Inflammation-Related Carcinogenesis: Current Findings in Epidemiological Trends, Causes and Mechanisms

Futoshi Okada*†
*Division of Pathological Biochemistry, Department of Biomedical Sciences, School of Life Science, Tottori University Faculty of Medicine, Yonago 683-8503, Japan and †Chromosome Engineering Research Center, Tottori University, Yonago 683-8503, Japan

ABSTRACT
Inflammation is a definite cancer-causing factor as revealed by cumulative basic, clinical and epidemiological studies. It is mostly induced by infectious agents. For instance, infection with papillomaviruses associates with anogenital cancers, especially cervical cancers; Helicobacter pylori infection of the stomach tends to increase the risk of stomach cancer; chronic hepatitis B & C viruses and fluke infections of the liver increase liver cancers; autoimmune diseases, e.g., inflammatory bowel diseases, associate with development of colorectal cancer, and aerial irritants (foreign bodies) such as asbestos or fine particulate matter (PM2.5) in outdoor air increase malignant pleural mesotheliomas or lung cancers. These are typical examples of inflammation-related carcinogenesis. It is apparent that the pathogens to induce inflammatory reactions in specific organs are not related to each other. However, the underlying pathogenesis in common is to induce and/or sustain inflammation. In this article, I would like to review the up-to-date findings of epidemiological trends, causes and mechanisms of inflammation-related carcinogenesis.

Key words carcinogenesis; inflammation; mouse model

Cancer is classified as noncommunicable disease as cardiovascular diseases, chronic respiratory diseases and diabetes are. They are mostly chronic diseases of long duration and generally slow development. While they are assumed to develop from aging, urbanization, and unhealthy lifestyles, it has also become known that low-grade chronic inflammation, which is characterized by increased systemic levels of inflammatory cytokines and inflammation-responsible protein (C-reactive protein), is one of the underlying key mechanisms. Indeed, estimated 20–25% of all cases of cancer worldwide are associated with inflammation induced by microbial infection. Extended life span, dietary factors and physical inactivity; mutation and replicating errors; environmental pollutants including aerial irritants and tobacco; and radiation and ultraviolet are linked to carcinogenesis today. Nevertheless, persistent inflammation resulting from infection or autoimmunity is most evidently associated with the onset of carcinogenesis.

The relation of inflammation to cancer was first postulated by Galenus around 1,800 years ago. He proposed that tumors arose from inflammatory tissue injury and that the tumors and the tissue were pathophysiologically similar. Centuries later in 1863, Virchow confirmed Galenus’s hypothesis from his own observation that lymphoreticular infiltrates, namely inflammation, preceded tumor development. This possible link between injurious inflammation and cancer was also pointed out later by Dvorak who revealed that tumor tissues resembled wound tissues because both tissues were composed of similar stromal cell types such as infiltrated inflammatory cells and angiogenesis-related cells; the only difference he pointed out was that tumor tissues did not terminate (heal) but wound healed finally. Antitumor immunity exists, since particular kinds of tumors are formed only in patients with iatrogenic immunosuppression such as melanoma and nonmelanoma skin cancer in organ transplant recipients, lymphoma in patients with lymphoproliferative disorders, or Kaposi’s sarcoma in patients with immunosuppressive infection such as with HIV. However, the generality of the arising tumors are sarcomas and hematologic malignancies, and carcinomas that account for the majority of human carcinogenesis seldom occur in the immunosuppressed patients. Discussions have suggested that antitumor immunity might work only in the very initial phase of carcinogenesis or work against particular kinds of tumorigenesis only. An opinion has even suggested that antitumor immune effector cells may act as stimulant to carcinogenesis. In the 1970s,
Prehn proposed that immune effector cells contributed to carcinogenesis, and named the phenomenon as “immunostimulation theory of tumor development.”6

From the achievements of our predecessors carried out over the two millennia, we have solid evidence that an inflammatory environment can be an essential risk for induction of various types of carcinomas. Recent results add that inflammation-related carcinogenesis is influenced not only by individual age and sex, but also by regional/geographical and economical development statuses of country. I review the current evidence on the inflammation-related carcinogenesis and propose possibly effective preventive/therapeutic strategies based on our elucidation of inflammation mechanism obtained by using our animal model.

EPIDEMIOLOGICAL TREND OF INFLAMMATION-RELATED CARCINOGENESIS

It is obvious that incidences of inflammation-related cancers are not in a homogenous background but in a complex one influenced by individual age, sex, living region, era and also development status of country as revealed in the recent epidemiological studies.

Chronologically the incidences of inflammation-related carcinogenesis also differ. In the United States, cancer epidemiologists estimated in the 1980’s that around 75% of cancers was due to three cancer-causing factors: daily diet, smoking and infection/inflammation.7 Currently the three major factors are thought to account for 43% of cancer causes.8 Involvement of inflammation in the total cancer incidences was reduced from 10% to 5%.9

There are geographical differences in the incidences of inflammation-caused cancers. Namely, contribution of inflammation to carcinogenesis greatly varies among continents, countries, and even in the regions within a country. Figure 1 shows the ratios of infection/inflammation to all the cancer death causes: around 25% in sub-Saharan Africa, around 6% in Europe.6 In general, the proportions were higher in less developed countries (23%) than in more developed countries (7%) including North America and New Zealand (10%). Lowest ratios were in Australia and New Zealand (3%), while other parts of Oceania showed higher ratios (18%). In contrast to the highest ratio in sub-Saharan Africa (25%), the rates are lower in North Africa and west Asia (13%). In east Asia, the rates are high: Japan (20%), China (26%), South Korea (21%) and India (21%).10 Considering the high ratios, east Asia including Japan is still a developing region.

The geographical and regional differences in the incidences of inflammation-related carcinogenesis may arise from the economic standing or development status of each country; i.e., the standard of life, the levels of medical care and education, etc. will make up the characteristic of a country as a whole. In addition, prevalence of the four main infectious agents, HPV, HBV, HCV and Helicobacter pylori, differs among economically and geographically different regions. Relative contribution of HPV to cancer burden is similar in both developed and developing countries. However, that of Helicobacter pylori is larger in developed countries, and those of HBV and HCV are larger in developing countries.10

There were estimated 14.1 million new cancer cases and 8.2 million cancer deaths globally in 2012; of the cancer deaths, about 65% (5.3 million) was in less developed countries.11 Since the infectious agents account for as much as 20% of all of the cancer-causing factors, we could estimate that around 2.8 million new cancer cases and around 1.7 million deaths would be attributable to infection/inflammation. It is greatly apprehended that new cancer cases/deaths due to inflammation would increase rapidly in the developing countries within a few decades as a result of upcoming population growth.12

Although the total number of cancer cases due to inflammation is much the same between men and women,10 there are some sex- and age-dependent differences in particular cancers: stomach cancer, liver cancer, oropharynx cancer, bladder cancer, Hodgkin’s lymphoma and Kaposi’s sarcoma are much higher in men than in women.10 And it is obvious that around 30% of inflammation-related cancers (cervical cancer, Hodgkin’s lymphoma and Kaposi’s sarcoma) are in individuals younger than 50 years, compared to other inflammation-related cancers which develop mostly in those older that 50 years.10

CAUSES OF INFLAMMATION-RELATED CARCINOGENESIS

Infections induced by certain viruses, bacteria, parasites or foreign bodies and following prolonged inflammation have been identified as grave risk factors for development of specific cancers. Table 1 shows infectious agents classified as presumably carcinogenic according to experimental and clinical reports.10

MECHANISMS OF INFLAMMATION-RELATED CARCINOGENESIS DETERMINED IN AN EXPERIMENTAL MODEL

Close association between inflammation and carcinogenesis has been indicated by clinical and epidemiological studies; however, there is hardly a solid animal model in which carcinogenesis by inflammation can
Inflammation-related carcinogenesis

be evidently observed. To demonstrate the direct link between inflammation and carcinogenesis, our group established several animal models in which tumorigenic conversion or acceleration of carcinogenic processes of rat, mouse or human cells occurs in the presence of inflammation. In this section, I summarize the results of our thorough investigation using one of our mouse models and introduce our elucidation of the mechanism responsible for inflammation-related carcinogenesis and theoretical preventive strategies.

To establish the experimental model for carcinogenesis especially focusing on acquisition of tumorigenicity in vivo, we had to choose cells which were immortalized, non-tumorigenic, and non-metastatic but would grow in vitro, bearing the concept of xenogenization in mind. “Xenogenization of tumor cells” is the term meaning immunologically spontaneous regression of tumor cells which have been infected with xenogeneic viruses, transected with the genes coding allogeneic antigen, or exposed to mutagenic chemicals, after injected into normal syngeneic host.

We obtained regressive clonal QR cells from clonal tumorigenic fibrosarcoma cells, BMT-11 cl-9, by exposing them in vitro to a mutagen/carcinogen (quercetin); they were non-tumorigenic and non-metastatic in normal syngeneic C57BL/6 mice, and we termed the phenomenon as “chemical xenogenization of tumor cells.” By using the regressive QR cells, we can easily detect internal/external factors which are closely associated with carcinogenic process through the conversion of their regressive phenotypes into lethally tumorigenic ones, after injecting QR cells previously treated in vitro with a candidate material, or co-implanting QR cells with it, into mice. As shown in the Fig. 2A, QR cells did not develop tumor after (2 × 10^5 cells) subcutaneously injected into mice. Since QR cells grew progressively in immunosuppressed hosts, we determined that their regression was mediated by host immunity.

Infiltrated inflammatory cells are necessary and sufficient to accelerate carcinogenesis

A serendipitous finding was that the regressive QR cells were spontaneously converted to grow lethal after implanted into a pre-inserted piece of hemostasis gelatin sponge which induced foreign-body-reactive inflammation at the implantation site (Fig. 2B). Significance of the foreign-body-induced inflammation on carcinogenesis was confirmed by using other materials such as plastic plate. In this case, too, various phenotypic alterations occurred following QR cell conversion. All of the arising tumors were found to have acquired tumorigenic and metastatic phenotypes, and the acquired malignant phenotypes remained stable as far as examined for decades at least under cultivation in vitro. An increase in prostaglandin E2 production followed the acquisition of tumor-forming ability, which particularly suppressed immunological host-defense against tumors. Angiogenesis, motility and invasion capacities of tumorigenic...
| Sites of inflammation-related carcinogenesis | Causes of inflammation/pathological condition | Definitely carcinogenic | Presumably carcinogenic |
|---------------------------------------------|------------------------------------------------|------------------------|-------------------------|
| Eye                                         | HIV type 1                                      | UV-associated skin inflammation |                        |
| Lip                                         | UV-associated skin inflammation                 |                        |                        |
| Oral cavity                                 | HPV type 16                                     | HPV type 18, gingivitis, lichen planus, leukoplakia |                        |
| Salivary gland                              | Sialadenitis                                    |                        |                        |
| Tongue                                      | HPV, caries, gingivitis                         |                        |                        |
| Tonsils                                     | HPV type 16                                     |                        |                        |
| Nasopharynx                                 | EBV                                            |                        |                        |
| Pharynx                                     | HPV type 16                                     | Asbestos               |                        |
| Oropharynx                                  | HPV                                            |                        |                        |
| Larynx                                      | Asbestos                                        | HPV type 16            |                        |
| Thyroid                                     | Chronic lymphocytic thyroiditis, Hashimoto's thyroiditis |                        |                        |
| Esophagus                                   | Gastric reflux, esophagitis, Burrett's esophagus, Neisseria mucosa, Neisseria sicca, Neisseria subflava |                        |                        |
| Lung                                        | Asbestos, coal gasification, outdoor air pollution,* tobacco smoke | Asthma, bronchitis, COPD, interstitial pneumonia, sarcoidosis, silicosis, tuberculosis, Chlamydia pneumoniae |                        |
| Lung mesothelium                            | Asbestos                                        | Silicosis              |                        |
| Stomach                                     | Helicobacter pylori                             | Asbestos, EBV, chronic atrophic gastritis |                        |
| Liver                                       | HBV, HCV, Clonorchis sinensis, Opisthorchis viverrini | HDV, HIV type 1, Schistosoma japonicum, hemochromatosis | alpha-1-anti-trypsin deficiency, alcohol |
| Bile duct                                   | Clonorchis sinensis, Opisthorchis viverrini     | Bile acids-associated cholangitis |                        |
| Gall bladder                                | Gall bladder stone-associated cholecystitis, Salmonella typhimurium |                        |                        |
| Pancreas                                    | Chronic pancreatitis, alcoholism-associated pancreatitis, hereditary pancreatitis, primary sclerosing cholangitis, alcohol |                        |                        |
| Colon & Rectum                              | Bile acids-associated coloproctitis, inflammatory bowel diseases, cytomegalovirus, EBV, HPV, JCV, Bacteroides, Clostridiumsepticum, Escherichia coli, Helicobacter pylori, Streptococcus bovis, Streptococcus gallolyticus, Schistosoma japonicum, asbestosis |                        |                        |
| Bladder                                     | Schistosoma haematobium                         | Cystitis, urinary catheter-associated cystitis |                        |
| Anus                                        | HIV type 1, HPV type 16                          | HPV types 18, 33, anal fistula |                        |
| Prostate                                    | Prostatitis, proliferative inflammatory atrophy, gonorrhea, chlamydia, mumps virus, Trichomonas vaginalis |                        |                        |
| Ovary                                       | Asbestos                                        | Pelvic inflammatory disease |                        |
| Uterine cervix                              | HPV types 16, 18, 33, 35, 39, 45, 51, 52, 56, 58, 59; HIV type 1 | HPV types 26, 53, 66, 67, 68, 70, 73, 82; herpes simplex virus |                        |
| Endometrium                                 | Endometriosis                                    |                        |                        |
| Penis                                       | HPV type 16                                     | HIV type 1, HPV type 18 |                        |
| Vulva                                       | HPV type 16                                     | HIV type 1, HPV types 18, 33; lichen sclerosis |                        |
| Vagina                                      | HPV type 16                                     | HIV type 1              |                        |
| Skin                                        | UV-associated skin inflammation                 | Chronic osteomyelitis, HIV type 1, HPV types 5, 8; MCV | UV-associated skin inflammation |
| Melanoma                                    |                                               |                        |                        |
| Non-melanomatous skin cancer                |                                               |                        |                        |
| Central nerve                               |                                               |                        |                        |
| Endothelium                                 | HIV type 1, KSHV                                | HIV-2                  |                        |
| (Kaposi's sarcoma)                          |                                               |                        |                        |
| Vasculature                                 |                                               |                        |                        |
| Hodgkin's lymphoma                          |                                               |                        |                        |
| Lymphoma                                    | EBV, HCV, HIV type 1, HTLV-1, KSHV              | HIV type 2, Hashimoto's thyroiditis, Sjögren's syndrome, childhood celiac disease, HBV, HTLV-1 |                        |
| Orbital lymphoma                            |                                               | Chlamydia psittaci     |                        |
| Thyroid lymphoma                            |                                               | Hashimoto's thyroiditis |                        |
| Lymphoma in the pleural cavity              |                                               |                        |                        |
| MALT lymphoma                               |                                               |                        |                        |
| Small-bowel lymphoma                        |                                               |                        |                        |

Continued on the following page
cells converted from QR cells were also augmented in parallel with their malignant potential.\textsuperscript{18} Histologically, we observed emergence of abundant microvilli on the surface of the tumorigenic cells, a common phenomenon observed in other malignant tumor cell lines of rodent and human.\textsuperscript{19}

We also determined several gene alterations through the inflammation-mediated conversion in this model (Fig. 3). The level of \textit{thymosin beta4} gene, which is known to be an actin-regulating protein and function for angiogenesis and wound healing, was elevated in all of the arising tumor cells. From the results of sense and antisense cDNA transfection experiments, we revealed that \textit{thymosin beta4} gene was responsible for tumor forming and/or metastasis through regulating cell motility.\textsuperscript{20} The expression of E1AF, a member of the \textit{ets} oncogenic transcription factor, was found high in the arising tumor lines.\textsuperscript{21} E1AF regulates tumor cell motility and invasive activities through induction of membrane-type 1-matrix metalloproteinase (MT-1-MMP) which converts the latent form of matrix metalloproteinase-2 (MMP-2) into active form.\textsuperscript{21} Thus E1AF makes tumor cells invasive.\textsuperscript{21}

We used foreign bodies to induce inflammation at the implanted site locally, which was to demonstrate direct association between inflammation and carcinogenesis in vivo. Evidence for the effects of inflammatory cells on carcinogenesis was also demonstrated by the following three experiments: i) By histological examination, we found that neutrophils predominantly infiltrated into the inserted gelatin sponge in the very early phase.\textsuperscript{22} ii) To confirm the role of infiltrated neutrophils in inflammation, we eliminated neutrophils by administering anti-neutrophil antibody (RB6). As a result, nearly all the arising tumors in the mice, non-treated or treated with control IgG, acquired malignant phenotypes. On the other hand, in RB6 antibody-administered mice, arising tumors did not acquire malignant phenotypes.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{A mouse model of inflammation-related carcinogenesis. Regressive cells (QR) spontaneously regress in syngeneic normal mice after subcutaneous injection (A). Tumorigenic conversion was observed in QR cells injected into subcutaneously pre-injected gelatin sponge (B). Tumorigenic conversion was also observed in QR cells which were mixed with gelatin-sponge-infiltrated inflammatory cells and injected in mice (C). The model was also utilized to screen candidate drugs to prevent inflammation-related carcinogenesis (D).}
\end{figure}
(Fig. 2D).22 iii) We further confirmed the results in integrin-beta-2 knockout mice (C57BL/6Itgb2tm1Bay equivalent to CD18-deficient). Integrin-beta-2 is the key adhesion molecule for the migration of neutrophils into an inflammatory region. Neutrophil infiltration into gelatin sponge was abolished and acquisition of tumorigenic phenotypes was suppressed in the integrin-beta-2 knockout mice.22 These findings show that neutrophils are one of the main components of inflammation-associated tumor development and progression. Interestingly, the capability of neutrophils to accelerate tumor cell malignancy varies depending on their activation phase, which we suggest from the finding that circulating or bone marrow neutrophils do not convert regressive cells into malignant ones but infiltrated (activated) neutrophils do.22

ROS produced by infiltrated inflammatory cells are the major cause for carcinogenesis
We assumed that reactive oxygen species (ROS) would be key molecules that stimulate carcinogenic process since ROS act on both initiation and promotion of cancer. To determine the direct contribution of ROS to the carcinogenesis in our model, we used gp91phox gene-knockout mice. Bactericidal function of neutrophils brings about generation of superoxide anions by forming NADPH oxidase complex (gp22phox, gp40phox, gp47phox, gp67phox, gp91phox and Rac1/Rac2) from interaction with cytochrome b558. The frequency of tumor development from the QR cells co-implanted with gelatin sponge was decreased in the gp91phox–/– mice.23 To determine whether phagocyte-derived ROS were actually involved in tumor development, we isolated phagocytes from wild-type mice and transferred them into gp91phox–/– mice.

![Diagram](image-url)

**Fig. 3.** Alteration of key molecules through foreign-body-induced carcinogenesis in mice. A diagram of stepwise molecular alterations in QR cells associated with acquisition of malignant phenotypes, accelerated by inflammation.

**Fig. 4.** Advantages of using gelatin sponge for investigating inflammation-related carcinogenesis. There are advantages in using gelatin sponge for analyzing the inflammation-related carcinogenesis since sponge-infiltrated inflammatory cells can be collected by brief collagenase treatment. Then we can quantify inflammation by counting the number of infiltrated cells. Moreover, by using the infiltrated cells, we are able to analyze the inflammation by biological, molecular genetical, and cytological methods.
As a result, wild-type-derived phagocytes increased the frequencies of tumor development. In contrast, the phagocytes obtained from gp91^phox^-gene-knockout mice did not have such activity. Moreover, administration of aminoguanidine, a broad inhibitor for inducible nitric oxide synthase, partially but significantly suppressed conversion in the model; thus we concluded that nitric oxide (NO) was also involved in the process. These results show that ROS and NO, derived from foreign-body-induced inflammatory cells, are an intrinsic factor in the conversion of regressive cells to more malignant ones.

**Attempts to prevent inflammation-related carcinogenesis**

When we determined the cause of inflammation-related carcinogenesis, it appeared that the carcinogenesis would be theoretically preventable: ROS are one of the most crucial genotoxic mediators to accelerate the carcinogenic process; then their antagonists, namely antioxidative enzymes or antioxidants, will be effective to prevent the process (Fig. 2D).

Accordingly, we tried to induce an antioxidative enzyme, superoxide dismutase (SOD), at the inflammatory site, hopefully by administration of orally active SOD, in our model. We used a newly developed SOD, named oxykine; as a result, the incidence of tumor formation was significantly decreased due to induction of manganese-SOD (Mn-SOD) in the inflamed region, compared to the one under control vehicle treatment. It should be noted that Mn-SOD was induced secondarily to activation of host intestinal immunity instead of the drug’s direct action to the inflamed site. Thus Mn-SOD was induced at the inflamed site and the inflammation-related carcinogenesis was suppressed. Based on these rationalies for effective prevention of inflammation-related carcinogenesis will be either by suppressing ROS production of inflammatory cells or by blocking infiltration of inflammatory cells into the inflamed site.

**CONCLUSION & PERSPECTIVE**

Inflammation, especially chronic one, is the definite cause for tumor development and progression, and it is well referred to as “inflammation-related carcinogenesis”. The pathogens that cause various types of inflammation-related carcinogenesis are obviously unrelated, whereas the essential pathological feature in common is continuous inflammation: initially infiltration of activated phagocytes/lymphocytes and then stimulated reaction of stroma composed mainly of fibroblasts and angiogenesis-related cells. It is assumed that continuous generation of ROS and NO by these infiltrated inflammatory cells is likely to injure normal cells. This could, in turn, cause compensatory cell proliferation, which will help accumulation of DNA damages/gene mutations and effectively incorporate internal/external carcinogenic factors into the growth of stimulated normal cells. Apart from those, it has recently been revealed that inflammatory environments accelerate epigenetic alterations and the alterations could cause inflammation-related carcinogenesis. All these events accompanying inflammation are essential to carcinogenesis. In this sense, we may understand that an inflammatory environment is a niche for carcinogenesis.

Intriguingly, we noticed that all the chronic inflammation and dysregulated immunity do not always lead to carcinogenesis; for instance, some of the chronic inflammatory diseases are not linked to cancer risk, and some are even leading to tumor regression. For instance, rheumatoid arthritis is not linked to cancer risk even though the inflammatory regions in rheumatoid arthritis patients show mutations of tumor suppressor genes at similar frequencies to those in the digestive tract tumors arising from chronic inflammatory reaction. Another thing to be noted here is that parasite (helminth, *Trichuris suis*) could diminish inflammatory response, and now its effects on inflammatory bowel diseases are under investigation. We may be able to determine the nature of inflammation which accelerates carcinogenesis by comparing the typical two types of inflammation, i.e., pro-carcinogenic and anti/unrelated-carcinogenic ones.

In our mouse model, inflammation induced by gelatin sponge insertion causes acute-phase inflammation, which will not become chronic since the sponge is absorbed spontaneously in the body. The actual inflammation leading to carcinogenesis is mostly chronic; possibly there is some link between acute-phase inflammation and chronic inflammatory diseases. A few techniques are available to pursue researches of this aspect: Apheresis technology has made it possible to eliminate granulocytes and monocytes specifically from the patients with ulcerative colitis. By meta-analysis study, those patients with intensive granulocytes and monocytes adsorption make the higher rate of shift to clinical remission. It is important to find out whether there are some types of regulatory inflammatory cells in the early phase of inflammation that may maintain and prolong inflammation. We have not fully elucidated the mechanisms of inflammation: how chronic inflammation is induced, activated, maintained and resolved; whether chronic inflammation is triggered by preexisting acute inflammation or it develops independently. We should now move on to identify key regulators for induction/maintenance of chronic inflammatory reaction that closely link to carcinogenesis, among which acute-phase inflammatory cells may be.
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