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Inflammation and Cancer: Is the Link as Simple as We Think?

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For investigative cutaneous biologists a link between inflammation and skin cancer is a topic frequently discussed when multi-stage chemical carcinogenesis and photocarcinogenesis models are presented. Indeed, the inflammatory process includes the release of cytokines, growth factors, chemotactic polypeptides, and prostaglandins, which have become favorite targets for prevention of chemical induced as well as UV-light-induced skin cancer (Marks and Furstenberger, 2000; Tripp *et al*, 2003; Wilgus *et al*, 2003; Bowden, 2004). Dissecting the mediators of inflammation in cutaneous carcinogenic pathways has revealed key roles for prostaglandins, cyclooxygenase-2, tumor necrosis factor-α (TNF-α), AP-1, nuclear factor-κB (NF-κB), signal transducer and activator of transcription (STAT)3, and others (Buckman *et al*, 1998; Moore *et al*, 1999; Suganuma *et al*, 1999; Young *et al*, 1999; Chan *et al*, 2004; Lind *et al*, 2004). Besides these experimental results, several clinical conditions associated with inflammation appear to predispose the patient to increased susceptibility for skin cancer including discoid lupus erythematosus, dystrophic epidermolysis bullosa, and chronic wound sites. Despite this vast collection of data and clinical observations, however, there are several dermatological settings in which chronic, and even lifelong, skin diseases associated with inflammation do not predispose to conversion of lesions into malignancies such as psoriasis, atopic dermatitis, and Darier's disease.

The purpose of this commentary is to summarize a rapidly accumulating body of evidence providing new molecular insights linking inflammation with the promotion of tumorigenesis, and to remind the reader that such a link may not be as simple as currently portrayed because certain types of inflammatory processes in skin (and possibly other tissues as well) may also serve a tumor suppressor function. Here we focus on such a dualistic viewpoint, and offer a new perspective on potential molecular mechanisms that regulate the pro-oncogenic, as well as the tumor suppressor, effects of chronic inflammation, and tumor development using psoriasis as our primary disease model.

Over the past few months, several publications in leading biomedical journals grappled with an important issue in oncology, namely, defining potential links between chronic tissue damage, inflammation, and the development of cancer (Beachy *et al*, 2004; Bhowmick *et al*, 2004; Greten *et al*, 2004; Pikarsky *et al*, 2004). In an essay concept entitled "Mending and Malignancy," Beachy *et al* (2004) point out the clinical link between persistent heartburn and adenocarcinoma of the esophagus. They focus on injured epithelium and highlight molecular pathways contributing to an expanded stem cell pool that, together with mutagenic agents, contribute to carcinogenesis. They conclude that understanding the response to epithelial injury may lead to useful strategies for cancer prevention and therapy. In addition, Balkwill and Coussens (2004) reviewed the role of the NF-κB signal transduction pathway that can regulate inflammation and also promote malignancy. Their review summarized the latest findings revealed in a letter to *Nature* by Pikarsky *et al* (2004). Using Mdr2 knockout mice in which hepatitis is followed by hepatocellular carcinoma (HCC), Pikarsky *et al* implicated TNF-α upregulation in tumor promotion of HCC, and suggest that TNF-α and NF-κB are potential targets for cancer prevention in the context of chronic inflammation. A similar conclusion was reached with respect to NF-κB by an independent group of investigators using a model of experimental dextran sodium sulfate-induced colitis, in which inactivation of the IκB kinase resulted in reduced colorectal tumors (Greten *et al*, 2004). Way before the molecular clues for cancer had been investigated, Hawkins (1835) made the clinical observation that squamous cell carcinoma can be a long-term sequela of chronic osteomyelitis in the overlying skin. Furthermore, it has been argued that the immune response contributes significantly to fostering a tumorigenic process through CD4+ T cells, or other inflammatory links (Daniel *et al*, 2003; Vakkila and Lotze, 2004).

Although there are many other clinical conditions supporting the concept that inflammation is a critical component of tumor progression (e.g., reflux esophagitis/esophageal cancer; inflammatory bowel disease/colorectal cancer) (Coussens and Werb, 2002), there is at least one notable example that does not fit this paradigm. As described below, psoriasis is a chronic cutaneous inflammatory disease, which is seldom if ever accompanied by cancer, suggesting the relationship between tissue repair, inflammation, and development of cancer may not be as simple as portrayed by the aforementioned reviews and experimental results. Besides psoriasis, other noteworthy observations pointing to more complexity include the observation that in the Mdr2 knockout mice, we rarely detect bile duct tumors despite extensive inflammation, NF-κB activation, and abundant proliferation of bile ducts in portal spaces (Pikarsky *et al*, 2004). Moreover, in a skin cancer mouse model, NF-κB was shown to inhibit tumor formation (Dajee *et al*, 2003). Thus, the composition of inflammatory

Abbreviations: NF-κB, nuclear factor-κB; TGFβ, transforming growth factor β; TNF-α, tumor necrosis factor-α

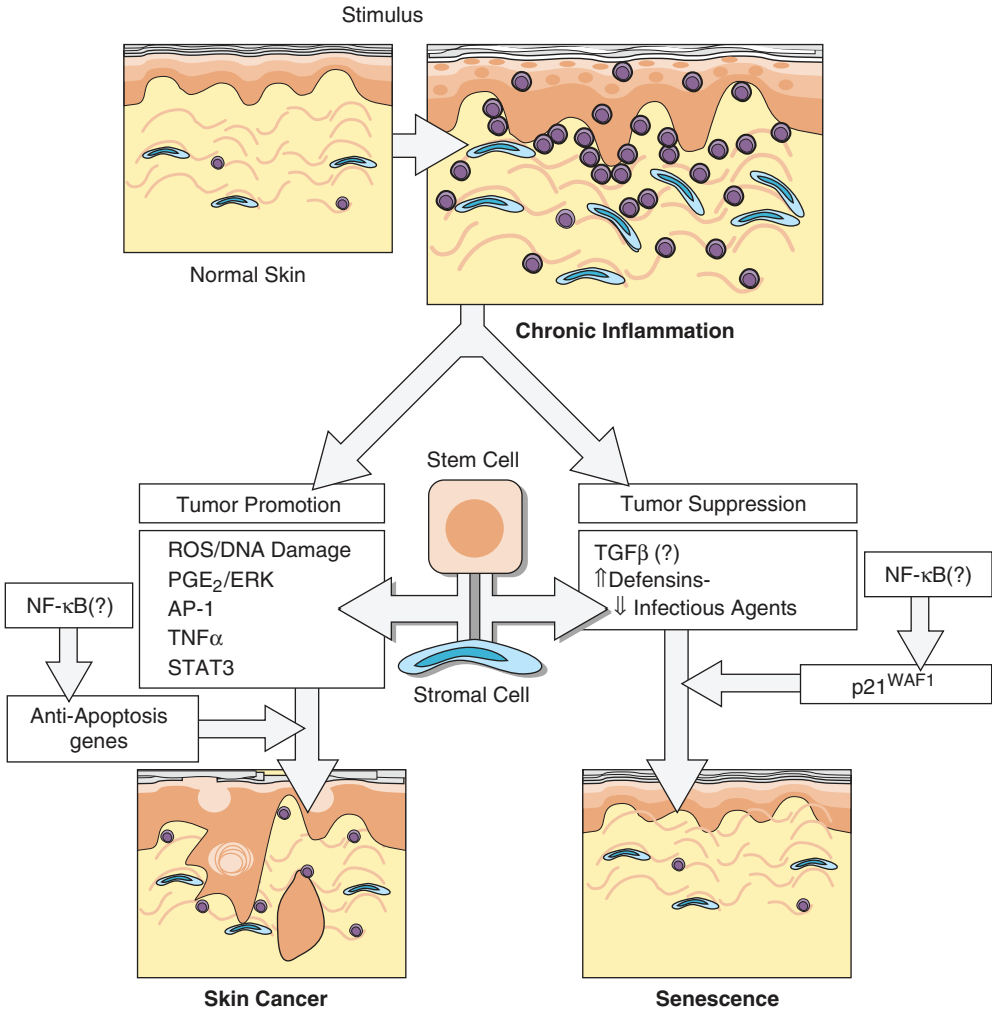

Figure 1
Proposed dualistic viewpoint for role of inflammation in both of the complex processes culminating in either tumor promotion (*left-side panel*) and tumor suppression (*right-side panel*). Note following a stimulus which leads to tissue damage and chronic inflammation in the skin, two possible pathways are envisioned that may involve the participation of keratinocytes, epidermal stem cells, and dermal stromal cells participating in signaling pathways including the following for tumor promotion (ROS, DNA damage, PGE_2/COX-2, AP-1, TNF-α, STAT3, NF-κB) and tumor suppression (TGFβ, defensins-infectious agents, $p21^{WAF1}$, NF-κB). Many questions remain to be answered in defining the precise mechanistic role for these mediators and signal transducers in determining whether skin cancer or senescence is the final biological pathway resulting from chronic cutaneous inflammation. ROS, reactive oxygen species; COX-2, cyclooxygenase-2; TNF-α, tumor necrosis factor-α; STAT, signal transducer and activator of transcription; NF-κB, nuclear factor-κB; TGFβ, transforming growth factor β.

mediators, or the properties of the responding epithelial cells (e.g. signaling machinery, metabolic status), may dictate either tumor promotion or tumor suppression, as summarized in Fig 1.

As highlighted in Fig 1, we suggest that chronic inflammation and tissue repair can trigger pro-oncogenic events, but also that tumor suppressor pathways may be upregulated at various sites of injury and chronic cytokine networking. The principal support for such a dualistic viewpoint is based on both clinical and biochemical characteristics of psoriatic plaques.

Psoriatic plaques represent a common tissue response to injury in genetically predisposed individuals (approximately 2%–3% of the population worldwide) with prominent and persistent inflammation that does not lead to cancer development (Nickoloff, 2001). Moreover, conversion from clinically symptomless skin to thick, erythematous scaling plaques includes a remodeling of both epidermal and dermal compartments with neovascularization accompanied by activation of CD4+ T cells and other immunocytes (Nickoloff and Nestle, 2004). The psoriatic plaque is further interrogated because STAT3 signaling, which is important in cutaneous carcinogenesis, is also dramatically increased in lesional keratinocytes (Chan *et al*, 2004; Sano *et al*, 2005). This remarkable set of cellular changes is entirely reversible, particularly when agents that neutralize TNF-α are administered to patients with psoriasis (Nickoloff and Nestle, 2004). Perhaps of greatest interest to this topic is that lesional keratinocytes are characterized by a high resistance to apoptosis, and yet only rarely, if ever, become converted to carcinomas (Wrone-Smith *et al*, 1997; Nickoloff, 2001). NF-κB has also been implicated in psoriatic lesions, as agents targeting this signal transduction pathway have shown pre-clinical efficacy (Zollner *et al*, 2002). Furthermore, in this issue, Lizzul *et al* (2005) demonstrate NF-κB signaling is activated in psoriatic plaques and is downregulated following administration of a TNF-α targeting agent (e.g., etanercept).

TNF-α signaling is of particular relevance to this topic of inflammation and skin cancer. On the one hand, psoriatic plaques are dependent on TNF-α signaling, as agents that block TNF-α are highly effective in treating psoriatic patients (Nickoloff and Nestle, 2004). TNF-α also appears to be essential for skin carcinogenesis, however, as mice genetically engineered to be deficient in TNF-α are resistant to skin carcinogenesis (Moore *et al*, 1999). Furthermore, TNF-α receptor 1-mediated signaling is required for skin cancer development in mice when accompanied by NF-κB inhibition (Lind *et al*, 2004). Thus, the interplay between inflammatory cytokines such as TNF-α and the NF-κB signaling pathway

must be taken into consideration when attempting to link inflammation and skin cancer (Pasparakis *et al*, 2002).

One cannot easily dismiss the many dilemmas raised by the psoriatic plaque that confound a simple link between tissue repair, inflammation, and carcinogenesis. Since it is easily visible to the naked eye, and patients may suffer from such lesions for decades, it is difficult to argue that various skin cancers such as squamous cell carcinoma, basal cell carcinoma, or melanoma actually do develop within plaques but are being overlooked by patients and dermatologists (Nickoloff, 2004). Remarkably, psoriatic plaques are intentionally exposed to mutagenic agents including excessive sunlight, topical administration of crude coal tar, or parenteral DNA cross-linking agent-psoralen followed by ultraviolet light (i.e. PUVA). Moreover, these treatments are known to induce skin cancer in non-lesional skin (Nijsten and Stern, 2003). To add insult to injury, prior to the use of new and effective biological agents selectively targeting TNF-α, thousands, if not tens of thousands, of patients were and are being treated with immunosuppressive agents such as corticosteroids, or cyclosporine A. Thus, since psoriatic skin is characterized by altered differentiation, angiogenesis, increased telomerase activity, proliferative changes, and apoptosis resistance (McKenzie and Sabin, 2003), one would expect that each and every psoriatic plaque would be converted to cancer, or at least serve as fertile soil for the presence of non-epithelial skin cancers over time (Nickoloff, 2001, 2004).

How can one reconcile the key characteristics of psoriatic lesions with the paucity of cancers that arise within such plaques? There is a biological context requiring consideration in which cells can simultaneously resist apoptosis and transformation—namely the senescent state (Campisi, 2001). Using normal keratinocytes in culture and exposing these cells to cytokines that are present in psoriatic plaques such as TNF-α or interferon-γ, the keratinocytes become irreversibly growth arrested and acquire a resistance to apoptosis (Chaturvedi *et al*, 1999, 2003). Many biochemical features are present in keratinocytes undergoing accelerated senescence including induction of senescence-associated β-galactosidase and cyclin-dependent kinase inhibitors such as members of the INK4a/Arf locus (p12, $p14^{ARF}$, p16) as well as $p21^{WAF1}$ (Healy *et al*, 1995). Several senescence markers can also be found within psoriatic plaques *in vivo* (Chaturvedi *et al*, 2003; Elias *et al*, 2004; Nickoloff, 2004).

Thus, we postulate that chronic inflammation in psoriatic skin induces a state of "tumor demotion" possibly through triggering premature, or accelerated, cell senescence. There may also be paracrine effects emanating from lesional keratinocytes or underlying fibroblasts that could effectively suppress neighboring non-epithelial cells, such as melanoma cells, as well. Secreted proteins over-produced by senescent keratinocytes potentially mediating an antitumorigenic response include maspin and transforming growth factor β (TGFβ) isoforms (Tremain *et al*, 2000; Nickoloff *et al*, 2004). As regards TGFβ, Bhowmick *et al* (2004) described the phenotype of $Tgfbr2^{fspKO}$ mice in which TGFβ receptor type II is selectively inactivated in fibroblasts, resulting in intraepithelial neoplasia in prostate and invasive squamous cell carcinoma of the forestomach. In addition, Becker *et al* (2004) reported that TGFβ suppresses colon cancer progression in an injury/inflammation model via inhibition of interleukin-6 trans signaling. Thus, a keratinocyte senescence program culminating in TGFβ may, through autocrine and paracrine mechanism, play a major role in suppressing tumorigenesis at or around the psoriatic plaque (Campisi, 2001). Perhaps the presence of senescent keratinocytes restricts expansion of transformed stem cells from small clones to large clones, which could account for the lack of tumorigenesis (Hennings *et al*, 1990); or the clonal expansion of keratinocytes in psoriatic plaques does not include a stem cell component (Chaturvedi *et al*, 2002). It should also be noted that in the case of psoriasis, epidemiological data on cancer incidence indicate there is no general skin protection as revealed by PUVA-induced lesions that occur on non-plaque containing skin (Nijsten and Stern, 2003). Thus, whatever the mechanism by which plaques resist transformation, it must be confined to the lesional skin itself, and not necessarily protect surrounding skin or create a more generalized field effect.

An alternative consideration mediating tumor suppression within psoriatic plaques is that the inflammatory infiltrate generates anti-infectious factors such as β-defensins (Harder *et al*, 1997), which compensates for barrier disruption by inhibiting invasion of various pathogenic organisms such as bacterial, fungal, and viral infections (Henseler and Christophers, 1995). The presence of such factors that sterilize lesions could serve to target and suppress potentially transforming infectious agents. In addition, factors like β-defensins may serve to bridge innate and adaptive immune responses, thereby combating neoplastic cells as they initially appear (Ganz, 2003).

Interactions between epithelial cells and microflora are gaining increasing attention in the gastrointestinal tract as resident commensal bacteria may activate cell survival signals via Toll-like receptors and enhanced NF-κB signaling (Clevers, 2004; Rakoff-Nahoum *et al*, 2004). The role of NF-κB signaling within keratinocytes may serve as a tumor suppressor by inducing growth arrest via $p21^{WAF}$ (Zhang *et al*, 2004), or as a tumor promoter by enhancing their survival and resistance to apoptosis. Thus, just as we have come to appreciate that AP-1 and Notch signaling may be double-edged swords when it comes to tumor promotion *versus* tumor suppression, so too may inflammatory reactions that activate such signaling pathways have dualistic, and perhaps even directly opposing influences depending on the cellular context, strength and persistence of signals, and other microenvironmental factors (Eferl and Wagner, 2003; Radtke and Raj, 2003).[1]

As suggested by Radisky *et al* (2001), anti-cancer research might be more effective if aimed at eradicating the cause or signaling context of abnormality, rather than just treating the end result. Devoting efforts at unraveling the signaling pathways and cellular context of keratinocytes within psoriatic plaques could provide novel insights into potent tumor suppressive pathways that lie within a chronic inflammatory network. It is likely that all inflammatory conditions are not alike, whether afflicting the skin or

[1]Nickoloff BJ, *et al*: JID—Montagna Symposium, 2004, submitted.

extra-cutaneous sites, and we need to distinguish between those chronic inflammatory sites that predispose to cancer development, and those that may prevent tumor formation.

In any event, exploring and discovering the essential elements mediating inflammation-induced tumor suppression may pay dividends beyond the heartbreak of psoriasis in skin to many other organ systems such as the liver, respiratory, and gastrointestinal tracts, in which the response to tissue injury is repair and chronic inflammation. In conclusion, it would seem prudent to remember the paradigm proposed by Weiss (1971) in which he suggested that premalignant cells do not comprise an isolated island, but are rather a focus of intense tissue interactions. The myriad inflammatory effects of the tumor microenvironment are important for understanding tumor development, as well as tumor suppression and senescence, and for the design of efficacious prevention strategies against inflammation-associated cancer.

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