Opinion

Inflammatory Bursts as Stochastic Triggers in Cancer Initiation

Xiuli Zhang, Qingshui Wang, and Yao Lin *

The Affiliated People's Hospital of Fujian University of Traditional Chinese Medicine, College of Integrative Medicine, Fujian-Macao Science and Technology Cooperation Base of Traditional Chinese Medicine-Oriented Chronic Disease Prevention and Treatment, Fujian-Hong Kong-Macau-Taiwan Collaborative Laboratory for the Inheritance and Innovation of Traditional Chinese Medicine, Fujian University of Traditional Chinese Medicine, Fuzhou 350122, China
* Correspondence: yaolin@fjtcm.edu.cn
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Abstract: This opinion article proposes the "inflammatory burst" model, positing that intense, transient inflammatory escalations superimposed on chronic inflammation act as decisive stochastic triggers for cancer initiation-complementing the permissive role of somatic mutations. We define inflammatory bursts as high-amplitude, short-lived exacerbations within a chronically inflamed microenvironment, capable of overriding cellular differentiation via sustained nuclear factor kappa B (NF-κB)/signal transducer and activator of transcription 3 (STAT3) activation and dysregulated Wnt/β-catenin signaling, thereby driving an atavistic reversion to a cancer stem cell state. The dual, stage-dependent role of inflammation is illustrated through mechanisms such as Williams syndrome transcription factor (WSTF) nuclear autophagy, which amplifies bursts during initiation but is suppressed to aid immune evasion during progression. This framework shifts the clinical paradigm toward "cancer interception"—a prevention-oriented strategy aimed at selectively dampening pathological inflammatory peaks while preserving immune surveillance, thereby preventing malignant transformation in high-risk individuals.

Keywords: inflammatory bursts; cancer initiation; chronic inflammation; cancer stem cells; atavistic reversion

1. The Incompleteness of the Somatic Mutation Theory

Cancer represents a fundamental breakdown of multicellular cooperation, in which certain cells escape regulatory constraints, proliferate uncontrollably, and ultimately threaten the host. The somatic mutation theory-which posits that cancer originates from a single cell that accumulates critical mutations in genes governing proliferation, survival, and genomic stability-has long dominated cancer biology [1]. This model has driven the discovery of numerous oncogenes and tumor suppressors, reshaping targeted therapy development.

Yet accumulating evidence suggests that the mutation-centric view is incomplete.

The clearest indication comes from human biology: deep sequencing frequently reveals cancer-driving mutations in healthy individuals, as epitomized by clonal hematopoiesis (CHIP), where such mutations often persist for years without provoking malignancy [2]. This demonstrates that mutations primarily establish a permissive cellular state, and that a non-mutational triggering event is often required for malignant transformation. This concept—that cellular state dictates oncogenic potential—is also illustrated by induced pluripotent stem (iPS) cells. Generated by reprogramming to a pluripotent state, their ability to form teratomas shows that a primitive, self-renewing cellular state carries an intrinsic potential for neoplastic growth. This potential can be unlocked not only by the accumulation of somatic mutations but also by the experimental reconstitution of a pluripotency network [3].

2. Inflammation's Multifaceted Role in Carcinogenesis

Inflammation has long been implicated in cancer development [4,5]. Chronic inflammatory diseases increase cancer risk, and immune cell infiltration is a hallmark of the tumor microenvironment [6,7]. However, the role of inflammation in cancer initiation remains contested, as only a small proportion of patients with chronic inflammation eventually develop cancer, albeit the ratio is significantly higher than healthy individuals. A valid

trigger for malignant transformation should be a potent, discrete event capable of provoking a decisive shift in cell state. While discrete acute inflammatory events appear to fit this triggering profile better than smoldering chronic inflammation, emerging data reframe the distinction. The critical difference may not be simply intensity versus duration, but rather the dynamics of the inflammatory response [8]. Chronic inflammatory processes are in fact punctuated by irregular, high-intensity bursts-transient escalations that resemble acute inflammation [8]. Therefore, we speculate that these intense, transient inflammatory bursts may serve as the long-sought stochastic triggers of carcinogenesis. It is important to conceptually distinguish these bursts from both isolated acute infections and smoldering chronic inflammation. While chronic inflammation acts primarily as a tumor promoter by creating a mutagenic and proliferative tissue microenvironment, the inflammatory burst represents a discrete, high-amplitude event capable of triggering a qualitative state change-the atavistic reversion of a differentiated cell into a cancer stem cell (Figure 1). In this framework, chronic inflammation sets the stage, but the burst acts as the decisive trigger.

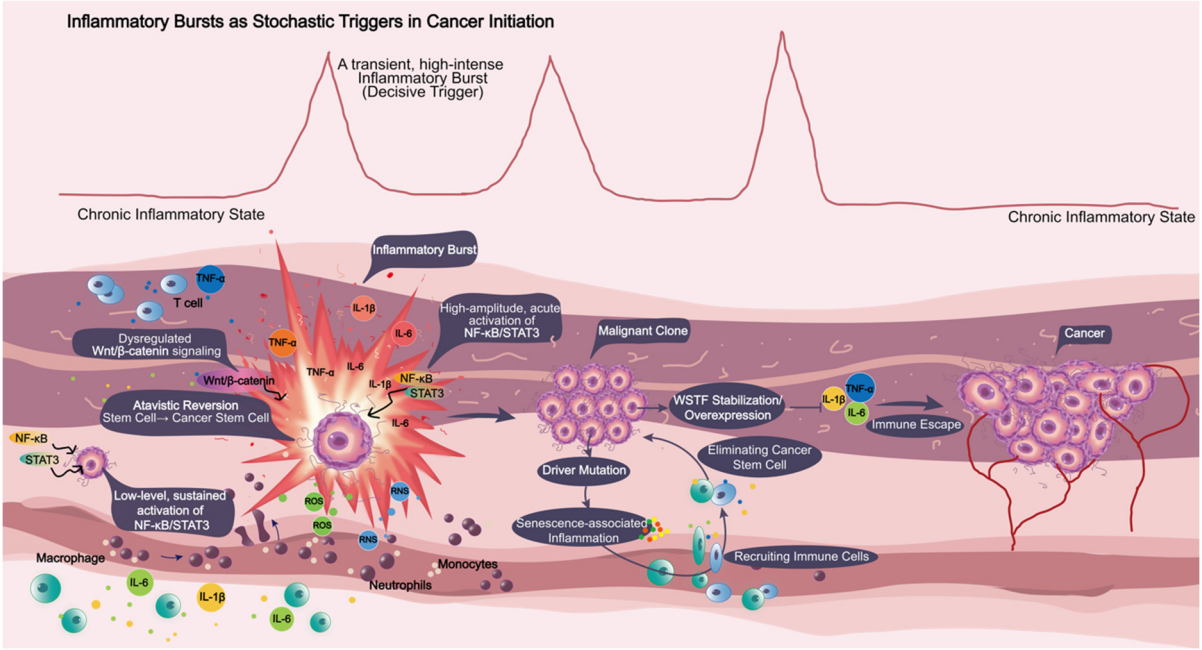

Figure 1. This schematic illustrates the multi-step "inflammatory burst" model of cancer initiation. The model begins with a state of chronic inflammation, characterized by persistent immune cell infiltration, elevated baseline cytokines, and altered stroma. During this phase, signaling pathways such as NF-κB and STAT3 exhibit low, sustained baseline activity (represented conceptually as a steady low-amplitude wave), and Wnt/β-catenin signaling remains inactive or tightly regulated in stem/progenitor cells. The central event is a discrete inflammatory burst, a sharp, transient escalation of pro-inflammatory mediators (e.g., IL-1β, TNF-α, IL-6) causing acute tissue damage. Crucially, this burst phase is defined by a high-amplitude, transient peak in NF-κB/STAT3 activation (depicted as a sharp waveform peak) coupled with the dysregulated activation of Wnt/β-catenin signaling. This concerted signal override forces a target cell into an atavistic reversion, generating a cancer stem cell. Thus, the model posits that the qualitative shift in signaling dynamics during a burst—not the chronic baseline—acts as the decisive stochastic trigger for malignant transformation. The model emphasizes that a burst initiates malignancy only when it surpasses a hypothetical threshold and coincides with a permissive microenvironment (e.g., pre-existing mutations, impaired immune surveillance), thereby distinguishing oncogenic from non-oncogenic inflammatory events.

3. Defining the Inflammatory Burst: Characteristics and Evidence

To operationalize the concept of an inflammatory burst, we define it as a transient, high-intensity escalation of the inflammatory response, embedded within and superimposed upon a pre-existing state of chronic inflammation [9]. This key distinction clarifies that an inflammatory burst is not an isolated acute inflammatory episode (e.g., a brief infection in otherwise normal tissue), but rather an episodic exacerbation within a chronically inflamed milieu [8,10]. Its defining characteristics include its contextual embedding within a background of persistent, low-grade inflammation that primes the tissue through immune cell infiltration, baseline cytokine elevation, and altered stromal signaling [11]; its distinctive cytokine profile marked by rapid, sharp peaks in pro-inflammatory mediators such as IL-1β, TNF-α, and IL-6, often far exceeding baseline chronic levels [12,13]; its

temporal dynamics, typically lasting from several hours to a few days, creating a sharp contrast with the surrounding chronic inflammation [8]; and its transient yet profound microenvironmental impact, inducing acute tissue alterations such as epithelial barrier disruption [14], local influx of immune cells (particularly neutrophils and inflammatory monocytes) [15], and a burst of reactive oxygen and nitrogen species (reactive oxygen species/reactive nitrogen species) capable of causing collateral macromolecular damage [16].

Direct evidence for such bursts comes from longitudinal studies in chronic inflammatory disease models [17]. For instance, in murine models of colitis, periodic flare-ups are characterized by sudden increases in mucosal IL-1β and TNF-α, coinciding with crypt damage and regenerative epithelial responses [18]. Similarly, in chronic hepatitis models, episodic spikes in inflammatory mediators like IL-6 and C-C Motif Chemokine Ligand 2(CCL2) correlate with hepatocellular injury and compensatory proliferation phases that are windows for malignant transformation [19]. These observations support the notion that it is not chronic inflammation per se, but its punctuated, high-intensity exacerbations that provide the critical disruptive trigger for cancer initiation [20].

Translating this conceptual definition into measurable biology presents a key challenge and opportunity. We posit that a carcinogenic burst is distinguished from background fluctuations by a temporal signature of high-amplitude, coordinated peaks in specific pro-inflammatory mediators (e.g., IL-1β, TNF-α, IL-6) that substantially exceed an individual's chronic baseline and correlate with acute tissue damage markers. Validating this requires the development of longitudinal monitoring tools (e.g., serial cytokine profiling, biosensors) to capture these transient dynamics *in vivo*. Identifying a unique biomarker signature—potentially a specific cytokine ratio or immune cell influx pattern—for such oncogenic bursts is a critical prediction of our model and a necessary step toward clinical interception.

How, then, can such bursts initiate cancer? Such bursts can disrupt stem cell differentiation, causing a daughter cell to revert to a primitive, self-renewing state-an atavistic event that spawns a cancer stem cell, the putative seed of tumors [21–23]. Mechanistically, this disruption may occur through the sustained activation of pro-survival and proliferation signals (e.g., NF-κB and STAT3) within the stem cell niche, overriding differentiation cues and locking a cell into a self-renewing, primitive state [9,21]. Notably, inflammatory bursts can also aberrantly activate the Wnt/β-catenin signaling pathway, a key regulator of stem cell maintenance and self-renewal [24]. Dysregulated Wnt signaling further reinforces the atavistic reversion by promoting transcriptional programs that suppress differentiation and enhance pluripotency, thereby synergizing with other pro-survival signals to stabilize the cancer stem cell state [21,25,26].

The frequent occurrence of inflammatory bursts in chronic diseases without universal progression to cancer underscores that not all bursts are equally oncogenic. We posit that a burst acts as a decisive stochastic trigger only within a permissive triad: (1) when its amplitude and duration exceed a threshold sufficient to cause sustained pathway dysregulation (e.g., NF-κB/STAT3, Wnt/β-catenin); (2) when it targets a cellular niche already primed by somatic mutations or epigenetic alterations; and (3) when the local immune context fails to resolve the burst and eliminate affected cells. Thus, the variability in cancer outcomes among patients with similar inflammatory burdens may be explained by differences in these conjunctive factors—a premise that can be tested by comparing burst responses in cancer-prone versus cancer-resistant genetic or immunological settings.

4. Molecular Mechanisms and the Duality of Inflammation in Initiation versus Progression

The dual role of inflammation in cancer-both as a trigger and a barrier-can be reconciled by distinguishing its functions at initiation and progression stages, a distinction illuminated by recent studies on mechanisms such as WSTF nuclear autophagy [27].

4.1. In Initiation: Inflammatory Bursts as Triggers via Chromatin Remodeling

During the initiation phase, intense inflammatory bursts within a chronically inflamed tissue can act as the decisive trigger. At the molecular level, these bursts engage specific pathways that rewire cellular identity. For example, the degradation of WSTF-a subunit of the Imitation Switch (ISWI) chromatin-remodeling complex-via nuclear autophagy during chronic inflammation enhances chromatin accessibility at inflammatory gene loci [27]. This mechanism is selectively activated in chronic, not acute, settings, and it amplifies the inflammatory response. In the context of an inflammatory burst, such amplification could critically disrupt differentiation signals in stem or progenitor cells, pushing them toward an atavistic, self-renewing state-the birth of a cancer stem cell. Thus, in initiation, WSTF degradation facilitates the high-intensity inflammatory environment that serves as the stochastic trigger.

4.2. In Progression: Immune Evasion via Suppression of Inflammation

Once a malignant clone is established, the role of inflammation and its mediators shifts dramatically during progression. Here, cancer cells must evade immune surveillance, which often involves suppressing the very inflammatory signals that may have aided their birth. This explains the seemingly paradoxical observation that WSTF overexpression promotes liver tumorigenesis in cells already expressing oncogenic NRAS(G12V) [27]. In this context, the pre-malignant cells exhibit senescence-associated inflammation, a form of immunosurveillance. Overexpressing WSTF stabilizes the protein, dampening this inflammatory response and thereby disarming immune-mediated clearance, allowing the nascent tumor to survive and expand. Therefore, in progression, WSTF stabilization/overexpression represents an adaptive strategy to suppress antitumor immunity.

This stage-dependent duality clarifies inflammation's complex role: intense, burst-like inflammation (facilitated by mechanisms like WSTF degradation) can trigger malignant initiation in predisposed tissue, while subsequent modulation of inflammation (e.g., via WSTF stabilization) becomes crucial for tumor progression and immune evasion.

In summary, cancer initiation entails a convergence of factors: intense inflammatory bursts act as stochastic triggers that disrupt differentiation; driver mutations enable sustained proliferation; and successful cancer cells must learn to modulate their inflammatory microenvironment to evade immune suppression. This integrated framework helps reconcile seemingly contradictory findings and offers a more coherent understanding of inflammation's role in cancer onset.

The causal sequence from an inflammatory burst to atavistic reversion is presented here as a synthesized, predictive framework. Its validation requires testing several key predictions: first, that a discrete burst within a primed niche can be observed to drive a defined cellular fate transition from differentiation to a self-renewing state; second, that cells undergoing this transition will exhibit a convergent 'reversion signature'—a specific coalescence of sustained NF-κB/STAT3 activity, dysregulated Wnt/β-catenin signaling, and re-activated stemness transcriptional programs; and third, that the likelihood of this event depends stochastically on burst intensity. Future studies employing lineage-tracing and single-cell multi-omics in burst-exposed, pre-malignant contexts are poised to directly test these predictions.

5. Unanswered Questions and Testable Predictions

The inflammatory burst model, while providing a cohesive framework, gives rise to clear, testable predictions. Key questions include: what measurable signature defines a carcinogenic burst; whether burst-induced atavistic reversion is a directly observable cell fate transition; and how genetic and tissue contexts modulate this process. We propose that validating these predictions—through longitudinal biomarker profiling, lineage-tracing, and comparative studies in differentially susceptible models—will transform the model from a schematic into a validated framework and define the parameters for effective cancer interception.

The context-dependency of our model also provides a framework for understanding seemingly contradictory clinical observations, such as the relatively low incidence of primary cancer in tissues like rheumatoid joints despite frequent inflammatory flares. This does not refute the model but rather underscores the necessity of its permissive components. We posit that the rheumatoid synovium, while chronically inflamed, largely lacks the abundant, active epithelial stem/progenitor cell compartments that are prime targets for atavistic reversion. Furthermore, the tissue's repair responses may favor fibrosis or metaplasia over the dedifferentiation programs that generate self-renewing cancer stem cells. Thus, the inflammatory burst model predicts lower malignant potential in contexts where one or more elements of the "permissive triad"—particularly a susceptible stem cell niche—is absent. This explanatory power for both high and low-risk scenarios strengthens the model's robustness and delineates its biological boundaries.

6. Future Directions and Clinical Implications

It is important to clarify that the inflammatory burst model, in its current form, is not proposed as a ready-to-use diagnostic tool. Rather, its primary contribution is to reorient cancer prevention research toward the initiation phase by framing malignant transformation as a stochastic but modifiable event. The clinical value of the model lies in its ability to generate falsifiable hypotheses, stratify high-risk populations conceptually, and nominate specific molecular nodes for early interception-all of which are prerequisites for eventual translational deployment.

To experimentally validate the 'inflammatory burst' hypothesis, several key approaches are warranted. Technologically, capturing the proposed spatiotemporal dynamics of inflammatory bursts requires moving beyond static measurements to achieve dynamic, in vivo mapping of cytokine activity at cellular resolution. A transformative methodological advance is the recent development of biosensors such as CyCLoPs (Cytokine

Cellular Locating Platforms), which convert cytokine-receptor engagement into a stable fluorescent signal, enabling the historical recording of cytokine exposure in single cells within living tissues [28]. This platform, and others like it, provides the essential toolset to directly visualize the high-amplitude, transient peaks central to our model, precisely identify target cells within the tissue niche, and temporally correlate burst events with downstream pathway activation and cell fate decisions.

First, *in vivo* models should be developed that superimpose defined, localized inflammatory bursts—such as microinjection of key cytokines (e.g., TNF-α, IL-1β) or Toll-like receptor agonists (e.g., LPS)—onto established models of chronic inflammation (e.g., DSS-induced colitis, DEN-induced hepatitis). These systems would directly test whether such discrete, high-amplitude events can act as stochastic triggers for malignant transformation in a primed microenvironment. Second, ex vivo and *in vitro* models using patient-derived organoids from pre-malignant, chronically inflamed tissues (e.g., Barrett's esophagus, ulcerative colitis) are crucial. Challenging these organoids with controlled cytokine 'bursts' (short-term, high-dose pulses) would allow real-time monitoring of the proposed molecular cascade—including sustained NF-κB/STAT3 activation (via FRET reporters), dysregulated Wnt/β-catenin signaling (via targets like AXIN2), and the induction of stemness markers (e.g., OCT4, NANOG). Such experiments can directly probe the causal link between burst dynamics and the atavistic reversion to a cancer stem cell state.

Looking ahead, several critical research directions emerge. First, we must decipher the precise molecular mechanisms underlying high-intensity inflammatory bursts in chronic inflammatory diseases. This includes identifying key cytokine networks involved in triggering these events, establishing quantitative definitions of what constitutes "high-intensity" inflammation at cellular and tissue levels, and developing advanced methodologies for monitoring such transient bursts *in vivo*.

Second, the development of non-invasive biomarkers capable of detecting and quantifying these inflammatory bursts represents an urgent clinical need. Before such biomarkers can be translated into clinical use, however, it is essential to confirm that the proposed "burst signature" indeed correlates with oncogenic risk. We propose that systematic meta-analyses of longitudinal clinical cohorts—examining whether high-amplitude, transient elevations in specific cytokines (e.g., IL-1β, TNF-α, IL-6) are associated with inflammation severity, histologic progression, cancer incidence, and survival—should be prioritized. Such studies would validate the clinical relevance of inflammatory bursts and provide the necessary evidence base for interceptive strategies. Such tools would be particularly valuable for managing chronic inflammatory conditions like gastritis and hepatitis, where patients face elevated cancer risks. By identifying individuals experiencing frequent or intense inflammatory bursts, we could stratify patient populations for targeted interventions.

Third, exploring the potential feedback loop between inflammatory bursts and the acquisition of new mutations is crucial. These bursts, through the production of reactive oxygen and nitrogen species, could directly promote genomic instability, thereby intertwining the triggering event with the evolution of the tumor [5,9].

The "inflammatory burst" model shifts the paradigm for clinical prevention from broad-spectrum anti-inflammatory strategies toward a more nuanced approach termed "cancer interception." The goal of interception is not to eliminate inflammation entirely-which would compromise essential immune surveillance and host defense-but to selectively dampen or "smooth" the pathological peaks of inflammatory bursts in high-risk individuals. By preventing these stochastic, high-amplitude events, we aim to reduce the probability of the atavistic reversion that initiates malignancy, while preserving the beneficial, homeostatic functions of the immune system. This approach is therefore guided by a stage-dependent logic, aiming to target pro-tumorigenic bursts during initiation while seeking to preserve anti-tumor immunity. Its practical application, however, is contingent upon the development of robust methods—like the cytokine biosensors discussed—to dynamically define these stages and guide intervention timing.

Furthermore, therapeutic strategies should aim to selectively suppress pathological inflammatory bursts while preserving beneficial immune surveillance functions. This nuanced approach, which can be termed "cancer interception," shifts the paradigm from broad anti-inflammatory suppression toward the targeted dampening of inflammatory peaks. The goal is to prevent the stochastic, burst-induced atavistic reversion that initiates malignancy, while maintaining the immune system's capacity for defense and tumor suppression. The WSTF nuclear autophagy pathway offers promising insights in this regard, suggesting that targeted modulation of specific inflammatory amplification mechanisms may achieve this delicate balance. Addressing these challenges will pave the way for effective interception strategies that prevent cancer initiation in high-risk populations while maintaining protective immune function.

The "cancer interception" paradigm necessitates a transition from conceptual framework to actionable therapeutic strategies. Informed by the inflammatory burst model, we propose several targeted approaches to achieve this: first, chrono-targeted and biomarker-guided therapy using short-term, intermittent biologic agents

(e.g., IL-1β, IL-6, or TNF-α antagonists) during predicted or detected burst windows in high-risk individuals; second, modulation of burst-amplification mechanisms, such as developing inhibitors of the WSTF nuclear autophagy pathway to reduce burst intensity without compromising protective acute inflammation; third, microenvironment normalization via agents targeting the chronically inflamed stroma (e.g., TGF-β modulators, chemokine receptor inhibitors) to lower burst propensity and disrupt the permissive niche; and fourth, scavenging burst-induced genomic stress with targeted antioxidants or reactive species inhibitors to limit collateral DNA damage. Collectively, these strategies exemplify how the inflammatory burst model—though still theoretical in its quantitative specifics—can already inform a prevention-focused research agenda by linking discrete inflammatory dynamics to defined molecular targets and cell-state transitions.

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