Indeed, the authors found that levels of ERV viral particles increased more in anagen-stage skin than in telogen-stage skin. However, the level of the viruses was reduced by depleting sympathetic nerves or lowering the expression of ADRB2 in HFSCs. To determine whether ERV reactivation is connected to autoimmune susceptibility, the authors treated mice in anagen with antiviral drugs after T_{reg} depletion, which resulted in a diminished influx of $CD8^+$ T cells into the skin and reduced alopecia. This result indicates that ERVs are sensed and targeted by the immune system at the anagen stage.

The authors found that this autoimmunity was dependent on the protein AIM2, which is a sensor of harmful DNA. Importantly, the authors surveyed small peptide fragments of ERVs and identified one that potently activated $CD8^+$ T cells during autoimmunity. Together, the results provide a comprehensive molecular explanation for autoimmune susceptibility of anagen-stage hair in mice.

Although this discovery might have implications for the treatment of human autoimmune alopecia, several questions need to be answered first. One regards the mechanism of sympathetic nerve activation, which occurs in a precise time window during early anagen onset, according to Cui and colleagues' work. Intriguingly, different molecular cues expressed by cells neighbouring HFSCs influence the delicate balance between telogen and anagen[7]. In addition, the composition of immune cells in skin fluctuates depending on the phase of the hair cycle, which might contribute to HFSC activation as well[8,9]. Therefore it is tempting to speculate that local factors expressed by cells in skin, such as stromal cells and immune cells, activate sympathetic nerves. Further studies should help to unlock this key piece of the puzzle.

It is unknown whether these findings will be confirmed for humans or whether the phenomenon is mouse-specific. Reactivation of ERVs has been implicated in human autoimmune disease but a precise role in causing disease has yet to be firmly established[10]. A study of the human autoimmune disease cutaneous lupus demonstrated expression of ERVs in a wide variety of cell types, including skin cells called keratinocytes[11]. It will be fascinating to determine whether sympathetic nerves control ERV reactivation in human anagen-stage skin.

Although the suggestion that ERVs have a harmful role in autoimmunity is interesting, it is currently unknown how ERV viral particles are usually ignored during normal hair growth. Cui and colleagues provide a clue by showing that T_{regs} restrain ERV-specific T cells. When developing T cells encounter the body's own proteins in the immune organ called the thymus, they are either eliminated or become T_{regs}, and a similar process occurs in immune-system structures called lymph nodes during normal processes that aid immune-system function. Interestingly, there is some evidence that ERVs are expressed in the thymus[12], suggesting that T cells capable of driving autoimmunity against hair tissue are potentially safeguarded from doing so by encountering viral proteins in this organ. Future work will be needed to uncover the precise mechanisms that normally keep ERV-specific T cells in check, and to understand how this process goes awry during autoimmunity.

Although many questions remain to be answered, Cui and colleagues' study provides a framework linking sympathetic nerve activation in anagen to ERV reactivation in HFSCs, which can initiate an autoimmune cascade in the setting of immune dysregulation. This study might pave the way for the discovery of therapeutic targets that modulate the nervous system or blunt ERV reactivation. Perhaps, by calming their nerve cells, those with autoimmune alopecia can one day reclaim a part of themselves and be as free as their hair.

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Cell biology

Glimpsing archaeal microbes on the move

Margaret A. Titus

How and when did cells gain the ability to crawl? Live imaging of cells from close relatives of early eukaryotes fills in a major gap in the understanding of cellular evolution. **See p.1218**

The ability of cells to move through the environment is crucial for their survival — enabling them to seek out food or flee from danger. On page 1218, Radler *et al.*[1] shed light on how such crawling motility evolved.

Many types of eukaryotic cell (defined as having nuclei) move by crawling. This process, which depends on the protein actin, is driven by protrusions of the cell membrane, rapid ballooning out of the membrane through a process termed blebbing and intracellular movement called cytoplasmic streaming[2]. Actin can form filaments that grow or shrink, and it can organize into filament networks that are a key component of an intracellular structure called the cytoskeleton.

The crawling movement of eukaryotic cells depends on the cells' ability to adhere to surfaces and on their dynamic cytoskeleton, which uses growing actin filaments to push membrane outwards or to pull it inwards if actin networks contract. By contrast, bacteria move through liquids using a tail-like appendage called a flagellum, or they can move on surfaces by 'twitching' — during which they tether and retract surface filaments called pili.

How did the eukaryotic crawling movement evolve? Enter the Asgard archaea, microorganisms considered to be an evolutionary link between bacteria and eukaryotes that were first identified by DNA sequencing of samples from ocean hydrothermal vents[3].

The first key clues came from imaging, using cryogenic electron tomography, of the Asgard archaeon *Candidatus* Lokiarchaeum ossiferum. This work revealed that the cells contained filaments of Lokiactin, a type of actin found in Asgard archea; genomic sequencing identified genes encoding these proteins that are closely related to eukaryotic actin[4]. The cells have a round cell body (the part of the cell that contains DNA) along with what seems to be a Lokiactin-filament network of actin proteins. They also have long, thin cellular protrusions containing parallel actin filaments, which are reminiscent of structures called eukaryotic filopodia — dynamic membrane protrusions that are supported by bundles of parallel actin filaments. These observations suggest that L. ossiferum has a dynamic actin cytoskeleton that might enable movement.

Radler and colleagues established a method

for imaging L. ossiferum under low-oxygen (anaerobic) conditions for different lengths of time (up to six hours) to investigate whether the cells have any type of cellular dynamics or motility. Similar to previous findings[4], the L. ossiferum cells have a round cell body. Each cell extends one to ten thin protrusions (five on average) that range from 1 to 15 micrometres in length (averaging 3.5 µm).

Interestingly, as the archaeal cells settle on a glass coverslip, they adhere and immediately extend single or branched protrusions (Fig. 1). These protrusions are remarkably dynamic, constantly undergoing extension and retraction, with a notable inverse correlation between the number and length of protrusions – the longer the protrusions, the fewer that the cell extends. This suggests that there might be a control mechanism or limitation regarding the amount of membrane components or lipids available to make protrusions.

Radler *et al*. observed that the cell body is dynamic, shifting from a spherical shape to an irregular elongated form accompanied by alterations in chromosome shape. An even more striking observation is that the L. ossiferum cell body undergoes random but smooth movements at a speed that is in the range of speeds of crawling eukaryotic cells[5]. This finding contrasts strikingly with evidence for jerky, random movement of a type of archaeon called Thermoproteota *Sulfolobus acidocaldarius*[6] that is from a group less closely related to eukaryotes than are Asgard archaeal species such as L. ossiferum.

The mobility of L. ossiferum seems to be associated with the dynamics of its thin membrane protrusions. Videos of migrating cells show them exhibiting two behaviours. One is pulling, during which the protrusion tip adheres in front of the cell and then the cell body springs forwards as it is pulled by protrusion shortening. The other is gliding, in which the protrusion and cell move together with the tip leading the way. Interestingly, the median speed of movement is close to that of protrusion extension, suggesting that there is a mechanistic link between protrusion growth and cell-body movement.

The authors also observed gliding motility and a correlation between protrusion rate and cell speed in a related Asgard, *Candidatus* Margulisarchaeum peptidophilum, which has a larger cell body and longer protrusions than those of L. ossiferum. The M. peptidophilum protrusions extend around three times faster than do those of L. ossiferum, and there is a corresponding increase in M. peptidophilum's cell speed.

These various modes of movement could be the result of actin dynamics; however, in the past, tools to track archaeal actin and inhibitors that can affect Lokiactin were unavailable. Armed with a dye that binds to Lokiactin in live cells, and an anti-actin toxin called swinholide A, which stabilizes actin subunits that are not in filaments and cuts actin filaments[7], the authors tested the role of actin proteins in the migration of L. ossiferum and M. peptidophilum. The dye stained the protrusions and cell bodies, as expected, and treatment with the toxin decreased the amount of actin filaments – resulting in a corresponding reduction in protrusion number and slowed cell-migration speed. The data conclusively establish that Lokiactin is essential for protrusion-mediated migration of L. ossiferum and M. peptidophilum.

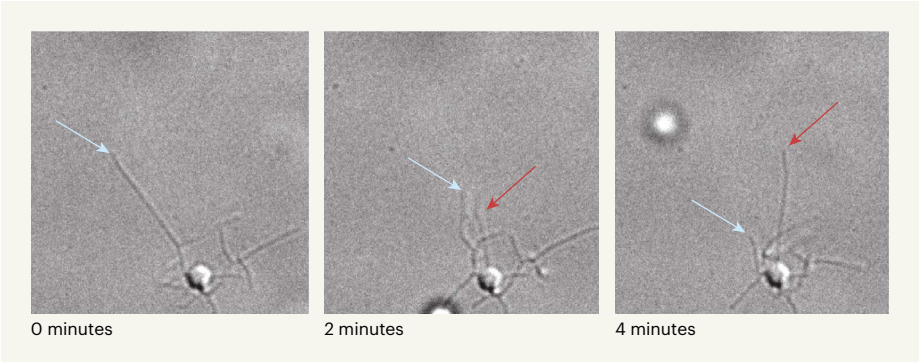


Figure 1 | Cellular protrusions dependent on actin protein in Asgard archaeal microbes. Radler *et al*.[1] present images of cellular protrusions in *Candidatus* Lokiarchaeum ossiferum. The images reveal that these structures, which need actin to form, can grow and shrink over time (arrows of the same colour mark the same protrusion tip as it changes position). (Adapted from Fig. 1 of ref. 1.)

Radler and colleagues' work strongly supports the idea that the first steps towards crawling in eukaryotic cells began with capacities that arose in Asgard archaea. The emergence of this behaviour is undoubtedly due to the evolution of a close relative of eukaryotic actin in Asgard archaea, along with the evolution of key regulators that control when actin filaments are built and disassembled to enable subunit recycling so that filaments can be formed on demand when cells move.

One matter for further investigation will be whether the dynamics of Lokiactins and their regulators affect processes such as filament elongation and retraction. Previous biochemical studies of archaeal Lokiactin regulators (profilin- and gelsolin-like proteins) used actin from the skeletal muscle of rabbits[8,9]. The results established that the archaeal regulators can interact with skeletal actin and affect filament formation and stability; however, the properties of archaeal actin probably differ in notable ways that reflect its cellular roles. It will be crucial to establish methods to purify Lokiactin to obtain a full understanding of how it assembles and disassembles and how regulators affect these processes.

Another question to answer is how L. ossiferum adheres to surfaces and whether adhesion proteins on the cell membrane connect to the Lokiactin cytoskeleton to enable migration. Migration speed slows when cells are placed on a highly adhesive surface, and images obtained using the technique of cryogenic electron microscopy show cell-membrane structures[4] that suggest the existence of platforms for proteins that function as adhesion complexes. However, the composition and role of these structures is unknown.

The identification of crawling motility in L. ossiferum now fills in a crucial gap in scientists' understanding of the evolution of eukaryotic cell crawling. It will be interesting to determine whether L. ossiferum's type of motility is evolutionarily conserved in this phylum, and whether other forms of Lokiactin-dependent Asgard archaeal movements exist. The discovery that another archaeal cytoskeletal protein, tubulin, can form filaments that lengthen and shorten suggests that tubulin filaments might drive chromosomal movement or collaborate with actin to promote cell-shape changes[10,11]. Together, these exciting findings make it clear that Asgard archaea have much more to tell us about the early emergence of eukaryotic motility.

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