Title
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Journal
Cancer Research, 77(14)

ISSN
0008-5472

Authors
Lasry, Audrey
Aran, Dvir
Butte, Atul J
et al.

Publication Date
2017-07-15

DOI
10.1158/0008-5472.can-16-3383

Peer reviewed

Published in final edited form as:

Cancer Res. 2017 July 15; 77(14): 3740–3744. doi:10.1158/0008-5472.CAN-16-3383.

Cancer cell autonomous parainflammation mimics immune cell infiltration

Audrey Lasry[1,*], **Dvir Aran**[2,*], **Atul J. Butte**[2], and **Yinon Ben-Neriah**[1]

[1]The Lautenberg Center for Immunology and Cancer Research, IMRIC, Hebrew University—Hadassah Medical School, Jerusalem, Israel, 91120

[2]Institute for Computational Health Sciences, University of California, San Francisco, California, United States of America, 94158

Abstract

Parainflammation is a unique variant of inflammation, characterized by epithelial-autonomous activation of inflammatory response. Parainflammation has been shown to strongly promote mouse gut tumorigenesis upon p53 loss. In a recent study, we explored the prevalence of parainflammation in human cancer and determined its relationship to certain molecular and clinical parameters affecting treatment and prognosis. Parainflammation can be identified from a 40-gene signature, and is found in both carcinoma cell lines and a variety of primary tumors, independently of tumor microenvironment. Here we discuss the implications of our findings in analyses of tumor microenvironment, suggesting that as tumor cell gene expression may often mimic immune and inflammatory infiltration, caution should be applied when interpreting tumor expression data. We also address the connection between parainflammation and prevalence of p53 mutations in specific types of tumors, and cancer prevention by regular usage of NSAIDs. We suggest that parainflammation may serve as a novel biomarker for screening patients who may particularly benefit from NSAID treatment.

Introduction

Inflammation and growth are tightly linked, and evidence for inflammation driving aberrant growth can be seen even in organisms with a simple immune system, such as corals [1]. It is now widely accepted that inflammation is one of the hallmarks of cancer [2], yet seems to drive only a minority of solid tumors, mostly distinct types of cancer such as hepatocellular, gastric and inflammatory bowel disease (IBD)-associated colon carcinoma, arising following prolonged periods of chronic inflammation [3]. Thus, it is unclear why non-steroidal anti-inflammatory drugs (NSAID) are effective in reducing mortality rates in many cancer types, not known to be associated with chronic inflammation [4–6]. NSAID act by inhibiting the inflammatory enzyme COX2, which may explain their beneficial effects in cancers with a clear inflammatory background, where COX2 is indeed elevated. However, their beneficial effects in cancers where there is no known background of chronic inflammation, indicates

Correspondence: Yinonb@ekmd.huji.ac.il.

*Equal contribution

The authors declare no conflict of interest.

that we are probably still not familiar with the full scope of inflammatory reactions, including atypical ones which are not readily diagnosed, yet may also contribute to cancer. One such type of atypical inflammation is parainflammation (PI), a low grade inflammatory reaction, which is an intermediate state between basal homeostasis and chronic inflammation [7]. PI can be caused by internal cell insults, rather than exogenous factors, and by tissue stress. It is characterized by activation of many genes involved in innate immunity, but includes remarkably few chemokines or cytokines, and thus it does not lead to recruitment of immune cells and remains undetected histologically through a microscope. PI was first identified in a mouse model of colorectal cancer, where it acts hand in hand with the tumor suppressor p53 to help maintain gut homeostasis during oncogenic stress [8]. After loss of p53, parainflammation loses its tumor-suppressive nature to function oppositely in tumor promotion. In the mouse model, PI attenuation by NSAID treatment prevented tumor development, suggesting that PI may be relevant to the mechanism of action of NSAID in human cancers.

In our recent study [9], we sought to identify covert inflammation in human cancers. Using two mouse models of colorectal cancer, we characterized a PI gene signature, and went on to examine its presence and contribution to human malignancies, using data from the cancer genome atlas (TCGA) and the cancer cell line encyclopedia (CCLE). We then examined the relationship between PI and p53 mutations in human cancers, revealing a tight association between PI, p53 mutations, and worse prognosis. Finally, we demonstrated that human PI can be attenuated by NSAID treatment. Here, we highlight unique findings of our study and discuss the possible physiological roles of PI, as well as the implications of PI in diagnosis and treatment.

Parainflammation resembles immune infiltration

Translating findings from mouse models to clinically relevant diseases in humans is not a trivial task and only a fraction of mouse translation studies are in fact predictive of human disease [10]. The recent explosion of unprecedented publicly available genomic data sets provides an opportunity to relate findings from mouse models to human disease to a depth and breadth that could not be imagined even several years ago. To study the importance of PI in humans, we first devised a PI gene signature based on inflammatory response genes in human that are upregulated in two mouse models of PI. As a compiled list of human inflammatory response genes is not available, we combined three data sources to construct a short list of 840 genes brought up in at least two data sets. When intersected with the mouse model transcriptome, our PI signature consisted of 40 innate immunity genes, strongly resembling a type I interferon (IFN) response.

What distinguishes PI from canonical inflammation? The role of inflammation in cancer has been widely examined, and several types of inflammatory processes have been documented in cancer [3, 11, 12]. Acute inflammation is characterized by the five hallmarks of inflammation: redness, pain, heat, swelling and loss of function, which are all due to infiltration and activation of immune cells at the inflamed organ. Chronic inflammation is also characterized by cell infiltration. These hallmarks show up due to secretion of chemokines and cytokines by damaged cells, leading to a systemic inflammatory response to

the damaging agent. Yet, PI lacks all of the inflammatory hallmarks, and remains autonomous to the cancer cells themselves, quite distinct from a systemic response. We have previously shown this phenomenon in PI mouse models [8], and in our recent study [9] we describe its occurrence in carcinoma cell lines, where PI gene expression cannot be attributed to the microenvironment. Interestingly, we found only modest levels of PI in liver cancer, one of the most prominent cancers associated with chronic inflammation, suggesting that the two types of inflammation are differentially regulated and possibly mutually attenuated.

Furthermore, in both primary tumors and cell lines, our analysis showed a strong resemblance of PI with macrophage infiltrations (Figure 1). Macrophages are key players in chronic inflammation. Tissue resident and circulating macrophages are recruited to sites of chronic inflammation, where they can mediate clearance of damaged tissue and induce suppression of the inflammatory response [13]. Macrophages also play a key role in maintaining tissue homeostasis [14]. During homeostasis, tissue-resident macrophages act as sentinels to identify and respond to extrinsic and intrinsic changes. Furthermore, macrophages can also assist in tissue remodeling during normal developmental processes or due to injury [14]. Thus, it is possible that in PI-bearing tumors, parainflammation has a capacity to fulfill certain normal macrophage functions. In addition, the ability of PI to mimic the gene expression of some other immune cells raises the possibility that different cancer types may harbor different forms of PI, mimicking different immune subsets according to the tumors' needs. Indeed, recently an immune subset of glioblastoma was identified, with close resemblance to complement response [15].

Epithelial-hematopoietic transition of tumor cells and its impact on deconvoluting tumor transcriptome profiles

A major obstacle in studying innate immunity genes in expression profiles of bulk tumors is distinguishing the contribution of tumor-infiltrating lymphocytes (TILs), or other infiltrating inflammatory cells from the cancer cells themselves [16]. Whereas in epithelial cell lines inflammatory gene expression can readily be associated with PI, in primary tumors, intricate analysis, differentiating the tumor from its microenvironment, must be performed. To this end, we developed a strategy for excluding the contribution of immune cells' gene expression from the tumor's gene expression, based on analysis of the relevant genes in normal tissues and expression correlation with the hematopoietic marker CD45. To our knowledge, this procedure is the first attempt to 'clean' transcriptomic profiles of mixed tumors to derive the expression profile of the cancer cells themselves. A strong validation of our adjustments lies in the resemblance of adjusted PI abundance of primary tumor types to that of corresponding cancer cell lines. Cancer types with high PI abundance, such as pancreatic, bladder and head and neck cancers, showed high levels of PI expression in both cell lines and relevant primary tumors. In total, we identified PI expression in a quarter of all tumor samples, over a wide range of cancer types.

Macrophage-mimic of PI raises a difficulty in the emerging field of digital dissociation of the tumor microenvironment. In the past several years a handful of techniques have been

published in an attempt to deconvolve the transcriptomic profiles of tumors to their cellular composition [16]. While these techniques may perform well to characterize the cellular composition of non-cancerous samples, we would argue that they are prone to fail as a result of the ability of the cancer cells themselves to express immune-related genes. This 'masking' performed by the cancer cells, such as the macrophage mimicry, may be termed in general as 'epithelial-hematopoietic transition' (Figure 1), and raises doubts on the ability of gene expression-based techniques to rigorously identify enrichments of immune cell types in tumors. This may also have an impact in prognosis determination. The presence and type of immune cell infiltration in a tumor has become an important criterion in determining the prognosis of tumors [17]. Yet, this correlation may be biased by the ability of the tumor cells themselves to adopt characteristics of immune cells, which should be carefully considered in the clinic.

Parainflammation and p53

p53 mutation occurs in approximately 50% of all human tumors, yet it does not occur at the same frequency in all tumor types [18]. While it is a common event in some cancers, such as colorectal, pancreas, bladder and lung, in other cancers, such as kidney, melanoma and prostate, it remains rare. Yet, the propensity of some cancer types to undergo p53 mutation, while others do not, remains unexplained. In the PI-driven mouse models, PI is tightly linked to cellular senescence and as long as p53 is unmutated and active, contributes to tumor suppression, possibly by reinforcing tumor senescence. Once p53 is mutated, PI switches its face and turns to be a tumor promoter [8]. Along the same line, PI abundance in human cancer, correlates with rates of p53 mutation; high PI tumors tend to have high rates of p53 mutation. This correlation suggests that PI may be a driving force in inactivation of the p53 pathway.

It is thus possible that similarly to the mouse models, in early stages of human cancers, when p53 is still intact, PI acts as a barrier to tumor progression; an example is colorectal adenomas. Only 5% of these adenomas progress to carcinoma, usually following a series of mutations culminating in loss of p53 [19]. Mice bearing germline mutations in the APC gene, resembling the human FAP syndrome, have multiple intestinal adenomas that display variable PI levels. Intentional PI boost may therefore constitute a chemoprevention option to halt progression of benign tumors to invasive carcinomas in FAP patients. A recent study [20] demonstrated that combination of Sulindac with the EGFR inhibitor Erlotinib can reduce the number and size of duodenal polyps in FAP patients, suggesting that PI attenuation, rather than PI boost, may be beneficial for these patients. However, previous studies have demonstrated that Sulindac alone is not effective in preventing duodenal polyps [21, 22], suggesting that the effect of the combined treatment might stem mostly from EGFR inhibition, rather than the effect of Sulindac on PI.

The link between PI and p53 has intriguing implications for organisms lacking an immune system. In such organisms, PI may fulfill the role of overt inflammation in regulating tissue regeneration, limiting tissue regrowth following damage. The association of PI with p53 may also point to a physiological role of PI in normal tissues of more evolved organisms. p53 is activated following physiological stress, such as hypoxia, metabolic stress and oxidative

stress, and not just due to oncogenic stress [23]. Similarly, these physiological stresses may also activate PI, which may then act together with p53 to restore tissue homeostasis. This again might be particularly relevant during tissue regeneration following stress or injury, where excessive proliferation should be avoided. Loss of p53 during a normal regenerative process may thus be detrimental to the organism, driving malignancy.

Parainflammation and NSAID

PI can be attenuated by NSAID treatment in both mouse models and human cell lines [9]. Prolonged NSAID treatment has a surprising beneficial effect in many cancer types, where they can prevent or delay tumor onset [5] or recurrence in surgically-removed colorectal cancer [24]. The beneficial effect of NSAID in cancer was first documented in patients with a hereditary form of colorectal cancer, when the NSAID Sulindac was shown to delay tumor occurrence [25]. This effect was later described also in a mouse model of colorectal cancer, where mice treated with Sulindac also developed less tumors [26]. While the effect of NSAID in IBD-associated colorectal cancer may be simply attributed to their anti-inflammatory effect, ameliorating the bowel inflammatory disease, NSAID have also been suggested to be effective in delaying onset and recurrence in cancer types in which inflammation is not considered as tumor driver. Observational cohort studies have shown that prolonged NSAID treatment may have an effect in preventing pancreatic and lung cancers, and mixed findings were reported regarding breast and prostate cancers [5, 6, 27–29]. While these observations are awaiting validation in randomized clinical trials, we noticed that cancer types with reduced risk following prolonged NSAID treatment are characterized with PI abundance. Notably, in spite of the encouraging results of NSAID trials, NSAID treatment is not yet used as a common strategy for cancer prevention for patients at risk of developing breast, lung or prostate cancer, and have only recently been recommended as a prevention strategy for patients at high risk to develop CRC. This is due to adverse effects of NSAID treatment, particularly increased risk for gastrointestinal and brain bleeding in certain patients [30].

Our data suggests an overall correlation between the anti-tumorigenic effect of NSAIDs and the PI status of the tumors – tumors having poor PI values are seldom affected by NSAID chemoprevention, or may even take advantage of the treatment. Indeed, prolonged NSAID treatment has even been reported to increase the risk of renal cell carcinoma (RCC) [31]. RCC is characterized by low PI and a low rate of p53 mutations, which may suggest that PI attenuation has a negative effect when p53 is not mutated. We thus suggest that NSAID may act by attenuating cancer PI. One of the PI components is prostaglandin E2 synthase (PTGES), which is part of the COX2 pathway and when targeted by NSAID in PI-positive tumors, may provide a link between overt and covert inflammation.

In light of the retrospective-based studies assigning beneficial effects of NSAID in PI positive cancers, we propose a prospective study adding the PI status in weighing the benefits vs. risk of NSAID treatment for cancer prevention, assuming that patients harboring PI-positive tumors will maximally gain from the treatment.

Future directions

We have characterized a novel type of covert inflammation, parainflammation, with important implications for diagnosis and treatment of cancer. PI is characterized by a signature of innate immune genes, which resembles macrophage gene expression profiles, possibly shedding light on physiological roles of PI, both cell autonomous functions and a cross-talk to the tumor microenvironment. Cancer PI is associated with high rates of p53 mutation and worse prognosis, and can be attenuated by NSAID treatment, possibly providing a mechanism for the vastly noted effect of NSAID in cancer prevention and treatment. PI may then serve as a novel tumor biomarker, and implementation of PI screens in tumors may help characterize a subset of patients who will mostly benefit from NSAID treatment. Strong association of PI with prognostic parameters, indicates that routine PI screening of tumor samples may also have a significant value in determining cancer prognosis and treatment design accordingly. Tumor PI may also act as an immunomodulatory mechanism influencing immunotherapy of cancer, either negatively or positively. For example, PD-1 ligand (PD-L1) expression is indicative of the success of anti-PD1 treatment [32]. We found that PD-L1 gene expression is strongly linked to PI: PD-L1 is induced in PI+ mouse $APC^{-/-}$ adenomas, and attenuated in response to Sulindac (Aran et al, unpublished); PD-L1 is also expressed in the majority of PI+ samples in both carcinoma cell lines and primary tumors. Previous reports have shown that PD-L1 is activated as part of the interferon response [33]. Our data suggest that PD-L1 is upregulated also in a PI setting, raising caution in combining NSAID treatment with immune checkpoint blockade: prolonged NSAID treatment may hamper the success of anti-PD1 treatment. Positive contribution of PI to immunotherapy may be also achieved by expression and release of damage associated molecular patterns (DAMPs), e.g., Anxa1, shown to enhance immunogenic cell death [34]. Developing means of extrinsic PI induction, may thus assist in immunotherapy of an established cancer, as well as in preventing the progression of benign to malignant tumors. Possible means of inducing PI may be radiomimetic agents, one robust example is CKIα inhibitors, mimicking the DNA damage response provoked by CKIα ablation [8, 35]. However, elucidating the innate immunity pathway of PI activation may avail many other means of PI induction for cancer prevention and therapy.

Acknowledgments

Relevant research in the laboratories of Y.B-N and A.B are supported by grants from Israel Science Foundation (ISF)- Centers of Excellence, the European Research Council within the FP-7 (294390 PICHO), the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (AMRF), the Israel Cancer Research Fund, the National Cancer Institute of the National Institutes of Health (U24 CA195858) and the Gruss Lipper Family Foundation.

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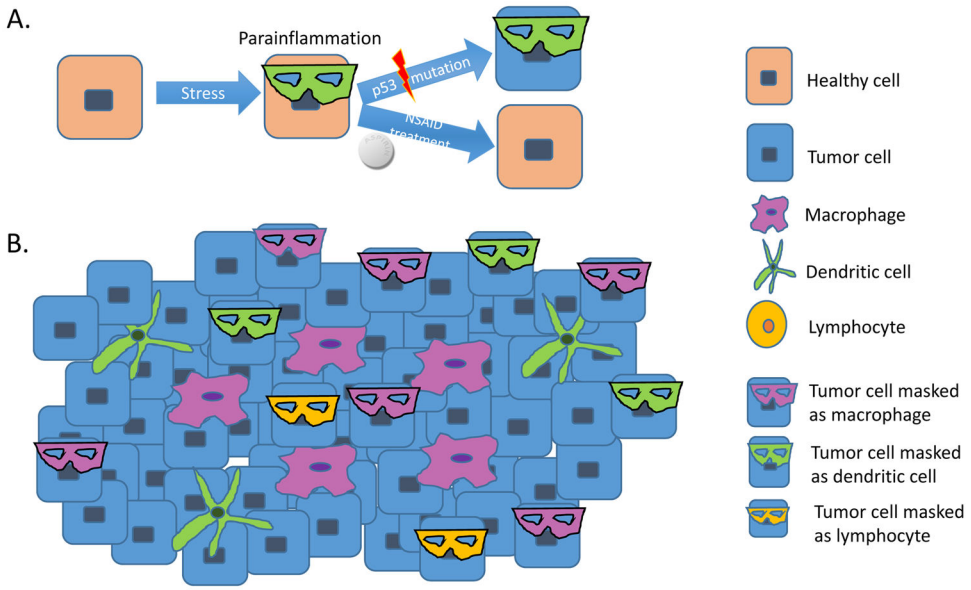

Figure 1. The parainflammation masquerade

A. Stress induces parainflammation in normal cells, leading them to adopt immune characteristics. Following p53 mutation, parainflammatory cells become tumorigenic. Parainflammation can be attenuated by NSAID treatment. **B.** The PI signature bears a strong resemblance to macrophage infiltration, suggesting that PI expressing cells in the tumor fulfill certain functions of macrophages and possibly some other immune cell types, either in suppressing or promoting cancer development. Tumor cells masked as macrophages should be distinguished from true immune-infiltration when determining cancer prognosis and treatment options.