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Innate inflammation and cancer: Is it time for cancer prevention?

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Abstract

Recently, studies have been reported indicating that daily aspirin treatment for a period of 5 years or longer has a significant protective effect against death by colorectal carcinoma (as has previously been shown) and also against death by other solid cancers, both gastrointestinal and otherwise. These studies have reignited interest in the possibility of using nonsteroidal anti-inflammatory drugs for cancer prevention and the possibility that the numerous recent studies identifying the molecular mechanisms of the link between inflammation and cancer may allow the identification of better drugs for cancer prevention. Cancer often originates in tissues that are chronically inflamed, either in response to infections or noninfectious inflammation. Innate inflammation receptors, proinflammatory soluble factors, and inflammation-induced transcription factors have been identified that provide an understanding of some of the molecular pathways underlying the link between inflammation and cancer. However, the important role of the innate inflammatory pathways in host defense against pathogens and tissue damage as well as the maintenance of tissue integrity and homeostasis means that additional careful studies will be needed to identify anti-inflammatory interventions with the beneficial effect of tumor prevention without unacceptable toxic side effects.

Introduction and context

What if taking aspirin could reduce your risk of cancer? Researchers have debated the relationship between inflammation and cancer for many years, but recent studies have reignited the discussion with evidence that taking aspirin daily for 5 years or longer can protect against death from colorectal and other solid cancers. If this observation indeed holds true, and aspirin can stave off cancer or reduce the risk of recurrence, this familiar, age-old drug could offer a tantalizingly simple treatment.

Unfortunately, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are not without problematic side effects, increasing the risks of liver toxicity and bleeding in the stomach and brain when taken over extended periods of time. Researchers who have been studying the molecular pathways at the intersection of cancer and inflammation hope their findings may lead to more selective ways of reducing inflammation, eliminating or minimizing aspirin's negative effects without sacrificing its benefits.

Recently, Rothwell et al. [1] analyzed individual patient data from eight randomized trials in which patients took daily aspirin originally planned for prevention of cardiovascular diseases and found that those taking aspirin had a lower incidence of cancer than controls. Many studies had previously shown that daily use of aspirin and other NSAIDs for extended periods reduced the risk of colorectal cancer or polyp recurrence, but no formal evidence in humans was yet available demonstrating that aspirin might also reduce risk in other cancers. Rothwell et al. [1] showed that the benefit was apparent after at least 5 years of aspirin use and that this benefit increased with duration of treatment. In trials in which the participants took aspirin for more than 7.5 years, the 20-year risk of cancer death was reduced by approximately 30% for all solid cancers and by 60%

for gastrointestinal cancers. For lung and esophageal cancer, the benefit was confined to cancers that originated in glandular tissue (adenocarcinomas). For colorectal cancer, the effect was high for cancer in the proximal colon but not in the distal colon.

These data clearly point to the importance of anti-inflammatory drugs in preventing the initiation and progression of both gastrointestinal and other solid organ cancers (including lung and prostate), and suggest that inflammation may be an underlying cause of cancer even in tumor types that had not been traditionally considered to originate within chronically inflamed tissues.

Inflammation and cancer

Although the role of inflammation in favoring carcinogenesis has generated much interest in the last 10–15 years, the Greek physician Claudius Galenus observed some similarity between cancer and inflammation almost 2,000 years ago. Galenus originally used Hippocrates's term "cancer" specifically to describe certain inflammatory tumors of the breast in which superficial veins appeared swollen and radiated, somewhat like the claws of a crab. Later the name was extended to include all malignant and infiltrating growths. In 1863 Rudolf Virchow noted white blood cells or leukocytes in neoplastic tissues and made a connection between inflammation and cancer. He suggested that the "lymphoreticular infiltrate" reflected the origin of cancer at sites of chronic inflammation. A seminal observation was made more than a century later, when Harold Dvorak of Harvard University noted that that inflammation and cancer share some basic developmental mechanisms (angiogenesis) and tissue-infiltrating cells (lymphocytes, macrophages, and mast cells), and that tumors act like "wounds that do not heal."

Infections, inflammation, and cancer

In many cases, one can see a direct connection between the inflammation caused by infectious pathogens and cancer. In developing countries, up to 23% of malignancies are caused by infectious agents, including hepatitis B and C viruses (liver cancer), human papillomaviruses (cervical and anogenital cancers), and *Helicobacter pylori* (stomach cancer). Some pathogens can directly induce cell transformation but most, if not all, also induce a state of chronic inflammation that favors initiation and progression of tumors. In developed countries, cancers caused by chronic infections are estimated to amount to approximately 8% of all malignancies. Because new pathogens associated with or causing cancer are continuously being identified, it is likely that these frequencies are underestimates. In addition to pathogens, several states of noninfectious chronic inflammation triggered by mechanical, radiation, chemical, or genetic factors have been associated with human malignancy.

However, even in the absence of specific infections by pathogens, the interaction of the organism with commensal microbes is likely to help establish inflammatory conditions favoring carcinogenesis either in epithelia exposed to the outside environment or affected systemically. The increased risk of colorectal carcinoma in patients with ulcerative colitis or Crohn's disease stems from colorectal inflammation caused by the patients' immune systems reacting to intestinal commensal flora. But a systemic inflammatory response to commensal microbes can also occur when bacterial transmucosal translocation takes place (because of immunodeficiency or epithelia damage). In these cases, the systemic inflammatory response is directly induced by bacteria and bacterial products or by the systemic diffusion of proinflammatory molecules such as cytokines and chemokines in the bloodstream. This phenomenon can be seen in the increased prevalence of tumors at sites other than the gastrointestinal tract in human colitis patients [2] and the state of chronic inflammation and immune activation in HIV-infected patients with altered mucosal permeability [3]. In experimental animals, notable examples are the innate inflammation-mediated development of mammary carcinoma in $Apc^{min/+}$ mice, a genetic model of intestinal carcinogenesis, when infection with *Helicobacter hepaticus* is present in the intestine [4], or the observation of systemic DNA damage observed in mice in which the integrity of the colon mucosa is damaged by treatment with dextran sodium sulphate (DSS) [5].

Inflammation promotes cancer by several mechanisms

Chronic inflammation can promote all phases of carcinogenesis, from favoring the initial genetic alterations that give rise to tumor cells, to acting as a tumor promoter by establishing an environment in the surrounding tissues that allows the tumor to progress and metastasize, to triggering immunosuppressive mechanisms that prevent an effective immune response against the tumors. Many molecular mechanisms of innate inflammation have several or all of these protumor effects. In the tissue in which cancer originates, infiltrating hematopoietic cells, epithelial cells, endothelial cells, fibroblasts, and other stromal cells are all responsible for the establishment of inflammation by secreting and responding to proinflammatory factors such as cytokines, chemokines, growth factors, and proteases. This proinflammatory environment attracts more infiltrating inflammatory cells and regulates tissue rearrangement, angiogenesis, and the ability of transformed cells to grow and to migrate. The tumor cells also participate in these processes by

activating mechanisms of intrinsic inflammation in the surrounding epithelial or stromal cells, which often show genetic and epigenetic oncogenic alterations similar to those in the tumor cells.

Oncogenes such as *RAS*, *RET*, *BRAF*, and *MYC* appear to play a role in inflammation. These genes turn on the inflammatory pathway within the cell and activate inflammation outside the cell by recruiting and activating inflammatory cells, creating an environment that reduces anticancer immune cell defenses [6]. Interestingly, by way of epigenetic changes, continued activation or overexpression of oncogenes may not always be required for maintaining this proinflammatory loop: transient activation of the SRC oncoprotein induces an epigenetic switch that uses microRNA regulation to stably maintain the production of interleukin (IL)-6, a key inflammatory cytokine [7]. Severe DNA damage, such as double-stranded breaks, activates the ataxia telangiectasia-mutated (ATM) enzyme, a kinase that repairs DNA but also turns on the secretion of proinflammatory factors. These same factors go on to create conditions that promote an oncogenic growth of cells with double-strand breaks, thereby maintaining the production of proinflammatory factors [8] through a positive feedback loop. Thus, the intrinsic inflammatory response in transformed or damaged tissue cells is an innate inflammatory response to genetic and other insults that may well represent a host response mechanism that is not yet fully understood but is likely to play an important role not only in carcinogenesis but also in the response to alterations of tissue homeostasis or pathogen-induced damages, and in the pathogenic mechanisms of chronic inflammatory diseases.

In recent years, researchers have begun to appreciate the role that a tumor's environment plays in its growth and survival. Indeed, inflammation of the tissue surrounding a tumor can hasten the oncogenic process by directly promoting genetic instability and favoring or inducing gene mutations. Reactive oxygen and nitrogen species (ROS and RNS), which are abundant during inflammation, can induce DNA mutations, epigenetic alterations, and post-translational modifications of proteins that control the cell cycle or survival [9]. In particular, ROS and RNS have been shown to reduce the expression and enzymatic activity of DNA mismatch repair proteins such as mutL homolog 1 (MLH1) and mutS homologs 2 and 6 (MSH2 and MSH6), resulting in an increased genetic instability [9]. Interestingly, the direct interaction of mucosal epithelial cells with oncogenic pathogens such as *H. pylori* also results in decreased expression of MLH1 and MSH2 [10]. Aberrant expression of activation-induced cytidine deaminase, an initiator of somatic hypermutation during B-cell maturation, was abnormally activated in inflamed epithelial cells—an effect linked to mutations seen in human colorectal cancer [11].

These mechanisms suggest that genomic instability, epigenetic changes, and functional protein modifications are involved in the early events of inflammation-induced cancer initiation.

Innate inflammation mechanisms in cancer initiation and progression

Nuclear factor kappa- B (NF-κB) targets many genes that regulate the cell cycle, angiogenesis, and cell survival as well as genes encoding proinflammatory cytokines, chemokines, and proteases—processes and gene products that can play major roles in cancer initiation and progression when not properly kept in check.

Signal transducer and activator of transcription 3 (STAT3) is another major transcription factor involved in immunity and inflammation. It is also overexpressed and phosphorylated in most types of cancer. STAT3 contributes to tumor cells' survival, proliferation, and dissemination by controlling the expression of several cell-cycle genes and of the proto-oncogene *c-MYC*. STAT3 also favors survival of malignant cells by preventing apoptosis, in part by transcriptional downregulation of *p53*, and by controlling pro-angiogenic and metastatic factors such as vascular endothelial growth factor (VEGF) and metalloproteases [12]. Interestingly, many soluble factors present in the tumor, such as VEGF, IL-6, IL-10, IL-11, and IL-23 contribute to STAT3 activation, and several of these factors are themselves transcriptionally activated by STAT3 via a positive feedback mechanism [12].

The discovery and functional characterization of the innate receptors expressed in inflammatory cells that recognize shared structures (patterns) on microbes, known as pattern recognition receptors, have greatly contributed to our understanding of the link between inflammation and cancer. The Toll-like receptors (TLRs) represent the major class of pattern recognition receptors but in these last few years an increasing number of other cell surface or cytosolic receptors have been identified. In particular, the role in inflammation of the cytoplasmic receptors known as inflammasomes, which activate caspase 1 to process the important proinflammatory factors IL-1 and IL-18 has been well established. In hematopoietic cells, pattern recognition receptors induce expression of the genes encoding proinflammatory factors, thus playing a central role in maintaining the inflammatory environment. These

factors include cytokines, chemokines, and proangiogenic and growth factors, as well as stroma processing factors such as metalloproteases. In addition, pattern recognition receptors such as the TLRs have been shown to have an even broader role: they are also expressed in nonhematopoietic cells and their activation can also directly affect cell proliferation, differentiation, and apoptosis [13].

In the last few years there has been much effort in analyzing the role of the signaling adaptor molecule myeloid differentiation factor 88 (MyD88) in carcinogenesis. It is required for signaling downstream of most TLRs and of all the receptors for the large IL-1 cytokine family and so is central for the activation of NF-κB and some of the most important innate inflammation molecular pathways. This can be seen in MyD88-deficient mice, which are viable but have many defects in their innate inflammation response and its interplay with adaptive immunity. Also, MyD88-deficient patients have a strikingly reduced ability to resist infection with piogenic bacteria, although they do eventually develop immunity resistance these infections.

In addition to this central role in innate immunity, MyD88 has recently been reported to have an important role in tumor promotion [14]. Tumor induction is inhibited in MyD88-deficient mice in chemically induced cancer models. Further evidence comes from the $Apc^{Min/+}$ mouse model of spontaneous intestinal tumorigenesis, where MyD88 signaling contributed to adenoma growth and progression. MyD88 signaling was also shown to be required for azoxymethane-induced colon carcinogenesis in IL-10-deficient mice. In many of these experimental models, the protumorigenic role of MyD88 signaling has been in part attributed to the induction of the IL-6–STAT3 axis either downstream of TLR or IL-1R signaling [14].

These data in experimental animals have recently been validated in human studies. In order to continually grow in humans, the activated B-cell-like (ABC) subtype of diffuse large B-cell lymphoma is dependent on a mutation in the MyD88 gene that results in a hyperactive molecule [15]. Mutated *MyD88* promoted tumor cell survival by spontaneously assembling the MyD88 signaling complex, resulting in NF-κB signaling, JAK (Janus kinase) activation of STAT3, and secretion of other inflammatory cytokines such as IL-6, IL-10, and interferon-β [15]. These findings fully support the concept that innate receptors' signaling in tumor cells regulated both intrinsic inflammation and the transformed and cancerous phenotype of the cells [13]. In an interesting exception, MyD88 signaling is protective in the azoxymethane plus DSS injury-induced experimental model of colitis-associated colorectal cancer. Innate receptors' recognition of commensal flora through MyD88 signaling is important to maintain mucosal homeostasis, and the inability of MyD88-deficient mice to heal ulcers generated by injury with DSS may create an altered inflammatory environment that exacerbates the mutation rate in mucosal epithelial cells following exposure to the mutagen azoxymethane and results in augmented adenoma formation and cancer progression [16]. The role of TLRs in MyD88-deficient mice is still unclear and may not be prevailing, as mice lacking the inflammasome NLRP3 (NOD-like receptor family, pryin domain-containing 3) and the inflammasome component caspase 1 or ASC (apoptosis-associated speck-like protein containing a CARD), as well as mice deficient for IL-18 or IL-18R1 expression, all have largely the same phenotype as the MyD88-deficient mice and are highly susceptible to azoxymethane plus DSS-induced colitis-associated colorectal cancer [14,16]. Thus, the susceptibility of MyD88-deficient mice to colitis and colitis-associated colorectal cancer is in part due to their inability to signal through IL-18R [16]. Following azoxymethane plus DSS treatment, the colon enterocytes of these mice express phosphorylated nuclear STAT3 and present evidence of induced activation of Wnt–β-catenin, EGF (epidermal growth factor) receptor, and MET proto-oncogene signaling pathways [16]. Genetic mutations in the β-catenin gene, or other genes, (possibly facilitated by a genomic instability secondary to the downregulation of mismatch repair genes in the absence of IL-18R–MyD88 signaling) may overcome the block in proliferation leading to colitis-associated colorectal cancer development [16]. In the $Apc^{Min/+}$ mouse model of spontaneous colorectal cancer, MyD88 is critical for the activation of the IL-6–STAT3 pathway [14]; however, in the azoxymethane plus DSS model, the damage-induced expression of the IL-6 family cytokines (IL-6 and IL-11) and STAT3-dependent genes is independent of MyD88 [16]. Other pattern recognition receptors that do not signal via MyD88 might be involved or, alternatively, an innate proinflammatory response might be intrinsically triggered by DSS-induced DNA damage and by an altered host–microbiota interaction without involving classical pattern recognition receptors.

The experimental studies and the clinical data on the role of MyD88 in cancer provide strong evidence that innate inflammation and innate immune receptors play a role in carcinogenesis. However, these findings also generate many new questions regarding which cell signaling pathway is most important, which cells are involved in the production of ligands for MyD88-coupled receptors,

and whether the TLRs or the IL-1-family receptors play the predominant role. Another key question is whether MyD88 signaling drives carcinogenesis by the induction of an inflammatory environment, or whether it directly affects the survival and proliferation of tumor cells.

Can we prevent cancer by targeting inflammation?

While these overlapping molecular pathways provide experimental evidence for the role of innate inflammatory responses in carcinogenesis, the strongest clinical evidence in humans comes from the association between chronic infections and cancer, and the finding that regular aspirin or other NSAID therapy decreases the incidence of cancer.

NSAIDs function by inhibiting the cyclooxygenases (COXs) COX-1 and COX-2, which are responsible for the production of prostaglandins from fatty acids. These enzymes catalyze the synthesis of prostaglandin E2, which promotes inflammation by dilating blood vessels, allowing immune cells to pass from the blood into the tissues. This same signaling molecule also regulates angiogenesis and enhances hematopoietic cell homing, sending progenitor cells to damaged tissue to differentiate into the many immune cell types needed for repair. The constitutively expressed *COX-1* contributes to the homeostasis of the gastrointestinal mucosa, whereas the inducible *COX-2* is regulated by various proinflammatory cytokines. NSAIDs such as aspirin inhibit both COX-1 and COX-2, explaining the considerable toxicity and damage to stomach and intestinal lining that can occur with these drugs. Selective COX-2 inhibitors, such as rofecoxib, only inhibit the inducible COX-2 enzyme, which is activated during inflammation, leaving the gastrointestinal homeostasis untouched. Many of these drugs were, however, pulled from the market because of reported cardiovascular toxicity due to the shunting of the COX-2 substrate—arachidonic acid—into the 5-lipooxygenase pathway, generating leukotrienes rather than prostaglandins.

Although initially identified as upregulated in colorectal cancer, COX-2 was found to be highly expressed in almost every type of tumor at the early stages of tumor formation. Indeed, COX-2-specific inhibitors increased both overall and recurrence-free survival following surgical resection, but only in the subset of colorectal cancer patients who overexpressed *COX-2* or had mutated forms of the gene. Interestingly, not only did COX-2 inhibitors prevent cancer formation, but they also decreased the number of already established polyps in patients with familial adenomatous polyposis—an inherited disorder characterized by the early onset of colon cancer [17].

Though such results are encouraging, both nonspecific COX inhibitors, such as aspirin, and COX-2-specific inhibitors have significant toxicity that needs to be balanced with their demonstrated benefits [17]. The interesting point raised by Rothwell and colleagues in their meta-analysis [1] is that the cancer-preventive effect of long-term daily treatment with NSAIDs is not limited to prevention of colon cancer in individuals with elevated risk due to reoccurring polyps or genetic predisposition. It is also effective for the prevention of sporadic colon cancer and many other gastrointestinal and nongastrointestinal solid tumors, including esophageal, pancreatic, stomach, lung, brain, and prostate cancers. Although the published analysis encompassed a very large number of individuals, the study had some limitations. For instance, the trials did not originally have cancer as an end point; the information available in the different trials was not always of the same precision; and the data for nongastrointestinal cancers (with the exception of lung cancer) did not reach full statistical significance despite the large number of patients analyzed. These data clearly provide a compelling case, however, for further assessment of whether targeting inflammatory pathways will result in cancer prevention.

Although COX inhibitors clearly have important anti-inflammatory activity, their preventive effect on cancer may also be due to other effects of these drugs, or to noninflammation-related effects of prostaglandins on vasodilation, angiogenesis, DNA mutation rate, epithelial cell adhesion, or apoptosis. Yet the Rothwell team's impressive clinical results [1], taken together with the extensive clinical and experimental evidence for a causative link between inflammation and cancer, raise the possibility that finely targeted studies of innate inflammatory pathways could lead to even more effective cancer prevention with fewer toxic side effects.

It is important to remember, however, that innate inflammation plays very important roles in normal tissue homeostasis, resistance to infections, and response to tissue damage, and that the same inflammatory pathways that are hijacked by tumors to promote their own progression also play important physiological roles in health. Obtaining a tumor-preventive effect by targeting these molecular pathways without negatively affecting the other physiological roles of these molecules may be a difficult task, one that will require a much deeper understanding of all the inflammatory molecular mechanisms involved in physiology, host defense, and carcinogenesis. Yet these are exciting times. Both the clinical evidence and the preclinical research raise the concrete possibility of a successful effort to prevent cancer by targeting inflammation, and this prospect

should encourage strong support for further scientific efforts in this field of indisputable medical potential.

Abbreviations

DSS, dextran sodium sulphate; IL, interleukin; MLH1, mutL homolog 1; MSH2, mutS homolog 2; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor kappa-B; NSAID, nonsteroidal anti-inflammatory drug; RNS, reactive nitrogen species; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TLR, Toll-like receptor; VEGF, vascular endothelial growth factor.

Competing interests

The author declares that he has no competing interests.

References

1. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW: **Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials.** *Lancet* 2011, **377:**31-41.

   F1000 Factor 13
   Evaluated by Janusz Jankowski 05 Jan 2011, Pagona Lagiou 14 Feb 2011, John Choe 22 Feb 2011

2. Bernstein CN, Blanchard JF, Kliewer E, Wajda A: **Cancer risk in patients with inflammatory bowel disease: a population-based study.** *Cancer* 2001, **91:**854-62.

3. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, Kazzaz Z, Bornstein E, Lambotte O, Altmann D, Blazar BR, Rodriguez B, Teixeira-Johnson L, Landay A, Martin JN, Hecht FM, Picker LJ, Lederman MM, Deeks SG, Douek DC: **Microbial translocation is a cause of systemic immune activation in chronic HIV infection.** *Nat Med* 2006, **12:**1365-71.

   F1000 Factor 14
   Evaluated by Dana Gabuzda 18 Dec 2006, Rupert Kaul 19 Dec 2006, Eva Guinan 08 Jan 2007, James Tartaglia 27 Apr 2007

4. Rao VP, Poutahidis T, Ge Z, Nambiar PR, Boussahmain C, Wang YY, Horwitz BH, Fox JG, Erdman SE: **Innate immune inflammatory response against enteric bacteria Helicobacter hepaticus induces mammary adenocarcinoma in mice.** *Cancer Res* 2006, **66:**7395-400.

5. Westbrook AM, Wei B, Braun J, Schiestl RH: **Intestinal mucosal inflammation leads to systemic genotoxicity in mice.** *Cancer Res* 2009, **69:**4827-34.

6. Borrello MG, Degl'Innocenti D, Pierotti MA: **Inflammation and cancer: the oncogene-driven connection.** *Cancer Lett* 2008, **267:**262-70.

7. Iliopoulos D, Hirsch HA, Struhl K: **An epigenetic switch involving NF-kappaB, Lin28, Let-7 MicroRNA, and IL6 links inflammation to cell transformation.** *Cell* 2009, **139:**693-706.

   F1000 Factor 6
   Evaluated by Martin Fernandez-Zapico 02 Feb 2010

8. Rodier F, Coppé JP, Patil CK, Hoeijmakers WA, Munoz DP, Raza SR, Freund A, Campeau E, Davalos AR, Campisi J: **Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion.** *Nat Cell Biol* 2009, **11:**973-9.

   F1000 Factor 10
   Evaluated by Marc Jeschke 21 Aug 2009, Ashani Weeraratna 03 Sep 2009

9. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A: **Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability.** *Carcinogenesis* 2009, **30:**1073-81.

10. Maddocks OD, Short AJ, Donnenberg MS, Bader S, Harrison DJ: **Attaching and effacing Escherichia coli downregulate DNA mismatch repair protein in vitro and are associated with colorectal adenocarcinomas in humans.** *PLoS One* 2009, **4:** e5517.

11. Endo Y, Marusawa H, Kou T, Nakase H, Fujii S, Fujimori T, Kinoshita K, Honjo T, Chiba T: **Activation-induced cytidine deaminase links between inflammation and the development of colitis-associated colorectal cancers.** *Gastroenterology* 2008, **135:**889-98.

12. Grivennikov SI, Karin M: **Dangerous liaisons: STAT3 and NF-kappaB collaboration and crosstalk in cancer.** *Cytokine Growth Factor Rev* 2010, **21:**11-9.

13. Hasan UA, Caux C, Perrot I, Doffin AC, Menetrier-Caux C, Trinchieri G, Tommasino M, Vlach J: **Cell proliferation and survival induced by Toll-like receptors is antagonized by type I IFNs.** *Proc Natl Acad Sci U S A* 2007, **104:**8047-52.

14. Saleh M, Trinchieri G: **Innate immune mechanisms of colitis and colitis-associated colorectal cancer.** *Nat Rev Immunol* 2011, **11:**9-20.

15. Ngo VN, Young RM, Schmitz R, Jhavar S, Xiao W, Lim KH, Kohlhammer H, Xu W, Yang Y, Zhao H, Shaffer AL, Romesser P, Wright G, Powell J, Rosenwald A, Muller-Hermelink HK, Ott G, Gascoyne RD, Connors JM, Rimsza LM, Campo E, Jaffe ES, Delabie J, Smeland EB, Fisher RI, Braziel RM, Tubbs RR, Cook JR, Weisenburger DD, Chan WC, *et al.*: **Oncogenically active MYD88 mutations in human lymphoma.** *Nature* 2010, **470:** 115-9.

   F1000 Factor 10
   Evaluated by Margot Thome 02 Feb 2011

16. Salcedo R, Worschech A, Cardone M, Jones Y, Gyulai Z, Dai RM, Wang E, Ma W, Haines D, O'Huigin C, Marincola FM, Trinchieri G: **MyD88-mediated signaling prevents development of adenocarcinomas of the colon: role of interleukin 18.** *J Exp Med* 2010, **207:**1625-36.

17. Menter DG, Schilsky RL, DuBois RN: **Cyclooxygenase-2 and cancer treatment: understanding the risk should be worth the reward.** *Clin Cancer Res* 2010, **16:**1384-90.