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Multifaceted functions of chronic inflammation in regulating tumor dormancy and relapse

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Abstract

Inflammation is a double-edged sword exhibiting multifaceted functions. On one hand, it either induces tumor cell apoptosis, or establishes tumor dormancy by inhibiting tumor cell proliferation; on the other hand, it either facilitates the tumorigenesis process or reawakens dormant tumor cells, resulting in disease recurrences. Each outcome would depend on the balance between type I and type II inflammation as well as the duration of inflammation being acute or chronic. In this essay, we provide a critical review of the empirical evidence suggesting that chronic inflammation, dominated by type I inflammatory cells and cytokines as a result of trauma and microbiome dysbiosis, could facilitate the carcinogenesis process in normal cells and retain nascent transformed cells in a dormant state. On the other hand, an elevated type II inflammation along with inefficient resolution of type I inflammation following trauma or major surgeries could delay the wound healing process and promote the growth and reawakening of dormant tumor cells, resulting in disease recurrences. Finally, cytokines exhibiting type I and II inflammatory functions, simultaneously, tend to promote tumor recurrence when become chronic. Therefore, the risk of reawakening dormant tumor cells should be considered in cancer survivors who experience major surgeries and trauma, or suffer from chronic inflammatory diseases.

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Keywords

Tumor dormancy; inflammation; periodontal disease; autoimmune diseases; trauma

The characteristics of tumor dormancy: relapse or not relapse?

Tumor cell dormancy is defined by the presence of viable malignant cells that either do not proliferate (quiescent tumor dormancy) or their sluggish proliferation is counterbalanced by apoptosis (indolent tumor dormancy). Tumor dormancy exists in two forms: i) naturally-occurring tumor dormancy in healthy individuals prior to the appearance of primary cancer, and ii) treatment-induced tumor dormancy in cancer survivors prior to the appearance of metastatic recurrences [1]. A trace of dormant cells can also be detected at the site of clinically active cancer as Ki67 negative quiescent cells, engulfing proliferating tumor cells and protecting their survival [2–4]. Naturally-occurring tumor dormancy is established as a result of the function of tumor suppressor genes and/or tumor immunosurveillance [1,5]. Treatment-induced tumor dormancy is the result of tumor cell clones responding to cancer therapies by becoming quiescent rather than undergoing apoptosis [6,7]. Therefore, tumor dormancy differs from drug resistance, where cancer cells continue to grow without responding to treatments. Although some dormant tumor cells might show stemness properties, they are not necessarily cancer stem cells [2]. The evolutionary conserved mechanisms of survival in normal cells from which tumor cells arise, protect some tumor clones from treatment-induced apoptosis by driving them into the state of dormancy. In fact, humans have evolved two major mechanisms of cell survival which include: i) tumor-intrinsic mechanisms such as, metastasis suppressor genes and cell cycle checkpoint molecules which could inhibit proliferation of malignant cells, and ii) tumor-extrinsic mechanisms regulated by the immune surveillance, which could either eliminate or inhibit proliferation of the nascent transformed cells, thereby facilitating the establishment of immunogenic tumor dormancy. In fact, Th1 cells have been reported to inhibit HER2 positive tumors such that loss of anti-HER2 or anti-HER3 Th1 response was found to be associated with tumor recurrences [8,9]. We have recently proposed the adaptation model of immunity in which several adaptation receptors regulating tumor cell survival and dormancy are discussed [10].

Dormant tumor cells could remain quiescent longer than the lifespan of a host without causing primary cancer or metastatic recurrences [11]. They could also exit from the state of dormancy and establish primary or metastatic cancers [12,13]. Among breast cancer types, HER2 positive and triple negative breast cancers (TNBC) have the highest recurrence rates within two years [14]. Within 10 years, the highest rates of distant recurrence and regional recurrence are reported in HER2 positive and TNBC, respectively [14]. The decision-making mechanisms to relapse or not relapse, as well as to relapse early or late, are not fully understood. Increasing evidence suggests that inflammation and microbiome dysbiosis play an important role in decision-making process and facilitate tumor recurrences.

Inflammation: from promoting carcinogenesis and retaining tumor dormancy to reawakening dormant tumor cells and resulting in tumor relapse

Inflammation is a process which contains two steps or components including type I and type II inflammation. Type I inflammation is characterized by the production of pro-inflammatory cytokines/chemokines, which is required during the induction of a host-protective immune response against pathogens or cancers. Type II inflammation is characterized by the production of either type I inflammation-resolving chemokines, or anti-inflammatory cytokines facilitating cell proliferation and wound healing mechanisms. During a normal wound healing process and natural defense mechanism, type I inflammation is resolved or replaced with a type II inflammation as soon as it has served its purpose. However, when type I inflammation fails to serve its purpose and becomes chronic, it promotes the carcinogenesis process in normal cells through STAT3 activation, the accumulation of oxidative DNA damage and gene mutations [15]. This is evident by detecting a higher incidence of colorectal cancer in patients with inflammatory bowel disease [16]. Anti-tumor function of type I inflammation could inhibit proliferation of the nascent transformed cells or primary tumor cells and support tumor dormancy. However, both types of inflammation could occur simultaneously, when becoming chronic, with one being predominant over another. In fact, subdominant levels of type II inflammation during type I inflammatory responses might induce wound healing mechanisms, facilitating the reawakening of dormant cells and tumor relapse. This could explain a strong correlation between inflammation and recurrence of endometrial cancer [17], oral cancer [18] and breast cancer [19,20]. Also, major accidents and trauma which induce inflammation and tissue healing mechanism could facilitate tumor relapse as suggested by case reports. A patient who was treated for non-small lung cancer experienced rapid tumor growth and reoccurrence following a minor car accident near a trauma site in his skull bone [21]. Therefore, an acute/transient type I inflammation would be an ideal because of its anti-tumor function without becoming chronic to induce carcinogenesis in normal cells. In contrast, a chronic type II inflammation could facilitate the reawakening of dormant tumor cells by producing tissue-regenerating factors VEGF and TGF-β, and result in disease recurrences.

Chronic type I inflammation promotes de novo cell transformation

Traumatic inflammation, oral cancer and beyond.

Chronic trauma induces type I inflammation characterized by the production of inflammatory cytokines, prostaglandins and TNF by injured tissues as well as infiltrating immune cells. This type of inflammation in turn leads to oxidative DNA damage and cell cycles arrest affecting both normal cells and nascent transformed cells. This could result in a malignant transformation of normal cells locally, or in distant organs if it becomes systemic. Very recently, it was demonstrated that inflammation-initiated tumorigenesis can be prevented by inducing the resolution of inflammation using dual COX-2/sEH inhibitor [22]. A retrospective study in Australia revealed that the lateral side of tongue is the most common site of oral cancer in nonsmokers, perhaps because of a chronic dental trauma [23].

This study confirmed a previously published work examining 28 patients with oral cancer in a dental set up, demonstrating that all tumors occurred in areas of contact with teeth and/or dental application [24]. A retrospective study conducted on 406 patients between the ages of 18 and 80 with oral potentially malignant disorders (OPMD), oral cancer or healthy controls showed that chronic trauma of the oral mucosa is associated with carcinogenesis, and should be considered in follow-up protocols [25]. Also, a case-control study in Brazil demonstrated a significant association between ill-fitting dentures and oral cancer [26]. These carcinogenic effects are not merely due to dentures because, while chronic trauma due to tooth loss shows a strong correlation with oral cancer, well fitted dentures show no association with cancer [27,28]. Some other studies have shown a significant association between oral hygiene and oral cancer [29,30]. In fact, oral trauma and related sores may be colonized by candida or human papillomavirus (HPV) and in turn promote inflammation and epithelial dysplasia [31,32]. Thus, trauma and injury might synergize with microbiome dysbiosis and promote chronic inflammation and cancer. A review of emerging evidence suggests a link between periodontal disease and oral cancer with chronic inflammation being a major factor in both diseases [33]. Chronic periodontitis was associated with chronic *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *candida*, and other microbes [33]. Examination of saliva samples from 45 patients with oral squamous cell carcinoma (OSCC) and 229 OSCC-free subjects showed that an elevated *Capnocytophaga gingivalis*, *Prevotella melaninogenica* and *Streptococcus mitis* was detected in patients with OSCC [34]. Several other periodontal bacteria have shown a strong association with squamous cell carcinoma [35]. The association is because of the production of inflammatory cytokines, including TNF-α, IL-1β, and IL-6, being induced by oral microbiome dysbiosis [35].

Periodontal disease could promote tumorigenesis at distant sites when chronic inflammation becomes systemic. The analysis of 50 studies published between 2011 and 2016 identified a positive association between periodontal disease and risk of oral, lung, and pancreatic cancers [36]. Examination of 1,337 postmenopausal women who participated in the Buffalo OsteoPerio Study demonstrated that periodontal diseases were associated with increased total cancer risk, as well as an increase in lung cancer risk specifically [37]. Another prospective study conducted between 1986–2004 in which 48,375 men aged 40–75 with no history of cancer were included, periodontal disease was associated with an increased risk of carcinogenesis, which persisted in non-smokers [38]. After adjusting for known risk factors, including smoking and dietary habits, those with history of periodontal disease showed a 14% increase in total cancer cases compared with those with no history of periodontal disease. In addition, the risk for hematopoietic cancers, lung cancer, esophageal cancer, kidney cancer, and pancreatic increased by 30%, 36%, 44%, 49%, and 54%, respectively [38]. Another study conducted in 15,333 patients showed increased cancer cases by 15% in those with periodontal disease, after adjusting for known risk factors [39]. Specifically, the risk for corpus uterine cancer, colorectal cancer, pancreatic cancer, and prostate cancer increased by 120%, 62%, 106% and 47% respectively [39].

Inflammatory chronic wounds and in situ cancers.

Chronic wounds are the result of a failure to resolve type I inflammation. Published evidence suggest a link between chronic foot ulcers observed in diabetes mellitus patients

and formation of cutaneous squamous cell carcinoma (cSCC) [40]. A chronic ulcer in a 35-year-old female with ringworm in the upper extremities for ten years developed to cSCC. The case report concluded that it could be a result of recurrent trauma over a long period [41]. Also, a 67-year-old male who suffered from an ulcer at the base of his foot for 8 years, which was infected with *E. coli*, *Pseudomonas aeruginosa*, *Staph. aureus*, and anaerobic species, developed highly differentiated carcinoma spinocellulare (SCC). The second case was a 72-year-old woman who also had a foot ulcer for 8 years suffering from PAD who developed SCC. The article concluded that histological samples should be taken from chronic wounds in order to test for possible carcinoma [42].

Inflammatory microbial dysbiosis and cancer.

Obesity is also associated with chronic self-directed tissue inflammation [43] and has been indicated in cancer prevalence. Western diet induces microbial dysbiosis by promoting an inflammatory microbiome [44] which facilitates carcinogenesis when it becomes chronic [45,46]. A low-grade inflammation is present in adipose tissue of obese individuals, making it similar to the tumor microenvironment by producing a high ratio of reactive oxygen species (ROS) to antioxidants. This in turn increases the risk of mutation as well as tumor relapse [47]. Adipose tissue in obese patients also produces high levels of tumor-promoting hormones such as leptin and estrogen, as well as low levels of the tumor suppressant hormone adiponectin [47]. Also, there is a strong association between inflammation and colorectal cancer [48], which is mediated by the gut microbiota [49]. In patients who received curative colorectal tumor resection, the Western diet Patients who underwent curative resection of colorectal cancer showed increased collagenolytic microbes in the intestine leading to tumor recurrence [50,51]. Another study showed that diet induced obesity accelerates chemically induced colitis-associated colorectal cancer (CAC) in mice via increased inflammation and immune cell recruitment [52]. Specifically, obesity induced IL-6 shifting macrophage polarization towards tumor promoting macrophages that produce chemokine CCL-20 in the tumor microenvironment [52]. The excess adiposity in overweight and obese patients is associated with mammary adipose tissue inflammation, which is an event that could contribute to breast cancer development and progression [53]. It was also reported that chemotherapy shifts the breast tumor microbiome, and that specific microbes, *Brevundimonas* and *Staphylococcus,* correlate with tumor recurrence [54].

Chronic type I inflammation eliminates some tumor cells and establishes dormancy in some other clones

Tumor elimination and equilibrium.

A recent review of literature on immunogenic tumor dormancy underscores the role of pre-existing T cell responses toward non-mutated tumor-associated antigens in healthy individuals in maintaining tumor dormancy [55]. The role of type I inflammatory cytokines released by CD8+ T cells, CD4+ Th1 cells, group 1 innate lymphoid cells (ILC-1) or M1 macrophages in inducing apoptosis or inhibiting proliferation of malignant cells is well established. Multifaceted function of the inflammatory immune responses against malignant cells is because of cell-intrinsic heterogeneity of tumor cells in responding to

inflammation as well as their heterogeneity in the expression of cytokine receptors. For instance, pro-inflammatory TNF-α could induce apoptosis or support cell survival and induce cell cycle arrest depending on the expression of TNFR1 and TNFR2 on tumor cells. While the engagement of TNFR1 induces apoptosis [56], activation of TNFR2 leads to increased cell survival [57]. TNFR2 lacks a death domain and activates pro-survival pathways through the recruitment of TRAF2 and subsequent activation of PKB/Akt and NF-κB pathways [57]. Kinase suppressor of Ras-1 (KSR1) also regulates TNF-activated anti-apoptotic signals in intestinal epithelial cells [58]. Therefore, TNFR2 could be a potential adaptation receptor relaying survival signal upon the engagement with the adaptation ligand, TNF-α [59]. Another pro-inflammatory factor is called endothelin 1 (ET-1), which is released during Th1 inflammation and T cell activation [60]. This ligand has receptors A (ET_A) and B (ET_B). Binding of ET-1 to ET_A results in the activation of anti-apoptotic Bcl-xL and support tumor cell survival whereas its binding to ET_B induces tumor cell apoptosis [61]. In fact, a higher responsiveness of melanoma to immunotherapy compared to prostate cancer or ovarian cancer is, in part, due to a higher expression of the ET_A in prostate and ovarian cancers but not in melanoma [62]. IFN-γ is another inflammatory cytokine released by Th1, ILC-1 and CD8+ T cells which is capable of inducing tumor cell apoptosis or cell cycle arrest and tumor dormancy [63], depending on the status of p53 expression in target cells [64,65]. Recently, we proposed the adaptation model of immunity to explain the multifaceted functions of the immune system in facilitating tumor growth, tumor cell death, tumor dormancy or relapse simultaneously [10].

Although type I inflammation has a dual function on inducing carcinogenesis and inhibiting the growth of nascent transformed cells, tumor specific inflammatory T cells could support tumor dormancy without inducing carcinogenesis in normal cells. For instance, CD8+ T cells can inhibit tumor growth such that their depletion results in the outgrowth and relapse of metastatic dormant cells [66,67]. In a murine model of B-cell lymphoma, IFN-γ–producing $CD8^+$ T cells were shown to establish and maintain tumor dormancy [68]. Very recently, we have reported that both local and distant breast cancer dormancy are associated with infiltrating T effector subsets while lack of tumor dormancy is associated with the tissue residing T central memory or T naïve subsets, suggesting that T effector cells retain tumor cells in the state of dormancy [2]. This possibility was further confirmed, ex vivo, by demonstrating that T effector cells inhibit the reawakening of freshly isolated dormant cells [2]. Ex vivo studies in human breast tumor cell lines showed that while M1 inflammatory macrophages contribute to tumor dormancy, M2 macrophages facilitate tumor relapse [69]. The results of this study suggest that inducing the MErT program in dormant micrometastases by M1 macrophages may be a novel approach to maintaining the dormant state [69]. Other studies have investigated the role of IFN-γ producing CD4+ Th1 cells on tumor dormancy showing that the combined effect of type I inflammatory cytokines, IFN-γ and TNF, induce T antigen (Tag)-expressing cancers and murine breast cancers into senescence [70]. Since long term dormancy is caused by senescent cells, it could be concluded that these inflammatory cytokines help drive the cancer cells into dormancy [71]. Studies in an experimental model of Tag-induced multistage carcinogenesis demonstrated that Tag-specific CD4+ Th1 cells induced tumor dormancy, while the absence of either IFN-γ signaling or TNFR1 signaling promotes carcinogenesis in the same Tag-specific Th1

cells [72]. Thus, they concluded that IFN-γ signaling and TNFR signaling on endothelia induces tumor dormancy [72]. In addition to Th1 cells, CD8+ T cells could regulate dormancy by producing inflammatory cytokines [72]. Very recently, it was demonstrated that ER- breast cancer cells that survived high-dose Doxorubicin and Methotrexate chemotherapies elicit a state of immunological dormancy by the activation of the IRF7/IFN-β/IFNAR pathway is critical to this process [73]. High levels of IFN-β activates STAT1, STAT2 and STAT3 signaling pathways to facilitate cellular dormancy in tumor repopulating melanoma cells [73].

Chronic inflammatory diseases and tumor dormancy.

Multiple studies have indicated a correlation between inflammatory autoimmune rheumatoid arthritis (RA) and incidence of cancer. For instance, one study performed a cross sectional analysis of patients with RA and demonstrated an increased risk of malignancy [74]. Another retrospective case control study collected data from the Veterans Integrated Service Networks database to investigate the association between RA and lung cancer and determined that patients with RA are 43% more likely to develop lung cancer than patients without RA [75]. Data analysis from a population based National Health and Nutrition Examination Survey (NHANES) determined an increased incidence of cancer in patients with RA, with an odds ratio of 1.632 [76]. Patients with inflammatory bowel disease (IBD) are twice as likely to suffer from colorectal cancer [77]. One study examined cancer risk in the early stages of IBD in Korean patients and showed that patients with IBD are at increased risk for overall intestinal and hematological cancer [78]. Patients with RA show chronically elevated levels of the type I inflammatory cytokine TNF-α, and type II inflammatory cytokines IL-33 and IL-6 being involved in both type I and II inflammation [79]. Similar observations were made in patients with IBD showing Th17 cells producing IL-17 and IL-22. It is likely that inflammatory immune responses in patients with RA or IBD maintain transformed cells in a dormant state such that immune suppressive drugs for the treatment of the disease rescue dormant tumor cells from immune surveillance and result in a higher incidence of cancer. This possibility is supported by a nested case-control study on patients with rheumatologic conditions including RA, psoriatic arthritis and ankylosing spondylitis currently receiving TNF inhibitors (TNFi) showing a positive association between TNFi and risk of non-Hodgkin lymphoma (NHL) [80].

Chronic type II inflammation facilitates tumor recurrences

Type II inflammation is associated with the elevation of M2 macrophages, group 2 innate lymphoid cells (ILC-2), and CD4+ Th2 cells, which play an essential role in the resolution of type I inflammation leading to tissue regeneration/repair during wound healing. Therefore, cell growth promoting wound healing mechanisms triggered following trauma or major injuries may also promote the reawakening of dormant tumor cells. To this end, ILC-2 cells were found to be associated with tumor relapse in an animal model of bladder cancer [81]. Also, Th2 and Tcm (T central-memory) cells have been shown to be associated with the recurrence of prostate cancer [82]. In breast cancer, perivascular M2 macrophages were found to induce tumor relapse after the completion of breast cancer chemotherapies [19]. The relapse inducing M2 macrophages promote revascularization, in part, via the release of VEGF-A angiogenic factor. While there are several cases suggesting that trauma can directly induce

tumor relapse, a study by Allawi et al. [83] suggested otherwise. This is because the patients included in their analysis were not representing an actual model of dormancy. The analysis was performed on 9366 patients with early-stage breast cancer who were receiving cancer therapies including Tamoxifen with anastrozole alone or the combination of anastrozole plus tamoxifen. About 64% of these patients had a primary tumor. In addition, patients who started chemotherapy more than 8 weeks after surgery, or completed their cancer therapies were not included in the trial. In their study, the patients' trauma may not have induced chronic inflammation, as they were treated with tamoxifen, which has been reported to bear anti-inflammatory properties [84].

In a biological system, type I and II inflammation are present concurrently with one being predominant than another. Therefore, inflammation exhibits multifaceted functions by inducing tumor dormancy and tumor relapse, simultaneously. For instance, ILC-3 and Th17 cells producing both IL-17, which inhibits tumor cell proliferation, and IL-22, which promotes tumor growth and relapse. The outcome would depend on which pathway may become predominant while interacting with other inflammatory cells. Preclinical and clinical studies of premalignant oral lesions have shown increased levels of inflammatory cytokines such as IL-6, TNF-α and IL-17; but these cytokines subside as premalignant lesions progress to squamous cell carcinoma [85,86]. Also, patients with benign salivary gland tumors had higher levels of IL-17 producing Th17 cells compared to those with malignant salivary gland tumors [87]. Similar observations were made in melanoma patients exhibiting higher levels of Th17 cells being associated with better survival following vaccination with survivin-derived peptides [88]. However, in breast cancer and colorectal cancer, Th17 cells promote tumor progression [89,90]. The tumor promoting effect of IL-17 was not due to the function of Th17; it was due to the recruitment of neutrophils that promoted tumor progression [89]. These data suggest the relapse inhibitory role of these cytokines during tumor dormancy such that their disappearance facilitates tumor relapse. Th17 cells also produce IL-22 by which they protect the intestinal epithelium from damage and promote its regeneration. It was demonstrated that IL- 22- induced proliferation of epithelial cells enhance the growth of colorectal cancer [91] and lung cancer [92]. IL- 22 producing Th17 and ILC-3 cells were identified in human non- IBD cancer samples compare to adjacent healthy tissue [93]. In breast cancer, the IL-22-induced MAP3K8 signaling pathway promotes tumor progression [94]. Periodontitis is associated with the presence of pathogenic bacteria that initiate inflammation with increased levels of tissue damaging inflammatory cytokines IFN-γ, TNF-α, IL-6 and IL-1β as well as the host protective IL-11 producing Th2 cells [95]. IL-11 counteract TNF-α, IL-6 and IL-1β and reduces tissue damage [95]. Another cytokine, IL-33 promotes TNF-α production by Th1 cells as well as inhibits apoptosis and promotes cell growth and proliferation during wound healing process [79].

The rate of distant recurrence of breast cancer is greater and faster in patients with TNBC than in patients with HER2 positive tumors. Also, patients with hormone receptor positive breast cancer show delayed tumor relapse compared with both TNBC and HER2 positive breast cancer. This is thought to be due to tumor intrinsic factors as well as the tumor stage, while less attention has been paid to the host-driven inflammatory immune responses to cancer therapies that varies for breast cancer types. Unlike TNBC, patients with hormone receptor positive breast cancer receive tamoxifen, and those with HER2 positive tumors

receive antibody therapies. Interestingly, the relapse promoting function of the angiogenic factors was ablated by tamoxifen which is an anti-inflammatory compound [84]. Preclinical studies demonstrated the anti-inflammatory activity of the tamoxifen derivative, Ridaifen-B (RID-B), by reducing NO, IL-6 and IL-1α [96]. IL-6 is involved during type I and type II inflammation associated with tumor recurrence [97]. Binding of IL-6 to the membrane IL-6 receptor α (mIL-6 Rα) induces anti-inflammatory classic signaling, whereas its binding to soluble IL-6 receptor α (sIL-6 Rα) induces pro-inflammatory trans-signaling [98]. In animal models of spinal cord injury (SCI), tamoxifen was able to reduce the expression of NF-kB p65, thereby inhibiting the production of pro-inflammatory cytokines [84]. In general, patients with ER+ breast cancer tend to have lower levels of sIL-6 Rα than those with ER- breast cancer, and patients with higher levels of sIL-6 Rα show increased recurrences [99]. sIL-6R is an inflammatory factor facilitating IL-6 trans-signaling in tumor cells and subsequent tumor cell proliferation and relapse [100,101]. In fact, a higher rate of recurrences of HER2+ and TNBC compared to ER+ breast cancer is associated with elevated levels of IL-6, facilitating an autocrine feedback loop through IL-6-activated STAT3 [102,103]. It is well-known that obesity is associated with a 35% to 40% increased risk of breast cancer recurrence due to chronic inflammation [104]. Interestingly, obesity tend to increase M2-biased macrophages [105] that are involved in wound healing and cell proliferation.

Conclusions

Chronic inflammation contains type I and II inflammatory cells and cytokines/chemokines exhibiting multifaceted functions by orchestrating tumor cell apoptosis, tumor dormancy and relapse. As shown in Table 1, a predominant type I inflammation such as Th1 cells, M1 macrophages and ILC-1 cells as well as their cytokines TNF-α, IFN-γ, IL-17 or sIL-6 Rα often promotes tumor dormancy. Therefore, the inhibition of anti-tumor inflammatory T cells could result in the rescue of dormant cells from immune surveillance and subsequent tumor relapse. On the other hand, a predominant type II inflammation including Th2 cells, M2 macrophages and ILC-2 cells as well as their cytokines IL-11, IL-22, IL-33 or mIL-6 Rα facilitates the reawakening of dormant cells leading to tumor relapse. To this end, the wound healing process following a traumatic event or surgery might trigger the reawakening of dormant tumor cells through the release of cell proliferation-inducing cytokines and growth factors. Finally, cells or cytokines that are involved in both type I and II inflammation tend to promote tumor relapse when their anti-inflammatory function becomes predominant over their pro-inflammatory function. For instance, a higher expression of mIL-6 Rα than sIL-6 Rα inhibits apoptosis and promotes anti-inflammatory function of IL-6 on tumor cells. Therefore, modulation of inflammation is expected to be more effective than the use of anti-inflammatory compounds for the prevention of tumor relapse.

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Conflict of Interest

A conflicting interest exists when professional judgment concerning a primary interest (such as patient's welfare or the validity of research) may be influenced by a secondary interest (such as financial gain or personal rivalry). It may arise for the authors when they have financial interest that may influence their interpretation of their results or those of others. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

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Table 1.

The role of chronic inflammation in tumor dormancy and relapse

Inflammation	Cytokines	Cells	Outcome
Type I	TNF-α, IFN-γ, IL-17, IL-6/sIL-6 Rα	Th1, M1, ILC-1	Tumor dormancy
Type II	IL-11, IL-22, IL-33, IL-6/mIL-6 Rα	Th2, M2, ILC-2	Tumor relapse
Type I/II	mIL-6 Rα > sIL-6 Rα	Th17, ILC-3	Tumor relapse