OPTICAL PHYSICS

Ultrashort light pulses shake atoms

The response of electrons in atoms to ultrashort optical light pulses has been probed by measuring the ultraviolet light emitted by the atoms. This reveals that a finite time delay occurs before the response. SEE LETTER P.66

KYUNG TAEC KIM

Characterization of the atomic and molecular response to a light wave is the first step in understanding the fundamental interactions between light and matter. Because the response of electrons in atoms to light waves is so rapid, tremendous efforts have been made to develop light sources that produce pulses as short as possible to study such ultrafast dynamics. In this issue, Hassan *et al.*[1] (page 66) report the generation of sub-femtosecond light pulses in the visible and near-visible spectral ranges (1 femtosecond is 10^{-15} s). The authors used these ultrashort pulses to probe nonlinear responses of electrons in krypton atoms to light, and find that there is a finite response time.

Atoms are composed of negatively charged electrons and a positively charged nucleus. The response of an atom to a light wave is often considered to be akin to the behaviour of a system of two masses — one for a bound electron and the other for the rest of the atom — connected by a spring (Fig. 1). When the atom is exposed to the light wave, the electron moves with respect to the nucleus because of the Lorentz force (the combination of electric and magnetic forces that acts on a point charge in the presence of an electromagnetic field), resulting in a charge separation. In a weak light field, the proportionality between the field strength and the charge separation is linear, which means that the electron oscillates with the same frequency as that of the applied field.

But the situation becomes complicated when atoms are exposed to a strong field (but not strong enough to cause much ionization). Electron oscillation becomes nonlinear with respect to the applied light field as the electron moves farther from the nucleus. The oscillating electron can emit radiation with a broader spectrum than that of the applied light. This radiation offers a key to understanding the nonlinear response of the atom to the strong light field.

To investigate such nonlinear responses, Hassan and colleagues have generated optical attosecond pulses — bursts of light in the visible and near-visible spectral ranges that last for several hundreds of attoseconds (1 as is 10^{-18} s). First, the authors passed laser pulses though a hollow fibre filled with neon gas[2], which broadened the spectrum of the pulses to encompass the near-infrared, visible and ultraviolet regions (equivalent to photon energies of between approximately 1.1 and 4.6 electronvolts). The spectrum was then divided into four different bands, each of which was optimized to produce shorter-duration pulses. Finally, the researchers combined the four pulses, controlling the pulses' phases (their progression through their electromagnetic wave cycles) in such a way as to generate optical attosecond pulses.

The resulting light-field synthesizer has an extraordinary performance: the initial laser-pulse duration of 22 fs is compressed to 975 as without serious energy loss. The synthesized pulse looks like a half-cycle pulse (Fig. 1). This is the first demonstration of the generation of isolated sub-femtosecond light pulses in the visible and ultraviolet spectral ranges.

Hassan *et al.* went on to irradiate krypton atoms with intense optical attosecond pulses. The temporal profile of these pulses changes dramatically depending on their phase. Accordingly, the ultraviolet spectra generated by the krypton atoms displayed pronounced phase-dependent amplitude modulation. The data reveal that the nonlinear response of bound krypton electrons to light is delayed, and that the delay increases, by up to 115 as, with the applied strength of the optical field.

The authors also devised and verified an equation to describe the nonlinear response, and showed that this reconstructs the experimental results, including the delay. They attribute the response to an increase in the total nonlinear polarizability of the atom during its interaction with the optical attosecond pulse.

This work has important implications for future research in ultrafast science. Until now, attosecond X-ray pulses have been the main tool for ultrafast 'pump–probe' experiments[3], acting as both the stimulus for a physical effect and a means of probing its outcomes. However, the applications of these X-ray pulses are quite limited because of their weak intensity. By contrast, Hassan and colleagues' optical attosecond pulses are intense enough to initiate strong-field processes, opening up routes to new experiments. Moreover, such pulses could be applied to molecules and solids, which may produce different nonlinear responses depending on their proton dynamics[4] and structure[5].

The demonstration of optical attosecond pulses and their application to probe non-instantaneous responses of atoms is

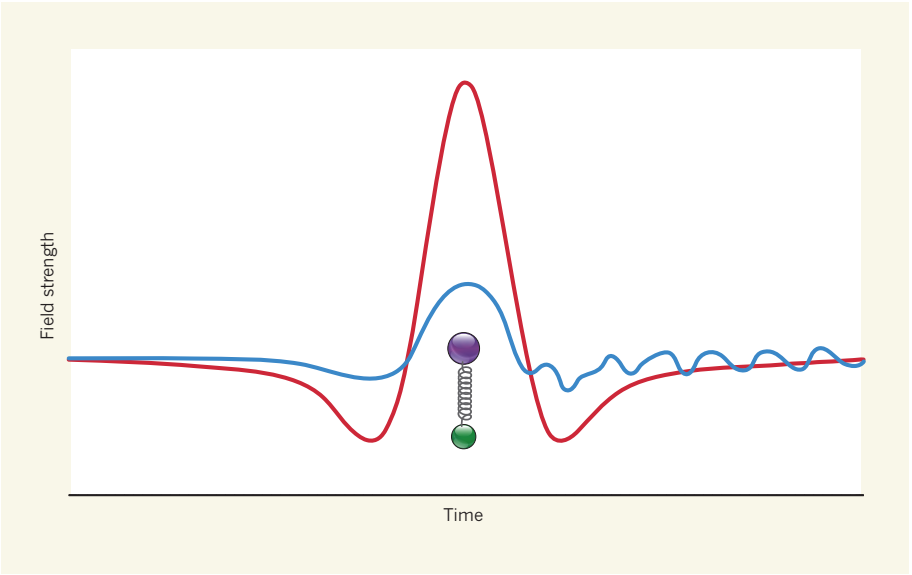

Figure 1 | Bound electron motion in a half-cycle light wave. An atom in a light wave can be considered to behave like a system of two masses — a light mass for a bound electron (green ball), and a heavy mass for the rest of the atom (purple ball) — connected by a spring. The electron oscillates with respect to the rest of the atom because of the electric force associated with the applied light field (red line indicates the light field; here, the light pulse corresponds to half an electromagnetic wave cycle). The oscillating electron can emit nonlinear radiation (blue line). Hassan *et al.*[1] have used sub-femtosecond light pulses in the visible and near-visible spectral ranges to probe the radiation emitted by krypton atoms.

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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1. Hassan, M. Th. *et al. Nature* **530,** 66–70 (2016).
2. Nisoli, M. *et al. Opt. Lett.* **22,** 522–524 (1997).
3. Corkum, P. B. & Krausz, F. *Nature Phys.* **3,** 381–387 (2007).
4. Baker, S. *et al. Science* **312,** 424–427 (2006).
5. Itatani, J. *et al. Nature* **432,** 867–871 (2004).

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.

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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[1]. Two papers[2,3] 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-κB–IKK signalling pathway, a major mediator of inflammation and cancer[4], on inflammation-associated colorectal cancer. Pallangyo *et al.*[2] find that such inhibition promotes cancer development in mice, whereas Koliaraki *et al.*[3] 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-κB–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.

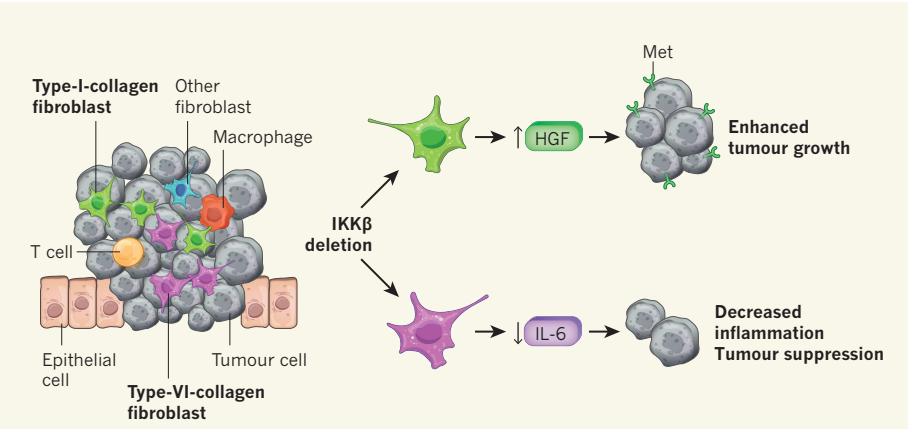

Figure 1 | Fibroblast functions in inflammation-associated colorectal cancer. Tumours contain non-cancerous cells that can influence the growth and progression of the tumour. Pallangyo *et al.*[2] and Koliaraki *et al.*[3] studied the effect of loss of the signalling protein IKKβ in fibroblasts in mouse models of inflammation-associated colorectal cancer. When Pallangyo *et al.* deleted IKKβ at tumour initiation in type-I-collagen-producing fibroblasts, they observed enhanced tumour growth, seemingly mediated through fibroblast production of hepatocyte growth factor (HGF), which binds to the receptor Met on tumour cells. By contrast, when Koliaraki *et al.* constitutively deleted IKKβ in a more-restricted population of type-VI-collagen-producing fibroblasts, they observed fewer tumours and decreased inflammation. They also saw reduced expression of the inflammatory molecule IL-6. These differences may be explained in part by how and in which cells the researchers deleted IKKβ, showing that different subpopulations in the tumour microenvironment have different effects on tumour regulation.

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-κB–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