present from the very initial to final phases of tumor development (1, 17). Thus, we propose here that inflammation is not only an enabling factor of tumor development but also one of the most important factors.

Blockade of the ErbB1 (EGF receptor) signal, a positive regulator and target of the inflammation amplifier as well as a tumor-related gene, significantly suppresses the development of inflammatory diseases (2, 7). Furthermore, the expression of epiregulin, an ErbB1 ligand and also target of the inflammation amplifier, is higher in patients with several

(*Continued*.) The tumor cells are usually eliminated during acute inflammation, whereas the expression of inflammation amplifier-related genes in the tumors and CAF, such as epiregulin-ErbB1, Vegf-α, cMyc, Aurora, and Pim1, might induce survival and/or gene mutations of the tumors to accelerate their malignancy during chronic inflammation. The amplifier in the endothelial cells, which might be activated by regional neural stimulations, etc., also triggers tumor metastasis via the expression of chemokines. Red loops show inflammation amplifiers at various stages of tumor development. Bigger loops indicate greater activation. The sizes of hatched marks in the nucleus of the tumors indicate the degree of their malignancy.

inflammatory diseases, suggesting the existence of an epiregulin-ErbB1 positive-feedback loop during inflammation development (2). It is reasonable therefore to conclude that tumor-associated inflammation activates the epiregulin-ErbB1 loop, which in turn affects tumorigenesis via the inflammation amplifier (Fig. 1). Consistent with this thought, ErbB1-mediated signaling is reported to enhance the survival and growth of various tumors (18). Therefore, the epiregulin-ErbB1 axis might be a specific and critical pathway for positively regulating tumor development via the amplifier.

At least three possible cell types have an activated inflammation amplifier during tumorigenesis: the tumor cells themselves, fibroblasts, and endothelial cells, all of which functionally interact with the tumor microenvironment (Fig. 1B). The inflammation amplifier in tumor cells might be related to tumor properties like growth advantage, metastasis, and angiogenesis via the expression of various functional molecules. For example, the epiregulin-ErbB1 pathway stimulates cellular growth and/or survival; chemokines, which are the chemotactic factors, are targets of the amplifier; and Vegf-α, which is an angiogenesis factor and found in the list of positive regulators and targets of the amplifier (Supplementary Fig. S1). Consistent with this thought, TNF-α, a NF-κB stimulator, increased CXCL1/2 from breast cancer cells to accumulate $CD11b^{+}Gr1^{+}$ myeloid cells around the cancer cells and led to the expression of S100A8/9, a survival factor secreted by myeloid cells (19), and IL-17 is reported to be critical for the tumor development that associates with Vegf-α (20)

Cancer is a genetic disease, and some malignant cancer cells having several mutations can survive and proliferate without cytokine stimulation, at least *in vitro*. We hypothesize that the inflammation amplifier is constitutively activated in such tumor cells by the genetic alteration of oncogenes (Fig. 1B). Consistent with this hypothesis, the NF-κB pathway is activated in a K-ras–dependent manner in cancer cells (21). Moreover, at least three target genes of the inflammation amplifier, cMyc, Aurka, and Pim1, induce genomic instability and mutations (refs. 22–25; Fig. 1B). Therefore, it is possible that some genetic alterations in tumors enhance inflammation amplifier activation. Thus, it can be argued that the inflammation amplifier is activated in various human cancer cells that have genetic alterations or are in the presence of activated immune cells rich in cytokines, including NF-κB and STAT activators, before the cancer malignancies being expressed.

Because many fibroblast cells have a certain level of amplifier activation, we hypothesized that cancer-associated fibroblasts (CAF) located around the cancer cells also have amplifier activation. CAF have the paradoxical role of attacking tumors while at the same time supporting them by expressing soluble and membrane molecules, including cytokines and chemokines (26, 27). The final set of candidate cells that may have activated inflammation amplifiers is endothelial cells. Indeed, there exists evidence that the inflammation amplifier in endothelial cells acts as a gateway for the entry of immune cells as well as tumors into target organs. For example, noradrenaline expression via regional neural activations, which enhance the inflammation amplifier in endothelial cells, marks a gateway for immune cells to enter the central nervous system (ref. 6; Fig. 1A). Interestingly, this gateway can be artificially manipulated by modulation of gravitational forces or electric pulses to the muscles of mice, resulting in an accumulation of immune cells at the intended regions via the induction of noradrenaline from sympathetic neurons (6). Gating blood vessels by regional neural stimulations, which we term the gateway theory, has potential therapeutic value not only in augmenting the effects of cancer immunotherapies, but also in preventing cancer metastasis (ref. 28; Fig. 1B). Consistent with this theory, automatic neural activations have been shown to play a role in the development of prostate tumors (29).

There are two aspects to inflammation regulation on cancer progression. One is to exterminate tumors, which is analogous to when infectious agents and/or infected cells are removed after an invasion by viruses or bacteria. In this case, inflammation induces an accumulation of various immune cells followed by the dysregulation of local homeostasis at the tumor sites (Fig. 1B). The inflammation induces the death of many cell populations, including not only tumor cells but also normal ones. If the tumor cells are completely eliminated at this stage, the inflammation attenuates and the tissue remodels. This phenomenon appears as acute inflammation in a limited area. However, tumor cells can also survive inflammation, with some microenvironments in the body even providing evacuation routes for the tumors. This phenomenon often induces chronic inflammation, which can promote or be promoted by malignant cancers (Fig. 1B). Thus, inhibiting tumor-associated inflammation might be a promising therapeutic approach at this stage (Fig. 1B; chronic inflammation stage). At the same time, enhancing the inflammation response at early cancer stages or shortly after surgical removal and/or successful chemotherapy of cancers may also be therapeutic (Fig. 1B; acute inflammation stage). In either case, the inflammation amplifier should be given special consideration, as it promotes both acute and chronic inflammation. Consistent with this property, inhibitors of ErbB1 or Vegf-α, both of which are positive regulators of the inflammation amplifier, have efficacies on several tumors.

These results suggest that new cancer therapies can arise from targeting the inflammation amplifier. To develop such new approaches, upstream stimulators of the amplifier, including the stimulators of NF-κB and STAT3, need to be identified (see Fig. 1A). We also need to analyze the activation status of the amplifier among cancers by monitoring the phosphorylations of NF-κB, STAT3, ErbB1, and Creb, a downstream target of noradrenaline, as well as expressions of chemokines and IL-6 (5–7). These molecules would make promising targets for therapy based on the amplifier regulation. We hypothesize that anti-TNF-α, IL-6 receptor, anti-IL-17, anti-IFN-γ, and anti-ErbB1 ligand antibodies or inhibitors of noradrenalin receptors are good drug candidates for inhibiting the chronic inflammation status, whereas local expression of the equivalent soluble factors (TNF-α, IL-6, IL-17, IFN-γ, epiregulin, or noradrenalin) could enhance the amplifier to induce acute inflammation around early cancer stages. Other candidate genes for therapy from our gene lists should also be considered (Supplementary Fig. S1; ref. 2).

At the same time, to establish inflammation amplifier–based cancer therapy, we must also consider that the inflammation status changes not only around tumors, but also around infectious areas to eliminate nonself agents via inducing acute inflammation. We know that the amplifier is activated at the dorsal vessels of the fifth lumbar cord even at physiologic steady state to maintain homeostasis in the central nervous system (6, 30). Therefore, it might be possible that complete suppression of the amplifier might induce infectious diseases due to the suppression of acute inflammation or promotion of homeostic dysregulation, particularly in the central nervous system.

To conclude, activation of the inflammation amplifier, which is critical machinery for inflammation, is associated with the development of various tumors. Further investigation of the inflammation amplifier at each stage of tumor development should cast light on a new paradigm for cancer progression and lead to potential therapeutic targets.

Disclosure of Potential Conflicts of Interest

T. Hirano and M. Murakami have received commercial research grants from Takeda Pharmaceutical Company Limited. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: M. Murakami
Development of methodology: M. Murakami
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Murakami
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T. Atsumi, R. Singh, L. Sabharwal, H. Bando, M. Yamada, M. Harada, J.-J. Jiang, D. Kamimura, H. Ogura, M. Murakami
Writing, review, and/or revision of the manuscript: M. Murakami
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Meng, Y. Arima, M. Murakami
Study supervision: M. Murakami
Discussion and advice: T. Hirano

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