by interacting with the structural elements that anchor the peptide's carboxy terminus in a pocket of the MHC class I molecule's peptide-binding groove.

The structure[10,11] of MHC class I molecules in complex with TAPBPR shows that the latter molecule does not detectably interact with ERp57, and that its binding site on the MHC class I molecule overlaps with the tapasin binding site. A structural feature of TAPBPR dubbed the scoop loop[10] helps to displace peptides that have modest affinity for the MHC molecule by competing for interaction with amino-acid residues in the groove that would otherwise stabilize interactions between the MHC molecule and the peptide.

Unlike tapasin, TAPBPR is found in locations other than the ER, and might even act downstream of the PLC as the final arbiter of the overall quality of newly formed MHC class I–peptide complexes. In the ER, TAPBPR associates with an enzyme called UDP glucose glycoprotein glycosyltransferase, which, in conjunction with other ER-resident enzymes, acts as a timer for the engagement and release of MHC class I molecules by the calnexin–calreticulin cycle (which controls glycoprotein maturation in the ER; ref. 4). Possible discrepancies between the way in which the calnexin–calreticulin cycle in the ER controls folding and assembly of MHC class I molecules, and TAPBPR-imposed quality control elsewhere in the cell, can now be addressed in greater detail.

Why does it help to better understand peptide presentation by MHC class I molecules? The visualization of the PLC in almost atomic detail might yield actionable information, for example by suggesting ways in which viral disablers of peptide presentation can be intercepted[12], or strategies to improve the presentation of peptides that are recognized on cancer cells. Tumour immunologists are increasingly turning their eye to neoantigens (variants of normal peptides that form only in cancer cells, and which can elicit an immune response when in complex with MHC products) as targets for immunotherapy[13]. So, the more detailed our understanding of how MHC products are put together, the better will be our predictions of how to manipulate immune processes and affect outcomes. ■

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ATMOSPHERIC SCIENCE

Thunderous nuclear reactions

The discovery that thunderstorms can trigger nuclear reactions provides insight into the physics of atmospheric electricity and unveils a previously unknown natural source of radioactive isotopes on Earth. SEE LETTER P.481

LEONID BABICH

Thunderstorms are some of nature's most spectacular phenomena. Almost a century ago, it was suggested that the strong electric fields in thunderclouds could accelerate electrons in the atmosphere and induce nuclear reactions[1]. However, these processes have been difficult to confirm experimentally. On page 481, Enoto *et al.*[2] report the first conclusive observational evidence for thunderstorm-produced nuclear reactions — with implications for our understanding of Earth's atmosphere and isotopic composition.

The idea that thunderstorms can trigger nuclear reactions was proposed[1] by the Scottish physicist and meteorologist Charles Wilson in 1925. However, the state of physics at the time meant that Wilson could not fully substantiate his idea. For instance, it is now known that neutrons are among the possible products of nuclear reactions and therefore that detecting these particles from a thunderstorm would provide evidence for Wilson's proposal. But neutrons were not discovered[3] until 1932.

Thunderstorms occur in the dense lowermost layers of the atmosphere. Electrons in these layers undergo frequent collisions with air molecules and are therefore subject to a strong drag force. Wilson's proposal requires electrons that have sufficiently high initial energies to overcome this force. It is now known that cosmic rays irradiate the atmosphere and produce such electrons, which multiply in thunderclouds to form an avalanche of high-energy electrons[4]. However, in the mid-1920s, cosmic rays were extremely mysterious and thought to be of terrestrial origin[5].

The first claimed detection of neutrons from a thunderstorm was reported[6] in 1985. These

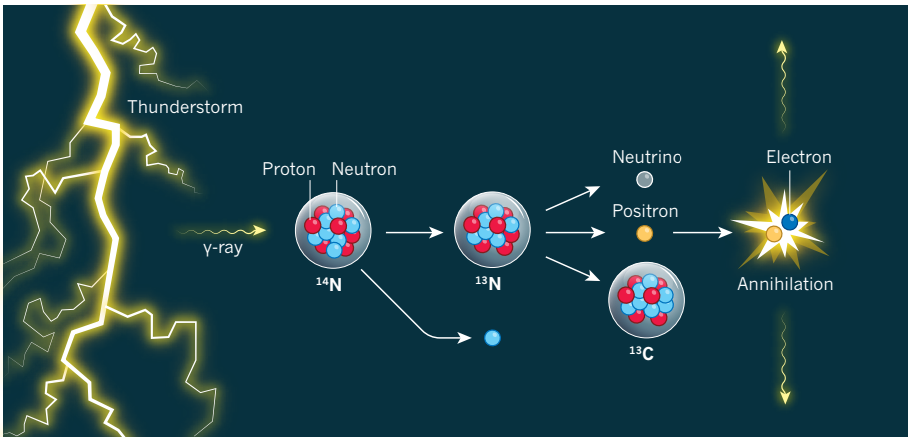

Figure 1 | Nuclear reactions triggered by a thunderstorm. Enoto *et al.*[2] report conclusive evidence that thunderstorms can induce nuclear reactions in the atmosphere. For example, the authors find that a thunderstorm can generate a high-energy γ-ray that knocks a neutron out of a nitrogen-14 nucleus, creating an unstable nitrogen-13 isotope. The isotope decays into a neutrino, a positron (the antiparticle of the electron) and a stable carbon-13 nucleus. Finally, the positron annihilates with an electron of an atmospheric molecule to produce a pair of γ-rays, each of which has a characteristic energy (0.511 megaelectronvolts).

observations were carried out in the Himalayas in a region that has extremely high thunderstorm activity (about 30 lightning strokes per day). Since the late 1990s, many other studies have also claimed statistically significant detections of thunderstorm-produced neutrons from all over the world[7–10]. However, the detectors could not distinguish neutrons from other particles such as electrons and γ-ray photons — all three would produce similar electric-current pulses in the detectors[11].

It was initially thought that thunderstorm-induced neutrons were produced in a nuclear reaction in which two nuclei of the hydrogen isotope deuterium fuse in the plasma created by lightning to form a helium nucleus and a neutron. However, it was later shown that the physical conditions in such a plasma do not allow this reaction to occur[12].

Instead, the avalanche of high-energy electrons produced in a thundercloud emits X-ray and γ-ray photons. Since the late 1980s, these photons have been detected on the ground, by aircraft flying inside thunderclouds, and by artificial satellites in near space (about 500 kilometres above Earth's surface)[13]. The photons have energies of up to hundreds of megaelectronvolts (MeV).

High-energy electrons, and γ-rays that have energies larger than about 10 MeV, can knock out neutrons from atmospheric nitrogen-14 and oxygen-16 nuclei — by electrodisintegration in the case of electrons and photonuclear reactions in the case of γ-rays[11,12]. Although the ability of thunderstorms to produce neutrons through photonuclear reactions has been demonstrated using computer simulations[11,13], direct experimental evidence has been absent.

Rather than focusing on the neutrons, Enoto and colleagues considered the other products of the photonuclear reactions involving nitrogen-14 and oxygen-16: namely, unstable nitrogen-13 and oxygen-15 isotopes (Fig. 1). These isotopes decay after a few minutes into stable carbon-13 and nitrogen-15 nuclei through the emission of a neutrino and a positron — the antiparticle of the electron. Finally, the positron annihilates with an electron of an atmospheric molecule to produce a pair of γ-rays.

Because both positrons and electrons have masses of 0.511 MeV (expressed in energy units), each emitted γ-ray has an energy of 0.511 MeV. Therefore, to confirm the existence of these photonuclear reactions, the authors simply needed to identify a line at this energy in the wide energy spectrum of all γ-rays.

To this end, Enoto *et al.* carried out ground-based observations of γ-ray emission from low winter thunderclouds above the coast of the Sea of Japan. On 6 February 2017, they detected an intense γ-ray flash that lasted for less than 1 millisecond, which they associated with a lightning stroke. After the initial γ-ray flash, the authors observed a prolonged γ-ray line at an energy of 0.511 MeV that lasted for about a minute (see Fig. 4 in the paper[2]). This line is a conclusive indication of electron–positron annihilation, and represents unequivocal evidence that photonuclear reactions can be triggered by thunderstorms.

Enoto and colleagues' discovery is important because it unveils a previously unknown natural source of isotopes in the atmosphere, in addition to the irradiation of Earth by cosmic rays. These isotopes include nitrogen-15, carbon-13 and carbon-14, the last of which is widely used in the dating of archaeological artefacts and artworks. In fact, the contribution of thunderstorms to Earth's carbon-14 abundance could be comparable in some regions to that of cosmic irradiation[14]. Future studies should check whether thunderstorms produce other isotopes (such as those of hydrogen, helium and beryllium).

Thunderstorm-induced nuclear reactions could occur in the atmospheres of other planets, such as Jupiter and Venus, and might therefore contribute to the isotopic composition of these atmospheres. However, determining the magnitude of this contribution will require detailed observations of γ-rays and neutrons from thunderstorms on these planets. Another implication of Enoto and colleagues' discovery is that the neutrons are formed outside the plasma created by lightning. This suggests that these neutrons cannot provide information about the plasma, in contrast to expectations[15]. ■

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CANCER IMMUNOTHERAPY

How T cells spot tumour cells

Immunotherapy can reawaken T cells to destroy tumour cells. Modelling of tumour and T-cell interactions suggests why certain tumour cells are targeted and improves predictions of immunotherapy outcome. SEE LETTERS P.512 & P.517

SIRANUSH SARKIZOVA & NIR HACOHEN

The T cells of the immune system have a key role in the identification and elimination of cells that pose a threat to the body, such as infected cells and cancer cells. Two papers by Balachandran *et al.*[1] (page 512) and Łuksza *et al.*[2] (page 517), which have many authors in common, propose a framework to assess how effectively tumours can be detected by T cells — a tumour property known as immunogenicity. The authors demonstrate that their models for assigning tumour-immunogenicity scores can be used to predict clinical responses to a type of cancer immunotherapy called checkpoint blockade.

Most cells in the body present peptide fragments known as antigens on their cell surface, which are generated from intracellular proteins. Each peptide is bound in a complex with a specialized receptor called an MHC class I protein (HLA class I in humans). T cells known as cytotoxic T cells police the body in search of cells displaying specific antigens, especially antigens from infectious organisms, or in the case of cancer, antigens known as neoantigens that have arisen as a result of a mutation (Fig. 1). If the T-cell receptor (TCR) of a cytotoxic T cell recognizes and binds an antigen that is not normally present, the T cell will often unleash an attack that kills the cell displaying that antigen. TCRs are highly variable and have slightly different antigen-binding regions, enabling the immune system to recognize millions of antigens[3]. Antigen binding to MHC proteins and TCR recognition of antigen–MHC complexes are key determinants of an immune response.

Tumour cells often fight back against this