induction of senescence is as follows: oncogenes or attrition of telomeres induce signalling pathways that depend on the transcription factor NF-κB and the protein kinase p38. These two proteins coordinately induce the expression of CXCR2 and its ligands. CXCR2, in turn, favours accumulation of the tumour suppressor p53. Intriguingly, there is specificity in the inhibitory signals controlled by CXCR2, because other classic tumour suppressors (p21, $p16^{INK4a}$ and $p19^{ARF}$) are not involved in CXCR2-controlled senescence.

Acosta *et al.*[3] further demonstrate high, albeit non-uniform, expression of CXCR2 in benign lesions in mice and humans. They identify a loss-of-function mutation in CXCR2 in a lung-cancer cell line. Although this mutation could be an artefact of cell culture, the observation serves as a proof-of-principle for the role of CXCR2 in tumour control.

It is noteworthy that IL-6, IL-8 and C/EBPβ have previously been linked to oncogene-driven senescence[7–9]. The new studies[2,3] provide mechanistic detail about the contribution of secreted proteins to cellular senescence, and show evidence for this activity *in vivo*. But secretory loops controlling premature senescence have other components. Another group[10] recently reported that the induction and secretion of insulin-like growth factor binding protein-7 (IGFBP7) is essential for $BRAF^{V600E}$-induced senescence in melanocytes and fibroblasts. In fact, if expressed at high enough levels, IGFBP7 is sufficient to drive premature senescence.

In contrast to classic tumour suppressors, which are inactivated or downregulated during tumorigenesis, the expression of IL-6, IL-8 or CXCR2 is not lost in advanced tumours. Therefore, it seems likely that the wiring of the secretome is fundamentally different in normal and tumour cells. In senescent cells, oncogenes induce some secreted proteins at levels 30–100 times higher than normal. This substantial increase in expression may saturate the protein-folding capacity of the endoplasmic reticulum, and the associated stress that this causes — the unfolded protein response — can also contribute to senescence[11].

These findings' significance is directly related to their clinical implications. Together, the three studies[2,3,10] describe more than 20 proteins whose inactivation bypasses oncogene-induced senescence. The immediate corollary is that there are at least 20 previously unknown genes that cancer cells can target to evade both natural suppressive mechanisms and the potential beneficial effect of treatments that depend on the activation of tumour-cell senescence.

What's more, Kuilman *et al.*[2] describe changes within discrete nodes in the cytokine network — for example, deregulation of IL-6 or C/EBPβ — that might be sufficient to revert senescence to a proliferative state, without the need for other genetic alterations. Nonetheless, it may still be possible to modulate the balance in the cytokine network in order to induce tumour-cell death by apoptosis. This pro-apoptotic activity of secreted proteins was demonstrated by forced expression of IGFBP7 in melanoma cells[10]. Understanding how to interfere with the cytokine secretome to efficiently kill advanced tumours, without activating compensatory mechanisms, is a challenge that will undoubtedly lead us to other unexpected loops and kinks in cancer cells and their microenvironment. ■

Maria S. Soengas is in the Melanoma Group, Molecular Pathology Programme, Spanish National Cancer Research Centre, Madrid 28029, Spain.
e-mail: msoengas@cnio.es

1. Finkel, T., Serrano, M. & Blasco, M. A. *Nature* **448,** 767–774 (2007).
2. Kuilman, T. *et al. Cell* **133,** 1019–1031 (2008).
3. Acosta, J. C. *et al. Cell* **133,** 1006–1018 (2008).
4. Campisi, J. & d'Adda di Fagagna, F. *Nature Rev. Mol. Cell Biol.* **8,** 729–740 (2007).
5. Chien, Y. & Lowe, S. W. *Cell* **132,** 339–341 (2008).
6. Michaloglou, C. *et al. Nature* **436,** 720–724 (2005).
7. Mason, D. X., Jackson, T. J. & Lin, A. W. *Oncogene* **23,** 9238–9246 (2004).
8. Schnabl, B., Purbeck, C. A., Choi, Y. H., Hagedorn, C. H. & Brenner, D. *Hepatology* **37,** 653–664 (2003).
9. Sebastian, T., Malik, R., Thomas, S., Sage, J. & Johnson, P. F. *EMBO J.* **24,** 3301–3312 (2005).
10. Wajapeyee, N., Serra, R. W., Zhu, X., Mahalingam, M. & Green, M. R. *Cell* **132,** 363–374 (2008).
11. Denoyelle, C. *et al. Nature Cell Biol.* **8,** 1053–1063 (2006).

PLANETARY SCIENCE

# Organic lakes on Titan

François Raulin

**While orbiting Saturn, the Cassini spacecraft has spotted lakes containing ethane on Titan, the planet's largest moon. Titan is so far the only planetary object other than Earth that is known to have liquid bodies on its surface.**

Titan is the largest satellite of the giant planet Saturn. Its diameter of 5,150 kilometres makes it bigger than Mercury and only 25% smaller than Mars. It is the second-largest satellite in the Solar System after Jupiter's Ganymede based on diameter alone, and would claim first place if its dense atmosphere, which extends more than 1,000 kilometres above its surface, were included. Fly-bys of Titan by the Voyager spacecraft in the early 1980s helped determine the main composition, temperature and pressure of this atmosphere. Although much colder than Earth's (around 90–94 kelvin at the surface), and lacking molecular oxygen ($O_2$), it shows many similarities to the atmosphere of our planet. It consists mainly of molecular nitrogen ($N_2$), with a surface pressure of 1.5 bar and, like Earth, it has a structure comprising a troposphere and a stratosphere. On page 607 of this issue, Brown *et al.*[1] confirm

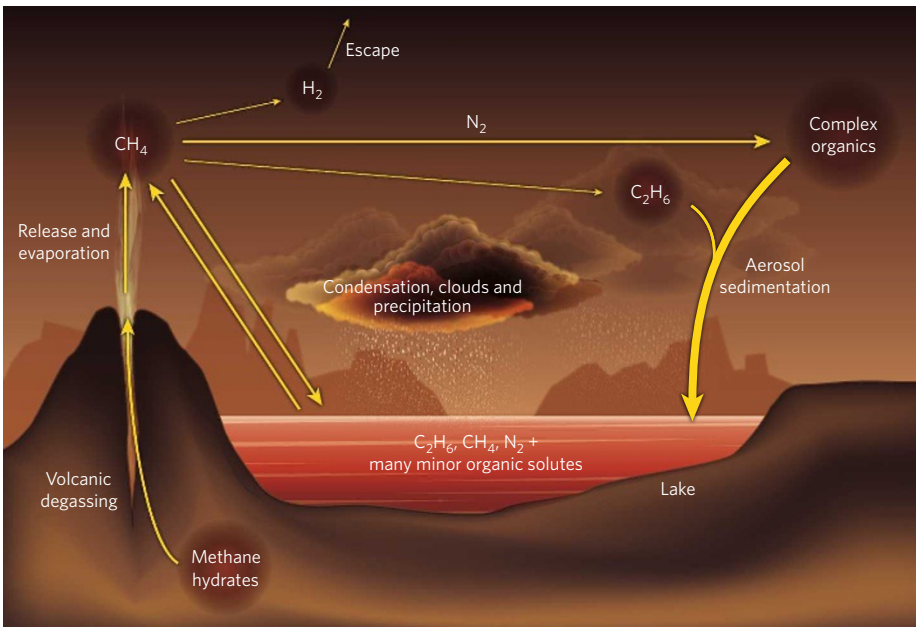


**Figure 1 | Titan's methane/ethane cycle.** Methane ($CH_4$) is released into the atmosphere from Titan's interior stores through volcanic action, and evaporates from the lakes of methane and ethane ($C_2H_6$) identified by the Cassini spacecraft on the satellite's surface[1]. Chemical reactions in the atmosphere convert it to ethane; complex organic aerosols consisting of carbon, hydrogen and nitrogen; and hydrogen gas ($H_2$), which escapes into space. Ethane and methane partly condense, forming clouds and hazes that precipitate, replenishing the lakes and bearing many organic species in solution.

the existence of a further similarity between Earth and Titan — the presence of open bodies of liquid on its surface.

The idea that liquid bodies exist on Titan's surface is not new. After the discovery that Titan's atmosphere contains a substantial amount of methane, the question of its origin and evolution was seen as a key to understanding Titan's mysteries. A combination of light from the Sun and high-energy electrons from Saturn's magnetosphere would have destroyed all methane in the atmosphere within a few tens of millions of years, implying that the methane was being replenished by a source on, or in, Titan. The main volatile organic product of the light-induced breakdown of methane is ethane, and it was proposed that an ocean consisting of liquid ethane and methane with dissolved $N_2$ covered Titan[2].

The Voyager probes were unable to get a peek at Titan's surface, as it was masked by hazy layers in the atmosphere. But with the Cassini-Huygens mission, this veil has finally been lifted. Several instruments on the Cassini spacecraft have been observing the moon in regions of the electromagnetic spectrum in which the atmosphere is transparent.

These observations quickly ruled out the possibility of a global ocean[3], but radar data strongly supported the possibility of smaller seas and lakes, mainly in the colder northern regions[4]. Furthermore, camera images taken in mid-2005 showed a dark surface feature near the south pole as big as North America's Lake Ontario, speculatively named Ontario Lacus. Brown *et al.*[1] have now identified the characteristic spectrum of liquid ethane in infrared spectra of Ontario Lacus.

The Cassini-Huygens mission has demonstrated the existence of a complex cycle of methane in Titan's geochemistry similar to the water cycle on Earth (Fig. 1). Large stores of methane seem to exist within Titan in the form of methane hydrates (clathrates) trapped during the formation of the satellite[5]. Methane may also be produced through the reaction of water with igneous rocks under high pressures, which would also form hydrogen gas. Ethane, formed by photodissociation of methane in the atmosphere, accumulates on Titan's surface, replenishing the surface lakes — which are therefore one possible ethane reservoir, as are haze particles in the atmosphere into which ethane can be sequestrated[6].

Titan's lakes are probably a liquid ethane–methane mixture together with dissolved nitrogen, as previously proposed for the speculative oceans[2]. Also dissolved in them will be a variety of solutes, mainly organic compounds produced in the atmosphere and rained down in aerosol particles consisting of a nucleus of macromolecular materials coated with volatile hydrocarbons and nitriles[7]. Such solutes will be much more concentrated in the lakes than in the atmosphere[8]. Despite the low temperatures, the action of high-energy cosmic rays reaching the satellite's surface may produce additional organic compounds in this exotic chemical reactor.

It has been suggested that cold liquids such as those found in the lakes of Titan could contain life[9], but they also have less speculative interests for astrobiologists[10]. Although composed of a low-temperature, nonpolar solvent very different from water, they provide an analogue to Earth's oceans and are a potential chemical reactor. It is to be hoped that these organic lakes are made a priority target for future exploration missions, such as the Titan/Saturn System Mission (TSSM), a joint venture between NASA and the European Space Agency currently undergoing feasibility studies. ■

François Raulin is at the Université Paris 12 Val de Marne, 61 avenue du Général de Gaulle, 94010 Créteil Cedex, France.
e-mail: raulin@lisa.univ-paris12.fr

1. Brown, R. H. *et al. Nature* **454,** 607–610 (2008).
2. Lunine, J. I., Stevenson, D. J. & Yung, Y. L. *Science* **222,** 1229–1230 (1983).
3. Porco, C. C. *et al. Nature* **434,** 159–168 (2005).
4. Stofan, E. R. *et al. Nature* **445,** 61–64 (2007).
5. Niemann, H. B. *et al. Nature* **438,** 779–784 (2005).
6. Hunten, D. M. *Nature* **443,** 669–670 (2006).
7. Israël, G. I. *et al. Nature* **438,** 796–799 (2005).
8. Dubouloz, N. *et al. Icarus* **82,** 81–96 (1989).
9. McKay, C. P. & Smith, H. D. *Icarus* **178,** 274–276 (2005).
10. Raulin, F. *Space Science Rev.* doi:10.1007/s11214-006-9133-7 (2007).

BEHAVIOURAL NEUROSCIENCE

# The circuit of fear

Pankaj Sah and R. Frederick Westbrook

**Do you find it difficult to overcome an irrational fear? Blame it on the specific neural circuits hardwired in the brain that control fear recognition, and fear renewal even when fear has seemingly been overcome.**

Learning to predict danger allows animals to defend themselves against harm and is crucial for survival. The neural mechanisms that subserve these functions are evolutionarily old, and their dysfunction is thought to underlie a host of anxiety disorders in humans, including post-traumatic stress and panic disorder[1]. Two papers in this issue, by Herry *et al.*[2] (page 600) and Likhtik *et al.*[3] (page 642), pinpoint the neural circuits that mediate the bidirectional transition between a defensive behaviour — fear — and the default exploratory behaviour.

To study the neural mechanisms that mediate fear responses, fear conditioning is widely used. In a typical procedure, animals are exposed to a normally harmless stimulus (such as a sound or light) before a brief exposure to an aversive stimulus — typically a foot shock. A few such rounds of pairing the harmless (conditioned) stimulus with the aversive (unconditioned) stimulus create an association between them in the animals' minds. So, on subsequent exposure to only the conditioned stimulus, they remember the association and express behavioural and physiological responses that correspond to fear in humans.

It is important to study how fear is first learned. However, the pertinent question for clinicians is how fear can be eliminated or reduced. Extinction of fear occurs when the association between the conditioned and the unconditioned stimuli is broken by repeated presentations of the conditioned stimulus only[4]. But does the association get completely erased from the memory? The answer is no. Although the conditioned stimulus eventually fails to elicit fear responses, much, if not all, of the original learned fear survives extinction[5]. So when the extinguished conditioned stimulus is tested either during, or shortly after, exposure to a dangerous context again, the conditioned fear is renewed spontaneously. Extinction therefore involves new learning, and its activation by situational cues inhibits the expression of fear responses to the conditioned stimulus.

Three brain regions implicated in fear conditioning and extinction are the amygdala, the medial prefrontal cortex and the hippocampus. The amygdala is the central structure involved in both fear conditioning and extinction[1]. It is divided into two main compartments: the basolateral amygdala, which receives sensory information about the conditioned and the unconditioned stimuli; and the central nucleus, which receives information processed in the basolateral amygdala. Neuronal projections from the central nucleus to the hypothalamus and brainstem then evoke the behavioural and physiological responses that constitute fear[6] (Fig. 1a, overleaf).

The learning of fear involves the co-occurrence of weak (conditioned stimulus) and strong (unconditioned) inputs to single neurons and leads to enhancement of neuronal activity known as excitatory postsynaptic potentials, which are elicited by the conditioned stimulus and mediated by NMDA glutamate receptors. This synaptic plasticity results in the conditioned stimulus evoking an increased response in basolateral-amygdala neurons that project to fear-output circuits in the central nucleus. Extinction results from NMDA-receptor-mediated changes in the amygdala[7] that block the effects of this long-term potentiation, possibly by activating local neurons that secrete the inhibitory neurotransmitter GABA. The medial prefrontal cortex mediates consolidation of extinction,