CELL BIOLOGY

When the tail wags the dog

Scott M. Landfear

Flagella are whip-like structures that power the movement of certain cells. Analysis of a single-cell parasite, the African trypanosome, reveals that flagella are also essential for viability in this organism.

Many cells can move from one position to another, by various means. One locomotive structure that emerged early in evolution is a whip-like appendage called the flagellum that propels the cell by a cyclical beating motion. Stationary cells also use flagella and their shorter relatives, cilia, to move liquid across their surface, as in the lining of air passages for example. In nucleated, or eukaryotic, cells, the flagellum is wrapped in cell membrane and encompasses a central, flexible rod — the axoneme — that generates the beating motion. The flagella from diverse organisms have a remarkably similar morphology for the axoneme, with a cylindrical array of nine filaments called microtubules surrounding two core microtubules, which hints that the building-blocks of these structures have been highly conserved during evolution.

On page 224 of this issue, however, Broadhead *et al.*¹ reveal a surprising diversity among organisms of the roughly 300 proteins that form the microscopic bricks and mortar of the axoneme. Nonetheless, they also discovered that molecular components of the axoneme in the unicellular African trypanosome parasite are conserved from these ancient protozoa to humans. In humans, abnormal forms of these proteins are linked with debilitating diseases. Perhaps most remarkably, the authors have uncovered a more fundamental role for flagella than cellular motility. Flagella are essential for trypanosome cell division, and thus viability — an observation that may help in developing therapies against African sleeping sickness, the fatal disease caused by these parasites.

Proteomic analysis has become an increasingly powerful tool for defining the structures of subcellular bodies, termed organelles, that perform specialized functions for cells. In this approach, a particular organelle (or sub-structure thereof) is purified and the constituent

Figure 1 | Failed flag. **a**, A scanning electron micrograph of the bloodstream form of a normal African trypanosome. **b**, A parasite in which expression of one of the flagellar axoneme proteins has been destroyed by RNA interference of the corresponding messenger RNA. Broadhead *et al.*¹ found that the contorted 'monster' parasite has multiple nuclei and flagella, and cannot divide. Scale bar, 1 μ m. Another example is shown on the cover of this issue.

proteins are identified by sophisticated mass spectrometry. When Broadhead *et al.*¹ applied this proteomic analysis to isolated flagellar axonemes from the African trypanosome, they discovered that there were many proteins in the trypanosome organelle that could not be identified from the sequenced genomes of other organisms (with the exception of two other parasitic protozoa closely related to African trypanosomes). A similar analysis by these authors of recently published data on flagellar axonemes from two other unicellular eukaryotes^{2,3} revealed similarly unique cohorts of axonemal proteins in all three organisms compared. So the apparently conserved morphology of the axoneme belies a hidden molecular diversity.

All the same, there are also axonemal proteins that are conserved between trypanosomes and humans. When the authors identified the human chromosomal regions encoding all these conserved axonemal proteins, they found 34 genes that mapped to 25 loci that had been implicated previously in a plethora of genetic diseases. The characteristics of these conditions are consistent with

defects in flagella or cilia. These diseases cover a broad spectrum ranging from hydrocephalus and polycystic kidney disease to epilepsy. Although in each case a rough genetic locus had been associated with disease, the specific disease-associated genes had not been identified previously. So Broadhead and colleagues' examination of the ancient trypanosomes has done a significant service to human biology and medicine by identifying likely candidates for disease-causing genes. These results highlight the often-overlooked virtues of studying unusual or 'primitive' organisms.

But of course trypanosomes cause a serious disease in their own right. African sleeping sickness is a fatal infection that currently afflicts an estimated 300,000–500,000

people in sub-Saharan Africa⁴. How does the new work¹ help in understanding this devastating disease? This is perhaps the most intriguing part of the story. The authors examined the role of five trypanosome axonemal proteins using RNA interference, a powerful genetic method that allows the selective degradation of an individual messenger RNA, specifically reducing the encoded protein. In all five cases, the trypanosomes underwent a fatal meltdown when they could no longer make each axonemal protein. Although the parasites continued to replicate their DNA, divide their nuclei, and generate new flagella and other organelles, they were unable to divide into independent daughter cells. Instead, they formed spectacularly distorted 'monster' cells (Fig. 1) with multiple nuclei and flagella, and rapidly died.

These results were initially astonishing, but they are consistent with observations from the same laboratory that trypanosomes use their flagella to determine cell polarity during division⁵. These previous revelations hinted at what the current paper now confirms, that flagella are indispensable for telling parasites

how to divide — especially in the stage of their life cycle when they are in the bloodstream, causing the human and animal disease. Indeed, the flagellum seems to be the tail that wags the dog. These results raise the intriguing possibility of developing drugs that act selectively against the trypanosome-specific axonemal proteins. It may be possible to identify compounds that cripple the parasite flagellum while leaving the distinct proteins of the human axoneme alone. ■

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ASTROPHYSICS

Ancient blast comes to light

Enrico Ramirez-Ruiz

Light from the oldest and farthest stellar explosion yet seen was emitted when the Universe was a mere infant. It provides a close-up view of how and when stars formed, and how they affect the primordial gas around them.

A trio of contributions to this issue^{1–3} presents observations of the most distant stellar explosion ever seen: a γ -ray burst (GRB) that took place when the Universe (currently accepted age, roughly 13.7 billion years) was only about 900 million years old. Thus, for the first time, the most distant objects that can be identified spectroscopically are not just galaxies — and therefore huge agglomerates of stars, gas and dust — but also individual stars.

The hunt for cosmic structures that ignited when the Universe was in its infancy takes us to the frontier of our current observational capabilities (Fig. 1). Not too long ago, the most distant objects known were quasi-stellar objects, or quasars⁴ — glaringly luminous objects powered by gas falling into massive black holes at the centres of galaxies. Over the past few years, however, extremely sensitive surveys with space- and ground-based telescopes have allowed us to observe ordinary galaxies beyond the farthest quasars⁵.

Since then, the race has been on to find the most distant star. As most stars lead relatively unexciting lives, they remain far less luminous than galaxies, and so distant stars are generally too faint to be detected with current technology. Some heavyweight stars, however, end their lives violently and spectacularly. These stars send out bursts of radiation so luminous that they appear bright even when viewed across vast stretches of the Universe.

On 4 September 2005, such a flash of γ -rays, lasting for 80 seconds, hit NASA's purpose-built GRB-detection satellite, Swift. Swift's γ -ray monitor established the position of the burst — prosaically labelled GRB 050904 — in the constellation Pisces. As Cusumano *et al.* describe (page 164)¹, within seconds Swift turned around to direct its X-ray telescope at the region where the burst occurred, pinpointing the location of a rapidly fading source of

radiation to within a hundredth of a degree. This in turn allowed powerful optical and infrared telescopes around the world to search for the decaying 'afterglow' signal within their wavelength ranges. On page 184, Kawai *et al.*² report measurements of the afterglow of GRB 050904 at optical wavelengths. And, on page 181, Haislip *et al.*³ detail the tightly choreographed sequence of observations necessary to detect the barely visible afterglow at even longer, near-infrared wavelengths.

In astronomy, distance, time and the wavelength at which observations are made are inextricably linked. Light travels at a finite speed, and so takes a finite time to get to us. Far-off objects are thus seen as they were in the past. Cosmologists generally use the redshift z to designate distance or, equivalently, look-back time. The quantity $1+z$ is the factor by which the Universe has expanded between the time when a source emitted the light we observe and the present, and is also the factor by which the wavelength of light reaching us has been stretched owing to the expansion of the Universe.

So by measuring the wavelengths of absorption lines in the spectrum of the optical afterglow of GRB 050904, and comparing these with wavelengths characteristic of the heavier elements such as carbon, sulphur and silicon that are found in stars, the redshift of GRB 050904 was found² to be $z = 6.295$. It is thus the most distant stellar explosion ever witnessed, and occurred when the Universe was about 7% of its current age. Setting a new record for the farthest stellar explosion might seem noteworthy enough, but distance alone does not make GRB 050904 interesting. Its attraction lies in what it can reveal about star formation early in the history of the Universe.

Over the past decade, astronomers have been particularly successful in tracing how

early stellar systems changed and coalesced to become the 'respectable' elliptical, spiral and irregular galaxies seen in the present-day Universe. These early galaxies are far less luminous than quasars, but are still (as we see them) forming new stars, and so emitting copious amounts of light. Among these, the galaxy hosting the youngest-known quasar⁴ gives the earliest example of a star-forming region⁶. The presence in this galaxy of a large amount of mass in the form of interstellar molecules and dust is proof not only that substantial star formation was taking place only 800 million years after the Big Bang, but also that the process of chemical enrichment — in which heavier elements synthesized by previous generations of stars are incorporated into the galaxy — was well advanced.

Star formation in these early epochs was therefore probably not too different from that taking place now in some regions of the local Universe. It is in itself no surprise that a GRB can occur at these early times: GRBs are thought to be produced by the deaths of a rare breed of massive stars⁷, and, the more massive a star, the shorter its lifetime. Stars slightly more massive than our Sun have lifetimes that are shorter than the age of the Universe at $z = 6.295$, and a star 20 times as massive can keep going for only a thousandth as long.

So far, however, GRB 050904 is the only example of a stellar explosion that occurred at a time in the evolution of the Universe before 'reionization', the point when the hydrogen between galaxies was completely ionized by ultraviolet radiation. Neutral hydrogen in the Universe at $z = 6.295$ would have been a very effective absorber of any photon from GRB 050904 emitted at a wavelength shorter than the hydrogen 'Lyman α ' line at 121.6 nm. Interestingly, such a damped Lyman α absorption profile of neutral hydrogen is not easily discernible in the optical afterglow spectrum² of GRB 050904. Instead, one sees flux absorbed by the presence of a dense screen of metal-enriched gas in the immediate surroundings, presumably ejected by the massive stellar progenitor prior to collapse. This might make GRBs less suited as clean markers of when, exactly, the reionization epoch occurred⁸. More optimistically, the detection of metal absorption lines in the afterglow spectrum from the gas around the burst site offers an unusual opportunity to study the physical conditions in the interstellar medium at these early epochs.

GRB observations will certainly pave the way for the discovery of more primitive objects than the galaxies presently known at $z = 6.5$. Distant galaxies are themselves difficult to study because they appear faint and small. GRBs will serve not only as signposts to such galaxies, but could be used to study the gradual build-up of heavy elements in them to determine the conversion history of primordial gas into stars. Although the light from GRB 050904 is likely to have come from a