remarkable. There is, however, one issue still to be resolved. The analysis reported in this work relies on measurements of spectral amplitude. To access the nonlinear response directly, both the amplitude and phase of radiation from atoms driven by a light field should be characterized. This is challenging, because there is no easy way to measure the phase of radiation at ultraviolet wavelengths. If such methods are realized, they would open up yet another horizon in ultrafast science.

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**CANCER**

Fibroblasts for all seasons

Connective-tissue cells known as fibroblasts display an increasing spectrum of functions. Different fibroblast subtypes are now shown to either promote or suppress inflammation-associated intestinal cancers.

**ERWIN F. WAGNER**

Cancer-associated fibroblasts (CAFs) are a key cell population in the tumour stroma, the term used for all cells of the tumour microenvironment except the cancerous ones. CAFs typically originate from mesenchymal cells, which are present in several healthy tissues. They frequently promote cancer progression by inducing cell proliferation, inflammation, blood-vessel growth and metastasis. However, they can also restrain tumour formation. Two papers in *The Journal of Experimental Medicine* highlight the complexity of these cells and remind us to be cautious in contemplating their use in therapeutic applications. Both research groups studied the effect of fibroblast-specific inhibition of the NF-kB–IKK signalling pathway, a major mediator of inflammation and cancer, on inflammation-associated colorectal cancer. Pallangyo et al. find that such inhibition promotes cancer development in mice, whereas Koliaraki et al. report a suppressive effect. Pallangyo and colleagues used the carcinogen azoxymethane (AOM) in conjunction with the inflammatory agent dextran sodium sulfate (DSS) to induce colitis-associated cancer in mice. They inhibited NF-kB–IKK signalling in CAFs by specifically deleting the gene that encodes IKKβ, and found that this promoted proliferation of cancerous intestinal epithelial cells. It also suppressed tumour-cell death, induced the formation of blood vessels and enhanced the recruitment of immune cells, all features that contribute to enhanced tumour growth. Furthermore, IKKβ-deficient CAFs showed activated TGF-β signalling, a pathway that can promote cell proliferation, and secreted elevated levels of hepatocyte growth factor (HGF), a major growth factor produced by CAFs (Fig. 1). The authors also show that pharmacological inhibition of Met, the receptor for HGF, reduced tumour growth in these mice.

Surprisingly, Koliaraki et al. come to the opposite conclusion, despite using similar protocols for inducing colitis-associated cancer and deleting IKKβ. The researchers report that inhibition of NF-kB–IKK signalling led to a reduction in the incidence and number of intestinal tumours. They observed reduced epithelial-cell proliferation and immune-cell infiltration, and lowered expression of inflammatory cytokine proteins, such as interleukin-6 (IL-6). A similar result was obtained when IKKβ expression was inhibited in the fibroblasts of mice that mimicked the familial colorectal cancer adenomatous polyposis (APC), but only when the mice were subjected to DSS-induced inflammation. This indicates that the tumour-suppressive effect of inactivating IKKβ in fibroblasts is restricted to cases of inflammation-associated colorectal cancer.

How can these results, which at first glance seem contradictory, be explained? One possibility lies in the fact that the studies use slightly different strategies to delete the gene that encodes IKKβ (technically speaking, they use different conditional alleles and different collagen gene promoters to express the Cre recombinase). The genetic background of the mice, the timing of IKKβ deletion and the population of fibroblasts targeted in the two experimental settings also differ (Fig. 1), as does the environment and possibly the resident microorganisms of the mutant mice. Pallangyo and colleagues’ deletion of IKKβ involved treating mice with the molecule tamoxifen, and the deletion effectively started at the tumour-initiation stage. Koliaraki and colleagues used
a constitutive gene-deletion approach. Because this leads to much earlier IKKβ inhibition, the cell population had a chance to adapt to the loss of IKKβ.

Another potential source of difference lies in the possibility that IKKβ was deleted in cells other than their targets. Pallangyo and colleagues did not detect gene recombination (indicative of deletion) in epithelial, endothelial or haematopoietic cells, whereas Koliaraki et al. have previously reported that their deletion system affects other cell types (chondrocytes, myocytes and keratinocytes) and results in recombination in certain haematopoietic cells. IKKβ deletion in gut epithelial and myeloid cells can protect against tumour formation, so it is possible that ‘unspecific’ deletion contributed to the tumour-suppressive effect observed by Koliaraki and colleagues.

Furthermore, different cell markers and experimental tools were used to characterize the targeted cell populations, and the extent of overlap between these cell populations is therefore difficult to assess. It is possible that Pallangyo and colleagues’ approach affects most CAFs, whereas Koliaraki and colleagues’ method targets just those that are sensitive to inflammation, which might explain why the latter group sees an effect of IKKβ deletion only when an inflammatory stimulus is added to the initial mutagen.

Besides these differences, the most exciting aspect of the two studies is that they raise the possibility that fibroblast subpopulations in the tumour stroma may have fundamentally different and even opposing functions in regulating tumour formation and development. Tumour-protective and tumour-promoting characteristics have been attributed to CAFs in various cancers, including pancreatic, skin and mammary cancers. The lack of CAF-specific cell markers and the use of different genetic tools has led to contradictory results and some controversies. Although Pallangyo et al. and Koliaraki et al. both define fibroblasts as collagen-producing cells, the two studies may suffer similar shortcomings.

Future work is needed to better characterize CAFs, and improved genetic tools need to be developed to specifically target distinct stromal cells in mice. If NF-κB–IKK signalling has opposing roles in different fibroblast subpopulations in colorectal cancer, then characterizing these subpopulations, dissecting the underlying mechanisms and extending these studies to other cancer types will provide new ideas about the role of such cells in cancer. Do these cell populations have potential clinical value? And will CAF-specific proteins ever serve as prognostic markers or targets for anticancer drugs? In my opinion, more basic research is essential to move this exciting field forward, and these two papers are a reminder of the value of multiple parallel studies to build hypotheses on solid experimental data.

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**A home for Xenoturbella**

Sometimes it is the most unassuming animals that cause the most consternation. *Xenoturbella* (pictured) are simple marine flatworms with no brain, anus, gonads, excretory system or through gut, so one would expect them to find a home among the acocels — similarly simple animals thought to lie at the base of the evolutionary tree of Bilateria, bilaterally symmetrical animals. Yet *Xenoturbella* have caused puzzlement since they were first described in 1949, because quibbles about their ultrastructure and mitochondrial DNA sequences have meant that the worms have never sat entirely happily in their assumed station.

Analysis of nuclear DNA sequences underlined the oddity: *Xenoturbella* were even thought to be highly degenerate molluscs until the revelation that molluscs are what *Xenoturbella* eat. Even stranger was the proposal that *Xenoturbella* and other acocels were most closely related to hemichordates (animals known as acorn worms and pterobranchs) and echinoderms (radially symmetrical marine animals such as sea urchins and starfish). This cast into question the timing of the evolution of several advanced characteristics, such as gill slits, that are shared by members of the deuterostome branch of Bilateria (to which hemichordates and echinoderms belong), but that are lacking in *Xenoturbella*. It even raised questions about the last common ancestor of Bilateria — perhaps *Xenoturbella* were not as simple as they looked, but had degenerated from a structurally more complex ancestor.

These questions are all but resolved by two studies in this week’s issue. Cannon et al. (page 89) present a robust phylogenetic analysis based on the gene-transcript profiles of eleven species of *Xenoturbella* and other acocels. This shows that the combined group, known as Xenacoelomorpha, indeed lies at the very base of the bilaterian radiation. Rouse et al. (page 94) add four new species of *Xenoturbella* from the eastern Pacific Ocean to the one already known from the waters of Scotland and Scandinavia. The authors’ anatomical and phylogenetic studies on these new forms add weight to the idea that these worms were the earliest to branch from other bilaterians. Zoologists can exhale, and their shy charges can resume their diet of molluscs in peace.

**Henry Gee**