

that as-yet-unknown, dedicated stem-cell populations might still await discovery. Their identification could have major clinical implications. ■

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Regeneration on call

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Unlike blood and muscle stem cells, which reside in protected niches, epithelial tissues that line or bud off from the body's tubes are often exposed to external or internal stressors. An HSC-like branching hierarchy in which a single progenitor sits atop a direct line of descendants seems a very unsafe evolutionary solution for this type of tissue — dependence on a single 'master' cell would put the tissue at risk of disintegration should that cell type die. An alternative approach involving overlapping hierarchies with two or more entry points seems a more secure means of solving the problem. This idea suggests that facultative stem cells, which can act as stem cells if needed, but do not always do so, must exist.

The debate about whether the hierarchical HSC-like model fits other systems¹⁰ has been influenced by the tendency of researchers to consider normal organ maintenance (homeostasis) as equivalent to regeneration and repair, despite the highly divergent intrinsic cellular responses involved in the two phenomena. Repair often requires a higher level of proliferation than does homeostasis — therefore, bone fide stem cells that can mediate homeostasis cannot always repopulate a damaged tissue. This is where facultative stem cells come in.

One example of this phenomenon can be found in the intestinal epithelium, which is highly proliferative both in homeostasis and following injury. A population of dedicated stem cells maintains this tissue under normal conditions. These are known as crypt-base columnar cells, and they self-renew and differentiate into several cell types¹¹. However, if the tissue is injured or the stem-cell population depleted, non-proliferative cells that have begun to differentiate or have even fully matured can revert to a stem-cell-like state to help repopulate the tissue¹¹. Thus, cellular plasticity is key to gut maintenance in different conditions.

Unlike the intestine, most tissues undergo cellular turnover only slowly in everyday life, and show an increased proliferative capacity

that enables them to repair some (but not all) structures following injury. However, a few tissues that typically have low turnover, including the liver and lung, can completely regenerate following injury. The cells that enable this remarkable response have been extensively investigated, and have provided further examples of facultative stem cells.

The lung, like the intestine, has a population of true 'HSC-like' stem cells that maintain the airway by means of homeostasis. Following injury, mature differentiated cells called club cells can dedifferentiate and behave as facultative stem cells^{12,13}. By contrast, the existence of any dedicated stem cell in the liver has yet to be confirmed. During homeostasis, two liver-cell types, hepatocytes and ductal cells, seem to maintain their respective cell types through proliferation. But following damage, at least in zebrafish¹⁴ and mice¹⁵, facultative stem cells arise from differentiated cells called cholangiocytes. In mice, cholangiocytes revert to a bi-potent stem-cell-like state that facilitates the regeneration of both hepatocytes and ductal cells¹⁵ (Fig. 1b).

These three examples highlight ways in which different organs have solved similar problems. That brings to mind the natural-selection pressures that lead different groups of animals to achieve various solutions to common habitat challenges — developing different strategies to combat the extreme cold weather at the poles, for instance. It is tempting to speculate that the battle to maintain tissues in a demanding environment that involves constant turnover and exposure to damage has resulted in the existence of a range of back-up strategies through

which facultative stem cells help to ensure tissue integrity. A definition of stem cells that encompasses the existence of the full range of these plastic cell types is essential if we are to truly understand the nature of regeneration. ■

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1. Pappenheim, A. *Virchows Arch. Eur. J. Pathol.* **145**, 587–643 (in German) (1896).
2. Ramalho-Santos, M. & Willenbring, H. *Cell Stem Cell* **1**, 35–38 (2007).
3. Becker, A. J., McCulloch, E. A. & Till, J. E. *Nature* **197**, 452–454 (1963).
4. Mauro, A. J. *Biophys. Biochem. Cytol.* **9**, 493–495 (1961).
5. Relaix, F. & Zammit, P. S. *Development* **139**, 2845–2856 (2012).
6. Lepper, C., Partridge, T. A. & Fam, C.-M. *Development* **138**, 3639–3646 (2011).
7. Sambasivan, R. *et al. Development* **138**, 3647–3656 (2011).
8. Chivu-Economescu, M. & Rubach, M. *Curr. Stem Cell Res. Ther.* **12**, 124–133 (2017).
9. Pini, V., Morgan, J. E., Muntoni, F. & O'Neill, H. C. *Curr. Stem Cell Rep.* **3**, 137–148 (2017).
10. Clevers, H. & Watt, F. M. *Annu. Rev. Biochem.* **87**, 1015–1027 (2018).
11. Tetteh, P. W., Farin, H. F. & Clevers, H. *Trends Cell Biol.* **25**, 100–108 (2015).
12. Tata, P. R. *et al. Nature* **503**, 218–223 (2013).
13. Rawlins, E. L. *et al. Cell Stem Cell* **4**, 525–534 (2009).
14. Choi, T.-Y., Ninov, N., Stainier, D. Y. R. & Shin, D. *Gastroenterology* **146**, 776–788 (2014).
15. Raven, A. *et al. Nature* **547**, 350–354 (2017).

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ASTRONOMY

A key piece in the exoplanet puzzle

The detection of a low-mass exoplanet on a relatively wide orbit has implications for models of planetary formation and evolution, and could open the door to a new era of exoplanet characterization. SEE LETTER P.365

RODRIGO F. DÍAZ

For decades, astronomers have looked for planets around a nearby star known as Barnard's star. On page 365, Ribas *et al.*¹ report evidence for such a planet, based on more than 20 years of data. Detailed information about the planet could be revealed by the next generation of astronomical instruments.

Planets around stars other than the Sun are known as exoplanets. They are extremely faint compared with their host stars, and their orbits are typically too small to be resolved — even

using the largest telescopes available today. As a result, the latest high-resolution imaging techniques are limited to giant planets on wide orbits around nearby stars^{2,3}.

Most of what is currently known about the properties, formation and evolution of exoplanets therefore comes from indirect methods that measure variations in the light received on Earth from host stars. One of the most fruitful of these methods, used by Ribas and colleagues, is the radial-velocity technique. It involves measuring changes in the velocity of a host star along the line-of-sight of an observer,

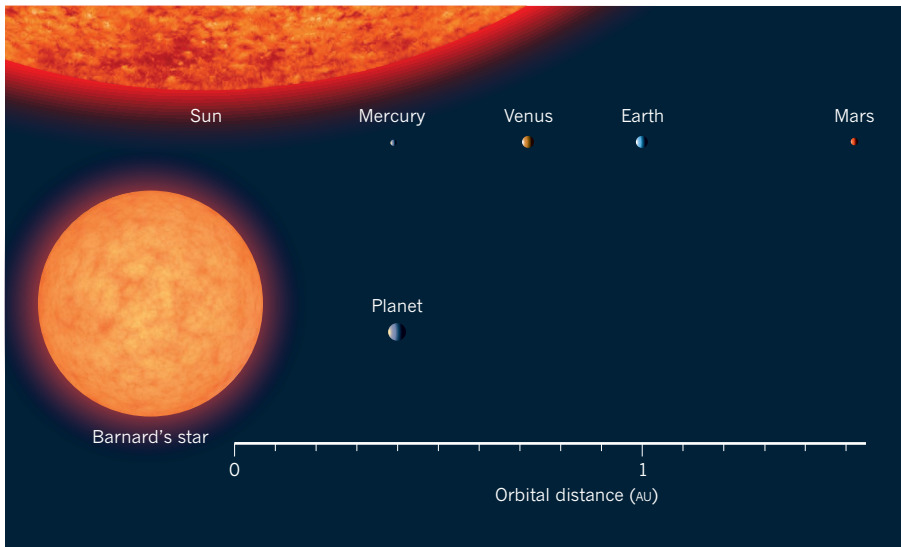


Figure 1 | A planet around Barnard's star. Ribas *et al.*¹ report evidence that a low-mass planet orbits a nearby star called Barnard's star. Shown here is the orbital distance of the planet, compared with those of the four inner planets of the Solar System. The distances are given in astronomical units (1 AU is the average separation between Earth and the Sun). The discovered planet is on a relatively wide orbit. The sizes of all the objects are approximately to scale.

and is sensitive to the mass of the exoplanet. However, because the measurements depend on an unknown value (the inclination of the planet's orbit), the technique provides only a lower bound on the planet's mass⁴.

Using the radial-velocity method to detect planets on long-period orbits is difficult, because the larger the orbital distance, the smaller the planetary signal. The transit method, which measures the drop in brightness as a planet passes in front of its host star, is also ineffective for planets on long-period orbits. This limitation has restricted the detection and characterization of exoplanets mostly to close-in companions, especially in the case of low-mass planets, whose signals are small.

Ribas and colleagues' announcement of a planet around Barnard's star with an orbital period of 233 days and a mass of at least 3.2 times that of Earth pushes the limits of the radial-velocity technique. Barnard's star belongs to a family of stars known as M dwarfs, which are cooler and much less massive than the Sun. M dwarfs are prime targets for planetary searches, because they favour the detection of small companions.

The orbital distance of the reported planet is similar to that of Mercury from the Sun (Fig. 1). This places the planet close to the snow line of Barnard's star — the region out from the star beyond which volatile elements can condense. The snow line is a key region of planetary systems. In particular, there are indications that the building blocks of planets are formed there⁵.

It is currently thought that these building blocks grow by collecting material from their surroundings to become planetary cores and then fully fledged planets as they migrate towards their host stars⁶. Until now, only giant planets had been detected at such a distance

from their stars. The authors' discovery of a low-mass planet near the snow line places strong constraints on formation models for this type of planet.

Ribas *et al.* report that Barnard's star seems to be devoid of close-in companions. In particular, the authors put stringent constraints on the presence of planets in the habitable zone around the star — the region in which liquid water could exist on the surface of a rocky planet. However, they do provide an unconfirmed hint of a planet farther away from the star than the detected planet.

What makes the authors' discovery even more remarkable is that Barnard's star is only 1.8 parsecs (less than 6 light years) away from the Sun⁷. This makes the planetary system the closest single-star system to the Sun. The Alpha Centauri triple-star system is the only system that is closer, and also hosts at least one low-mass planet⁸.

Barnard's star has been monitored for more than 20 years. Ribas and co-workers used hundreds of radial-velocity observations that were obtained with different instruments by many different projects and researchers. These measurements were crowned by an intense observing campaign with the CARMENES spectrograph⁹, which is located at the Calar Alto Observatory in Spain.

In their analysis, the authors had to be particularly careful in accounting for stellar activity. For many years, exoplanet researchers have been struggling with the effects of stellar activity — for example, rotating stellar spots and active regions, and long-term activity cycles similar to the 11-year cycle of the Sun. These phenomena can easily mimic the effects of planetary companions¹⁰, especially in the case of low-amplitude signals^{11,12} such as the one detected by Ribas and colleagues.

The authors used a few different methods to account for the effects of stellar activity, and to check whether the planetary detection depended on how such effects were corrected for. One of these methods resulted in a drastic reduction in the statistical significance of the detection, and therefore casts doubt on the discovery. However, this method is prone to false negatives¹³ and, using simulations, the authors showed that their detection can be reproduced by stellar activity in only 0.8% of cases.

Difficult detections such as this one warrant confirmation by independent methods and research groups. Amassing an independent radial-velocity data set to confirm the existence of the planet seems unfeasible in the near future, but the closeness of Barnard's star to the Sun means that confirmation should be possible through other means. For example, a signal for the planet might be detectable in astrometric data — precision measurements of stellar positions — from the Gaia space observatory that are expected to be released in the 2020s. Such a signal would confirm the presence of the planet, reveal the planet's actual mass (as opposed to a lower bound on the mass) and provide complementary information on the planet's orbit.

Even more excitingly, the next generation of ground-based instrumentation, also coming into operation in the 2020s, should be able to directly image the reported planet, and measure its light spectrum. Using this spectrum, the characteristics of the planet's atmosphere — such as its winds and rotation rate — could be inferred. This remarkable planet therefore gives us a key piece in the puzzle of planetary formation and evolution, and might be among the first low-mass exoplanets whose atmospheres are probed in detail. ■

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- Ribas, I. *et al.* *Nature* **563**, 365–368 (2018).
- Wagner, K. *et al.* *Science* **353**, 673–678 (2016).
- Vigan, A. *et al.* *Mon. Not. R. Astron. Soc.* **407**, 71–82 (2010).
- Murray, C. D. & Correia, A. C. M. in *Exoplanets* (ed. Seager, S.) 15–23 (Univ. Arizona Press, 2010).
- Drażkowska, J. & Alibert, Y. *Astron. Astrophys.* **608**, A92 (2017).
- Ida, S. & Lin, D. N. C. *Astrophys. J.* **719**, 810–830 (2010).
- Gaia Collaboration. *Astron. Astrophys.* **616**, A1 (2018).
- Anglada-Escudé, G. *et al.* *Nature* **536**, 437–440 (2016).
- Trifonov, T. *et al.* *Astron. Astrophys.* **609**, A117 (2018).
- Queloz, D. *et al.* *Astron. Astrophys.* **379**, 279–287 (2001).
- Feroz, F. & Hobson, M. P. *Mon. Not. R. Astron. Soc.* **437**, 3540–3549 (2014).
- Robertson, P., Mahadevan, S., Endl, M. & Roy, A. *Science* **345**, 440–444 (2014).
- Feng, F., Tuomi, M., Jones, H. R. A., Butler, R. P. & Vogt, S. *Mon. Not. R. Astron. Soc.* **461**, 2440–2452 (2016).