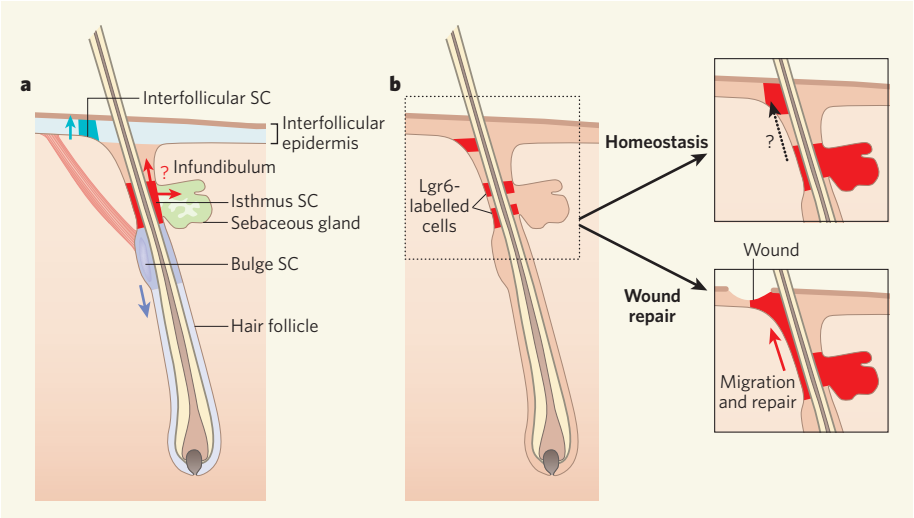

Figure 1 | Various stem cells ensure skin homeostasis. a, The anatomy of the skin epidermis. Arrows indicate the flux of the different stem cell (SC) progeny. **b**, Snippert *et al.*[2] show that, as part of the skin's homeostasis, Lgr6-expressing progenitor cells originally residing in the isthmus region of the hair follicle give rise to new isthmus and sebaceous-gland cells. Moreover, these cells might even migrate to, and replenish cells in, the interfollicular epidermis, as they do during wound repair.

sebaceous gland, whereas a few may have the potential to differentiate into other epidermal lineages. It remains unclear whether a single subpopulation within the Lgr6-marked cells regenerates both the isthmus and sebaceous gland or whether Lgr6 is expressed in both the previously identified[12–14] isthmus progenitors expressing Lrig1 and MTS24, and the Blimp1-expressing sebaceous-gland progenitors[9].

Snippert *et al.* also find that, like isthmus stem cells[13,14], Lgr6-expressing cells transplanted into immunodeficient mice give rise to all epidermal cell lineages. Moreover, like bulge stem cells, Lgr6-expressing stem cells are activated by wounding and migrate towards the epidermis to aid wound repair (Fig. 1b). These intriguing observations suggest that at least two different hair-follicle stem-cell populations can actively contribute to the repair of the damaged epidermis.

The presence of Lgr6-derived cells in the interfollicular epidermis during tissue homeostasis is more puzzling. According to previous cell-lineage tracing of embryonic skin[6,8], all cells of the mature hair follicle, including those of the isthmus region, are derived from cells expressing two other progenitor markers, Shh and Sox9. By contrast, the interfollicular epidermis is not labelled with these markers unless wounded, suggesting little or no contribution of hair-follicle cells to the maintenance of the interfollicular epidermis[6,8].

Three scenarios could explain Snippert and colleagues' observation that Lgr6-derived cells are present in the interfollicular epidermis. First, some rare Lgr6-expressing isthmus cells might originate from a pool of hair-follicle progenitors different from those expressing Shh and Sox9, and these would then migrate to the interfollicular epidermis to contribute to its maintenance. Second, Lgr6 might be more broadly expressed than Shh or Sox9, thus marking a population of progenitors that resides in the interfollicular epidermis, and contributing locally to the development and homeostasis of cells there. Finally, micro-wounding or stress to the epidermis might cause migration of cells from the follicle into the interfollicular epidermis.

This study[2] adds yet another piece to the complex puzzle of skin homeostasis, clearly demonstrating that Lgr6-expressing progenitors actively cycle to ensure the renewal of the isthmus region and the sebaceous gland under physiological conditions. During wounding, both bulge stem cells[5,7,8] and Lgr6-expressing stem cells[2] are actively recruited to repair the interfollicular epidermis. For most skin stem cells, the natural turnover of cells serves several purposes: to replace the dead cells that are shed from the skin surface (interfollicular epidermal stem cells), to fuel hair growth (bulge stem cells) or to make oil cells (sebaceous-gland stem cells). But Lgr6-expressing cells are constantly cycling and are not known to die frequently. So where are their progeny going?

One possibility is that the proliferation of Lgr6-marked isthmus cells essentially serves to fuel the high turnover of sebaceous-gland cells. It would be interesting to determine the intrinsic and extrinsic signals that dictate the fate of different skin epidermal progenitors during development, and to define factors that control their regionalization during both development and homeostasis. Moreover, deciphering the mechanisms that allow the migration of isthmus and bulge stem cells across these boundaries during wound healing will be essential. ■

Cédric Blanpain is at the Interdisciplinary Research Institute, Université Libre de Bruxelles, 1070 Bruxelles, Belgium.
e-mail: cedric.blanpain@ulb.ac.be

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EARLY EARTH

Faint young Sun redux

James F. Kasting

Given that the Sun was dimmer in its youth, our planet should have been frozen over for much of its early history. That it evidently wasn't is a puzzle that continues to engage the attention of Earth scientists.

The 'faint young Sun' problem refuses to go away. It was first pointed out by Sagan and Mullen[1] almost 40 years ago, and many potential solutions have been offered since. The latest proposal comes from Rosing *et al.*[2] on page 744 of this issue.

Early in the history of the Solar System, the Sun's brightness may have been as little as 70% of what it is today, a difference caused by the higher ratio of hydrogen to helium in its core at that time. All other things being equal, Earth should have been frozen over for the first half of its existence, a time known as the Archaean. But it wasn't — evidence for liquid water, and life, abounds in the geological record of that time. Sagan and Mullen themselves suggested that enhanced concentrations of reduced greenhouse gases, specifically ammonia (NH_3) and methane (CH_4), kept the early Earth warm. This was based on the premise, now widely accepted[3], that levels of atmospheric oxygen were low before 2.4 billion years ago.

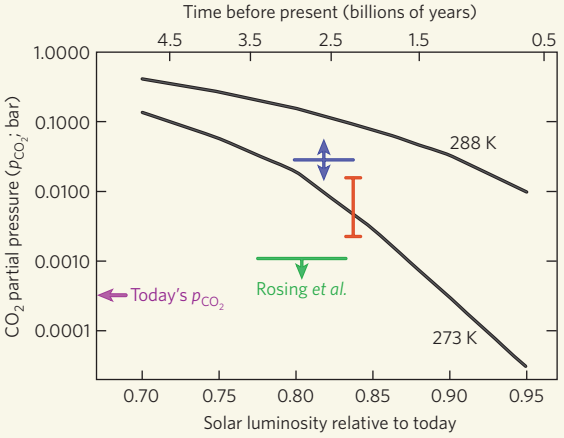

Figure 1 | Possible variation in atmospheric CO_2 partial pressure (p_{CO_2}) during Earth's history. Previous geochemical estimates for Archaean p_{CO_2} were in rough agreement with values derived from climate models, but the new estimate from Rosing *et al.*[2] is much lower (they invoke a reduced planetary albedo to compensate for the lesser warming effect). The black curves[7] show estimated p_{CO_2} values needed to keep Earth's average surface temperature at freezing point (273 K), or at the modern value, 288 K, if CO_2 and H_2O were the only important greenhouse gases and if the planetary albedo was the same as today. The downward blue arrow indicates an upper limit on p_{CO_2} derived from ancient soils[14], and the red error bar denotes another ancient-soil estimate[15] for p_{CO_2}. The upward blue arrow shows an estimate[13] of the lower limit on p_{CO_2} based on the presence of siderite in banded iron formations (BIFs); the green indicates the upper limit on p_{CO_2} estimated by Rosing *et al.*[2] on the basis of the same BIFs. The relationship between solar luminosity (bottom scale) and time (top scale) is from ref. 16.

However, it didn't take long for revisionists to appear. Kuhn and Atreya[4] showed that ammonia is photochemically unstable with respect to conversion to N_2 and H_2. Others argued that carbon dioxide was the key greenhouse gas that kept the early climate warm[5,6]. Water vapour is an important greenhouse gas, too, but because it can condense it actually makes the faint young Sun problem worse by amplifying the temperature change induced by low solar luminosity. By contrast, CO_2 is part of a negative feedback loop that causes CO_2 concentrations to increase when the climate cools[6]. Thus, in principle, CO_2 and H_2O — even including the positive water-vapour feedback — are the only greenhouse gases needed to offset the faint young Sun.

The problem might have been considered resolved at this point had data on ancient CO_2 concentrations not become available. Geochemists studying the composition of ancient soils concluded that Archaean CO_2 levels were too low to counteract the faint young Sun (Fig. 1). Rosing *et al.*[2] have strengthened this argument by analysing specific marine sediments called banded iron formations (BIFs), copious amounts of which formed during the first half of Earth's history but not since then. These are composed of various iron-rich minerals, including magnetite (Fe_3O_4) and siderite ($FeCO_3$). Magnetite is a moderately oxidized mineral, meaning that the iron has partly reacted with oxygen, whereas siderite is reduced. Their coexistence in Archaean BIFs suggests that atmospheric concentrations of H_2 and CO_2 were close to the phase boundary at which both minerals would be stable. If too much CO_2 (or H_2) was present, siderite should have been formed, but not magnetite. Conversely, if too little CO_2 (or H_2) was present, magnetite, rather than siderite, should have formed. Rosing *et al.* further note that atmospheric H_2 concentrations should have been regulated by methanogens — anaerobic, single-celled organisms that convert H_2 and CO_2 into CH_4.

Taken together, these constraints suggest that Archaean CO_2 concentrations were no higher than 900 parts per million (p.p.m.) — only about three times the present value. By contrast, climate models that rely only on CO_2 and H_2O require roughly 70 times current CO_2 (partial pressure of CO_2, $p_{CO_2} = 0.02$ bar) to keep late Archaean surface temperatures above freezing[7,8]. (This value applies specifically at 2.8 billion years ago.) But the actual discrepancy is probably much larger than this, because the CO_2 concentration required to bring surface temperatures up to today's values is a factor of ten higher (Fig. 1). Most of the Archaean seems to have been ice-free, so this is arguably a minimum surface temperature for which to shoot with a one-dimensional (1D) model. Put another way, if this calculation were to be repeated with a 3D climate model (which is certainly possible with today's computers), one would probably need to maintain surface temperatures equal to or greater than today's; otherwise, any continent near one of the poles — as Antarctica is today — should have been glaciated.

How, then, can one resolve the problem? Sagan and Mullen's original suggestion about reduced greenhouse gases may have been at least partly correct. Although NH_3 seems to have been ruled out, CH_4 remains a likely early atmospheric constituent and could have provided perhaps 10–12 °C of surface warming[8,9]. The methane greenhouse effect is limited, however, because organic haze starts to form at CH_4/CO_2 ratios higher than ~0.1, and this creates an anti-greenhouse effect that cools the surface if the haze becomes too thick[8]. (This could pose problems for Rosing *et al.* because they assume 900 p.p.m. of CH_4 in their base model, giving them a 1:1 CH_4/CO_2 ratio, and possibly a very hazy atmosphere.)

Rosing *et al.*[2] have revived another hypothesis — the idea that Earth's albedo, or reflectivity, may have been lower in the past, allowing it to absorb more sunlight. They argue, quite plausibly, that the continents were originally much smaller, and that cloud droplets were bigger and less numerous because there were fewer biogenic sulphur gases to act as cloud condensation nuclei. Both effects would have tended to lower early Earth's albedo, and hence warmed the young planet. Other processes, not discussed in the paper[2], might also have contributed to surface warming. An alternative cloud-feedback model[10] suggests that tropical cirrus clouds were more widespread in the past, thereby creating an enhanced cloud greenhouse effect. Yet another idea[11] is that higher concentrations of N_2 could have warmed the surface by broadening the absorption lines of CO_2 and H_2O.

Despite all of these proposed warming mechanisms, there are still reasons to think that the faint young Sun problem is not yet solved. Ice albedo feedback has been neglected in all of these 1D climate calculations. On the real Earth, polar ice caps start to grow when the surface temperature is low, and this further destabilizes Earth's climate. Thus, 3D climate simulations are needed to test all of these hypotheses. The Archaean Earth may also have been significantly warmer than the planet is today (although probably not as warm as the ~70 °C estimate based on oxygen isotope data[12]). Cirrus-cloud feedback explicitly fails to operate under these circumstances, and any warming mechanism that does not include additional greenhouse gases would be severely challenged. The BIFs, which are used by Rosing *et al.* to estimate an upper limit on p_{CO_2}, have been used previously by others[13] to estimate lower limits on p_{CO_2}. Only by understanding the details of BIF precipitation can one decide which interpretation is appropriate.

Finally, one of the strongest arguments for the presence of reduced greenhouse gases in the Archaean atmosphere is that it could explain why Earth became glaciated at the end of this era. When atmospheric O_2 rose, the concentrations of CH_4 and other reduced gases should have decreased dramatically, possibly triggering the observed glaciations[8]. The mechanism proposed by Rosing *et al.* might explain this as well, if the flux of biogenic sulphur gases increased strongly when O_2 levels rose. This is not an unreasonable assumption, because many of these gases are produced by algae that require free O_2 for their metabolism. But we clearly need additional constraints to understand why the Archaean Earth remained habitable. ■

James F. Kasting is in the Department of Geosciences, The Pennsylvania State University, University Park, Pennsylvania 16802, USA.
e-mail: jfk4@psu.edu

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DRUG DISCOVERY

Fat-free proteins kill parasites

George A. M. Cross

The addition of a fatty acid to certain proteins is vital for the survival of protozoa that cause sleeping sickness and of their mammalian hosts. Compounds that target this process in the protozoa are now reported.

No safe and effective drugs exist for the treatment of human African trypanosomiasis (HAT, also known as sleeping sickness; Fig. 1), the fatal disease caused by *Trypanosoma brucei* protozoa and their relatives. More than a century of study has left the impact of HAT on individuals almost undiminished. To make matters worse, the disease has received little attention recently amid the many woes that afflict equatorial Africa, home of the tsetse flies that act as the main agent of transmission. But on page 728 of this issue, Frearson *et al.*[1] describe a giant step towards improving this situation with their report of a new class of compounds that cures trypanosomiasis in mice.

The *T. brucei* parasite is a small, unicellular organism with many biological similarities to its human host cells, but which has taken different routes in the evolution of certain critical cellular pathways. It also has some unique cellular pathways. There is therefore widespread optimism that it should be possible to develop treatments for HAT by identifying drug targets that are specific to the organism — assuming that the financial resources are available. What's more, *T. brucei* lives outside its host's cells (unlike its distant cousins *Trypanosoma cruzi* and the many varieties of *Leishmania*), which should facilitate drug development. The human immune system cannot eradicate *T. brucei* because the parasite has developed an apparently insurmountable capacity for antigenic variation. This allows HAT infections to persist until (usually) the death of the infected person, following the coma that occurs once the parasite invades the patient's brain.

In recent years, a myriad of processes have been discovered through which proteins are chemically modified after their translation, resulting in the attachment of groups that influence the proteins' properties in important ways. Frearson *et al.*[1] targeted the modification known as *N*-myristoylation[2], in which an unsaturated fatty acid (myristic acid) is attached to one end of a small subset of cellular proteins. Discovered[3] in the early 1980s, *N*-myristoylation enables many proteins with essential signalling functions to associate with cell membranes.

The enzyme responsible for this modification — *N*-myristoyltransferase, NMT — is found in the cells of trypanosomes[4,5] and mammals[2], and is necessary for their survival. Because the signals associated with *N*-myristoylated proteins are sometimes disrupted by viral infections or cancer-causing mutations, NMT has been widely studied. Crucially, this has resulted in the preparation of libraries of potential NMT inhibitors, and has facilitated detailed comparisons of the trypanosome and mammalian enzymes, and of their interactions with potential drugs.

Frearson and colleagues' landmark discovery[1] is the development and validation of a potent and selective NMT inhibitor that cures trypanosome infections in mice at low oral doses. They began by screening 62,000 chemical structures, a process that identified several moderately active NMT inhibitors. These included some pyrazole sulphonamide compounds (see Fig. 1a on page 729), which can be synthesized relatively easily in a modular manner — a fact that made them attractive candidates for optimization of their pharmacological properties.

The team went on to prepare more than 200 additional sulphonamide derivatives, including some that were not only active at 1,000-fold lower concentrations than the compounds identified in the screening, but that also showed selectivity for trypanosome NMT over the human variant of the enzyme. One such structure, DDD85646, killed trypanosomes in culture at very low (nanomolar) concentrations. Notably, these concentrations were 200-fold lower than those at which the compound killed mammalian cells in culture.

Frearson *et al.* obtained several lines of evidence to show that the trypanocidal activity of their sulphonamides was specifically due to their ability to inhibit NMT. For example, they observed that the compounds were less lethal

A. CRUMP, TDR, WHO/SPL

EYE OF SCIENCE/SPL

Figure 1 | A forgotten disease. These teenagers in Uganda have sleeping sickness, a potentially fatal disease caused by the protozoan *Trypanosoma brucei* (inset). Frearson *et al.*[1] have identified compounds that kill trypanosomes in mice.