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Microbiology of ancient and modern hydrothermal systems

Anna-Louise Reysenbach and Sherry L. Cady

Hydrothermal systems have prevailed throughout geological history on earth, and ancient Archaean hydrothermal deposits could provide clues to understanding earth's earliest biosphere. Modern hydrothermal systems support a plethora of microorganisms and macroorganisms, and provide good comparisons for paleontological interpretation of ancient hydrothermal systems. However, all of the microfossils associated with ancient hydrothermal deposits reported to date are filamentous, and limited stable isotope analysis suggests that these microfossils were probably autotrophs. Therefore, the morphology and mode of carbon metabolism are attributes of microorganisms from modern hydrothermal systems that provide valuable information for interpreting the geological record using morphological and isotopic signatures.

'Beginnings are apt to be shadowy' Rachel Carson
Microorganisms thriving in high-temperature terrestrial and deep-sea hydrothermal systems have stimulated new theories of life's origins^{1,2}. In these extreme environments, the microbial and

geochemical interactions are tightly interwoven, providing many of the basic constituents for the primordial synthesis of organic molecules and for the evolution of fundamental metabolic processes³. Given that the early earth was a much warmer environment, rich in compounds such as CO₂ and H₂⁴, perhaps life could have arisen in an environment analogous to present-day hydrothermal systems. In other words, modern hydrothermal systems represent analogs of an 'ancestral niche' for life, and provide the basis for interpreting the BIOSIGNATURES (see Glossary) for ancient hydrothermal ecosystems⁵. As the deep-rooted phylogenetic lineages within the small subunit rRNA tree of life are all thermophilic and many grow chemolithoautotrophically^{6,7}, some of the earliest ancestors of all life might have been CHEMOLITHOAUTOTROPHIC THERMOPHILES^{8,9}. Whether life

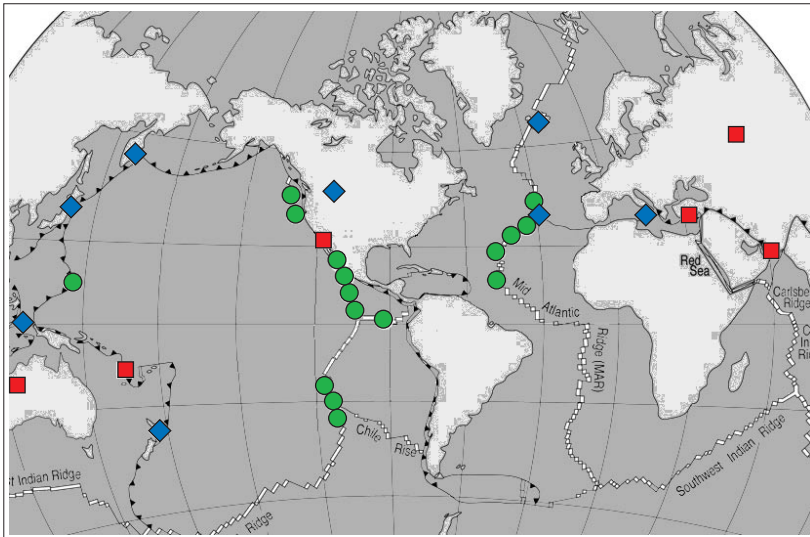


Fig. 1. A world map showing some of the deep-sea vent sites (circles), terrestrial hydrothermal sites (diamonds) and ancient volcanic massive sulfide (VMS) deposits (squares).

originated at vents in the ARCHAean age (3.8–2.5 Ga) and whether chemolithoautotrophic thermophiles are ancestors of life is unresolved^{10,11}; however, hydrothermal environments probably did support the early evolution of chemolithoautotrophs and thermophiles.

In this review, we will use what we know of the microbial biodiversity in modern hydrothermal systems to interpret some of the fossil evidence from hydrothermal systems in the geological record. However, reconstructing the paleobiology of ancient microbial ecosystems from the evidence preserved in the geological record has its limitations: the early atmosphere, hydrosphere and LITHOSPHERE differed substantially from that of today's biosphere, and the fossil record of microbial life in ancient hydrothermal deposits is sparse, consisting mostly of reports of deep-sea hydrothermal vent macrofauna fossils of the late Paleozoic¹².

Ancient and modern hydrothermal systems – the geological setting

*The study of Archaean rocks is like a forensic investigation based on heavily smudged fingerprints*¹³

Although there is no record of the first 750 million years of our planet's history, hydrothermal activity prevailed once liquid water became stable at the earth's surface. The earth has always been a volcanically active planet and, as soon as water condensed to form oceans, hydrothermal systems analogous to those found at deep-sea vents would have developed. Estimates of a threefold greater heat flux on the early earth suggest there was perhaps three times more hydrothermal activity early in the development of our planet¹⁴.

Present-day hydrothermal venting occurs both in terrestrial and marine environments, primarily as a direct result of plate tectonic movement (Fig. 1). SPREADING CENTERS, SUBDUCTION ZONES and HOT SPOTS release heat from the crust and generate high-temperature water. Wherever fissures develop

Glossary

- Archaean:** a part of the Precambrian age beginning 3.8 billion years ago, and ending 2.5 billion years ago.
- Biosignatures:** any signature that reveals the former presence of life in the geological record. Examples of biosignatures include biominerals, biomarker compounds, isotopic signatures, microfossils and biogenic stromatolites.
- Chemolithoautotrophy:** an organism that obtains its energy from oxidizing inorganic compounds and its sole carbon source from CO₂.
- Chemorganotroph (heterotroph):** an organism that uses organic carbon for both energy and carbon sources.
- Chert:** a sedimentary rock composed predominantly of silica minerals.
- Diagenesis:** the set of processes that alter sediments and any organics they contain at low temperatures after burial.
- Hot spots:** the expression at the earth's surface of a mantle plume or column of hot, buoyant rock rising in the mantle beneath a lithospheric plate.
- 3-hydroxypropionate cycle:** a unique pathway for fixing CO₂ found in green non-sulfur bacteria. Two molecules of CO₂ are reduced to glyoxylate, with hydroxypropionate as the key intermediate in the pathway.
- Lithosphere:** the rigid outer layer of earth, which includes the continental and oceanic crusts, and the outer rigid zone of the upper mantle.
- Photoautotrophy:** an organism that obtains its energy from light and its sole carbon source from CO₂.
- Photoheterotrophy:** an organism that obtains its energy from light and uses organic compounds as its source of carbon.
- Phylotype:** a small subunit rRNA (SSU) sequence of a clone obtained from environmental SSU clone library.
- Spreading centers:** a tectonic zone, usually associated with tectonic plate boundaries, along which new lithosphere forms as magma of relatively low density rises and cools.
- Stable isotopes:** non-radiogenic (stable) isotopes of an element have the same number of protons but different numbers of neutrons in their atomic nucleus.
- Subduction zones:** an elongate tectonic zone in which one tectonic plate descends beneath another.
- Stromatolite:** a laminated, lithified sedimentary structure. Biogenic stromatolites are typically laminated microbial mats built from layers of filamentous and other microorganisms that become fossilized.
- Thermophile:** an organism that grows best >45°C, and can be further defined as thermophile (best growth between 45–80°C) and hyperthermophile (grows best >80°C).

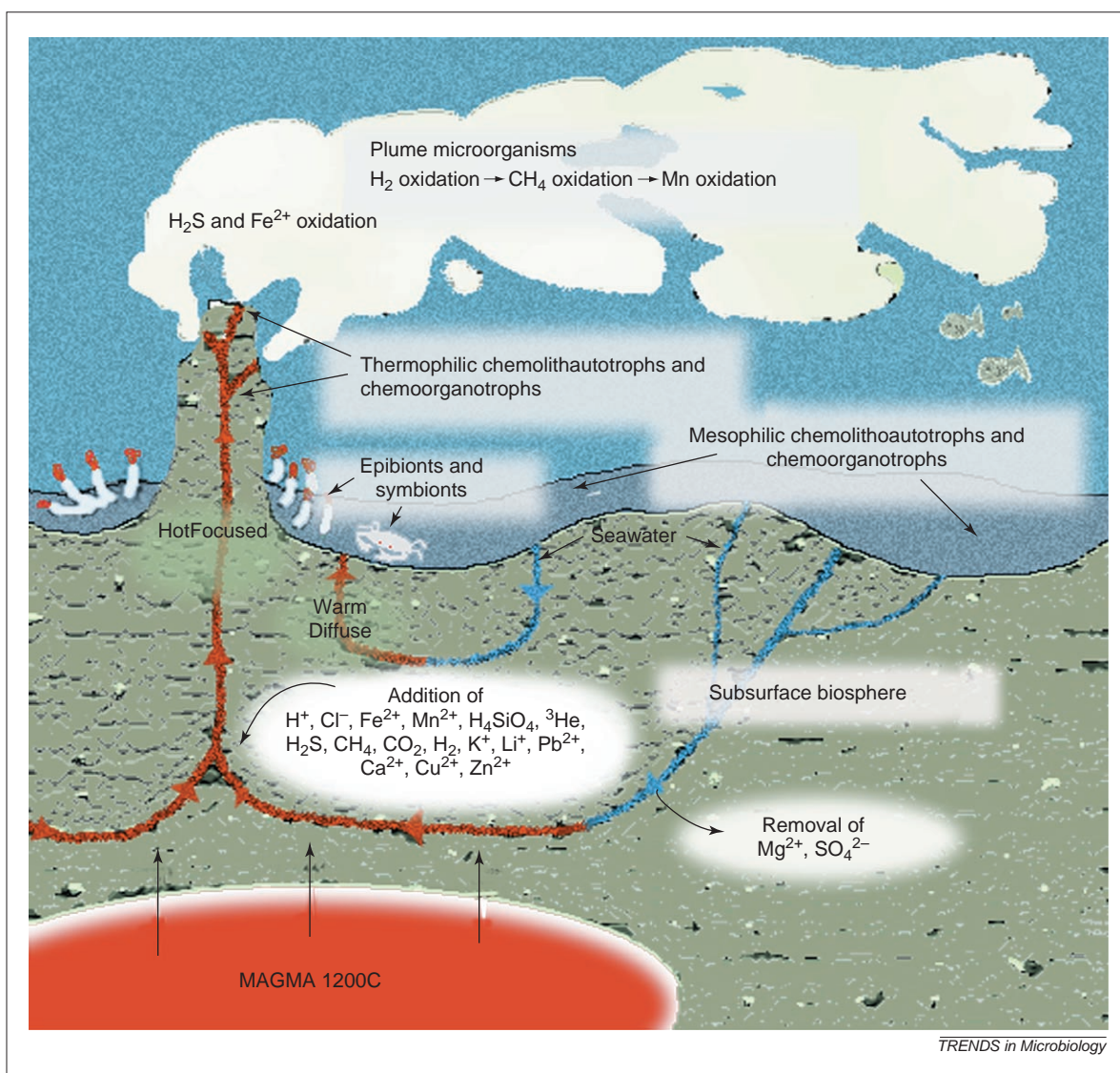
around hydrothermal vents, seawater or groundwater can percolate into the crust and react with the surrounding rocks, heating the fluid and altering its chemistry. In marine and terrestrial hydrothermal systems, the altered water will eventually be forced back convectively to the surface as superheated, highly reduced, hydrothermal fluid rich in gases and dissolved minerals (Fig. 2). The hydrothermal fluid chemistry is a record of its path within the earth's crust, and differs as a function of the underlying rock composition and the residence time of the fluid in the subsurface¹⁵.

Given that hydrothermal activity has continued throughout geological time, thermophilic communities have probably evolved and been maintained in these environments, leaving biosignatures in the rock record. Paleontological interpretation relies on modern comparisons: paleobiological interpretation, which places fossils in a phylogenetic and functional framework by

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Fig. 2. Diagrammatic representation of a cross-section through a deep-sea hydrothermal system depicting the possible niches for different microbial communities. At spreading centers, as the cold oxygenated seawater (blue) travels through fissures in the Earth's crust, the seawater is heated and reacts with the surrounding rocks. The chemically altered seawater, or high-temperature hydrothermal fluid (red), is forced back convectively to the seafloor. As the hydrothermal fluid mixes at the seafloor, minerals are precipitated out of solution to form porous sulfide structures, which are ideal niches for thermophilic microorganisms. The ascending hydrothermal plume is rich in energy sources for microorganisms. Additionally, the animals and surrounding rocks provide attachment sites for a diverse array of mesophilic microorganisms.



comparisons with modern-day organisms and fossilization mechanisms; and paleoenvironmental interpretation, which places the fossils in their chemical and physical framework¹⁶. However, as one examines older deposits, biological and environmental analogies become harder to draw. For example, very old rocks can be highly altered owing to DIAGENESIS and metamorphism (see, for example, Ref. 45). Furthermore, it is unlikely that extant microbial communities are exact homologs of their ancient counterparts, given the reduced and anoxic early atmosphere. Therefore, comparison of the fossils, isotopes and minerals preserved in both modern and ancient deposits provides a framework for interpreting ancient microbial communities.

The Paleomicrobiological record

Walter¹⁷ has summarized the many marine and terrestrial ancient hydrothermal deposits; some of these sites are depicted in Fig. 1. With the exception of the 3.5-Ga deposits located near Barberton, South Africa¹⁸ and the 3.26-Ga deposits in the Pilabara Craton, Australia, no Archaean oceanic crust is

thought to be preserved¹³. Hydrothermal features and volcanic massive sulfides (VMS) have been interpreted from the 3.5-Ga Barberton Greenstone Belt deposits^{18–20}, although this interpretation is tenuous¹⁷. However, the Sulfur Springs and Kangaroo Caves VMS deposits (3.26-Ga old) in the Pilabara Craton are perhaps the most well preserved and least altered early Archaean hydrothermal deposits.

Recently, Rasmussen²¹ reported the presence of pyritic filaments (Fig. 3a) in the 3.2-Ga VMS deposit at Sulfur Springs, Australia. These deposits were formed in at least 1000m of water in a backarc basin, and many of the sulfide textures are indistinguishable from modern deep-sea-vent black smokers. The composition of the basal parts of the deposits suggests that fluid temperatures reached at least 300°C (Ref. 22), similar to temperatures measured for modern deep-sea hydrothermal end member fluids. The filamentous microfossils in these deposits are reminiscent of similar morphologies reported by Juniper and Fouquet, 1988 (Ref. 23) from the Cyprus Troodos, Phillipino Zambalans and the Californian Coastal Range ophiolite deposits. Rasmussen²¹

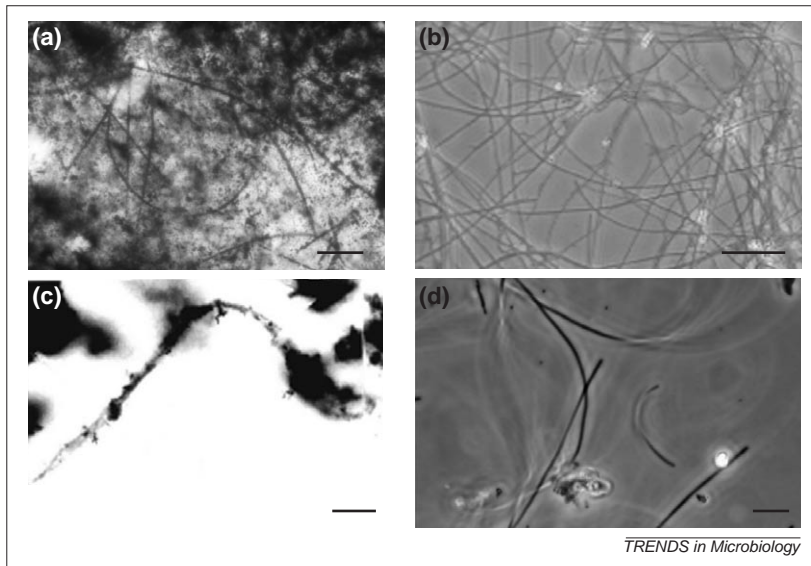


Fig. 3. Morphological characteristics do not reflect phenotypic characteristics. (a) and (c) are microfossils, and (b) and (d) are examples of two very different filamentous thermophiles, a photoheterotroph (b) and a chemolithoautotroph (d). (a) Filamentous microfossils obtained from the Sulfur Springs VMS deposit. Courtesy of B. Rasmussen. (b) Phase-contrast micrograph of *Chloroflexus aurantiacus*, an example of an extant filamentous thermophile. (c) Filamentous (sheathed?) microfossil with pyrite precipitates (dark) from the Barberton Greenstone Belt, South Africa. Courtesy of Maud Walsh. (d) Phase-contrast micrograph of the *Aquificales*-related 'pink filaments from Octopus Spring, Yellowstone National Park.

proposed that, although it is difficult to ascribe a metabolism based on morphology alone, based on the location of the Sulfur Spring filaments within a hydrothermal system, the metabolic characteristics

Table 1. Morphology and basic metabolism of some of the major thermophilic group^a

Group	Shape ^b	Metabolism	Marine(M) or Terrestrial(T)
Bacteria			
<i>Aquificales</i>	R, F	CA, CO	M, T
<i>Thermotogales</i>	SR	CO	M, T
' <i>Thermales</i> '	F, R	CO	M, T
' <i>Thermodesulfobacteriales</i> '	R	CO	M, T
' <i>Chloroflexales</i> '	F	PA, PH	T
' <i>Chlorobiales</i> '	R, F	PA, PH	T
Cyanobacteria- <i>Synechococcus</i>	R	PA	T
<i>Proteobacteria</i>			
e.g. <i>Desulfurella</i> spp.	R	CO	T
' <i>Thermothix</i> ' spp.	F	CA	T
Gram-positive bacteria			
e.g. <i>Thermoterrabacterium</i> spp.	R	CO, CA	T
<i>Thermoanaerobacter</i> spp.	R	CO	T
Archaea			
<i>Archaeoglobales</i>	C	CO, CA	M
<i>Thermoproteales</i>	R, F	CA, CO	M, T
<i>Thermococcales</i>	C	CO	M, T
<i>Thermoplasmals</i>	C, F	CO	M, T
Methanogens	C, R, F	CA	M, T
' <i>Desulfurococcales</i> '	C	CO, CA	M
' <i>Sulfolobales</i> '	C	CA, CO	T

^aAbbreviations: C, cocci; CA, chemolithoautotroph; CO, chemoorganotroph; F, filaments; P, photoautotroph; PH, photoheterotroph; R, rods; SR, sheathed rod.

^bMorphology can vary depending on culture conditions.

might be similar to the chemolithoautotrophic sulfur-metabolizing thermophiles found in modern hydrothermal sulfide deposits (discussed later). However, without additional evidence such as sulfur and carbon isotope fractionation data, these interpretations remain speculative.

Implications of early metabolisms from stable isotope analysis

Interestingly, similar filamentous microfossils have been reported from laminated sedimentary Archaean deposits in the Warrawoona Group (3.0–3.5 Ga) in Western Australia, and the Barberton Greenstone Belt (Fig. 3c) in southern Africa. Fortunately, these fossils have enough associated preserved organic carbon that STABLE ISOTOPE analysis was possible. Because of the metabolic fractionation of naturally occurring carbon isotopes, it is possible to interpret from relative isotope abundances (of ^{12}C and ^{13}C) whether the organic carbon was acquired by autotrophy or organotrophy (HETEROTROPHY). The low $\delta^{13}\text{C}$ values for the organic matter and the unusual $\delta^{13}\text{C}$ enrichment values obtained for carbonates in the Warrawoona Group deposits have been used as evidence for methanogenic and/or photosynthetically derived carbon^{24–26}. Although these interpretations are plausible, alternative possibilities¹⁶ such as mesophilic or thermophilic chemolithoautotrophic microbial mats using pathways such as the 3-HYDROXYPROPIONATE and reductive-TCA pathways, cannot be ruled out²⁷.

Stable isotope measurements have also provided clues to the early atmosphere of the Archaean. Using thermophilic cultures obtained from deep-sea vents and modeling sulfate reduction rates and sulfate concentrations in a hypothetical Archaean sediment, Canfield *et al.*²⁸ have proposed that concentrations of sulfate and oxygen were very low in the early Archaean (3.4–2.8 Ga), with probably low sulfate-reduction rates. During this time, nitrate was probably also absent or in very low concentrations, and microorganisms used reduced forms of nitrogen, as reflected by the negative ^{15}N values obtained for compositions of kerogens in Precambrian CHERTS²⁹. Later (2.5–0.54 Ga), sulfate, nitrate and oxygen began to accumulate^{28,29} shifting the redox conditions on the early earth.

Microbial diversity at modern hydrothermal vents-analogs for interpreting the microfossil record?

Nearly all of the microfossils associated with ancient hydrothermal deposits reported to date are filamentous, even though the microbial communities of most hydrothermal ecosystems also contain mesophilic and thermophilic cocci (Table 1). The lack of examples of such morphotypes as microfossils could reveal a biased fossil record, perhaps owing to differences in the susceptibility of various types of organisms to preservation, in the mechanism of preservation, and in post-fossilization alteration processes. It is often difficult to recognize fossilized

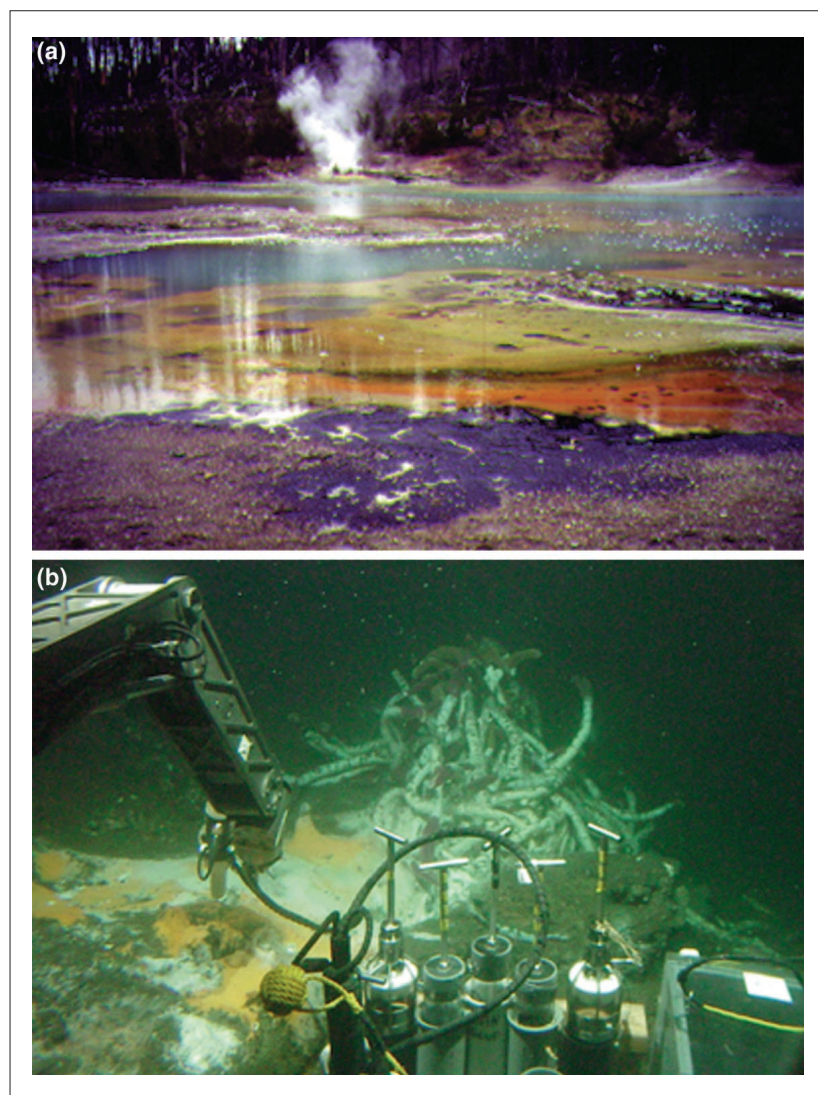


Fig. 4. (a) Thermal spring with colorful photosynthetic microbial mats in Norris Geyser Basin, Yellowstone National Park, USA. (b) Orange and white chemolithoautotrophic microbial mats near deep-sea hydrothermal vents in Guaymas Basin, Mexico.

cocci in the geological record. Unless the cocci are organically preserved and display high-fidelity structural preservation, they are difficult to distinguish from inorganic colloids, which commonly precipitate from hydrothermal fluids. Additionally, most isotopic studies of early microfossils have implicated autotrophy as the inferred metabolism of the fossilized microorganism²⁵. Consequently, rather than review the diversity of thermophiles, we refer the reader to reviews on this topic (e.g. Ref. 6), and will focus on rod-shaped and filamentous autotrophic thermophiles, with limited discussion of mesophilic chemolithoautotrophic filaments in marine hydrothermal systems, as these are all possible analogs of filamentous microfossils. Table 1 includes some of the major groups of thermophiles, their general morphology and mode of carbon metabolism. Both of these attributes provide valuable information for interpreting the geological record using morphological and isotopic signatures.

The microbial diversity at deep-sea and terrestrial hydrothermal systems primarily differs in two ways. In terrestrial hydrothermal systems, light energy plays a significant role in selecting for thermophilic

PHOTOAUTOTROPHS that often form conspicuous photosynthetic microbial mats (Fig. 4a), whereas at deep-sea vents, the abundant available reduced sulfur and iron compounds in the highly mixed low-temperature zones around the vents favors mesophilic sulfur- (Fig. 4b) and iron oxidizers³⁰ that, in turn, form conspicuous microbial mats. In addition, the prevalent macrofauna at deep-sea vents are absent from the terrestrial hydrothermal ecosystems. Clearly, there are many other significant geochemical characteristics that define the environmental conditions between these different systems. For example, the pH can vary from 1 to 10 in terrestrial hydrothermal systems. Although pH gradients do occur as high temperature hydrothermal fluids (pH <4) mix with cold oxygenated seawater (pH ~8), these pH gradients are very steep and fluctuate continually. These geochemical constraints must affect the structure of microbial communities, however such a discussion is beyond the scope of this review.

Some filamentous and rod-shaped thermophilic autotrophs

Many of the thermophilic lineages have representatives that are rod-shaped or filamentous. These observations are based primarily on organisms that have been isolated in culture, some of which might have different morphologies in the natural environment or under differing culture conditions^{31,32}. Members of the deeply rooted bacterial lineage the *Aquificales* form perhaps some of the more conspicuous microbial communities in terrestrial thermal springs. These communities are often associated with large amounts of sulfur and iron mineral precipitates^{33,34}. All the members of the *Aquificales* are filamentous or rods and, in laboratory culture, they can take up different morphotypes. One member, *Thermocrinis ruber*, forms long pink-colored filaments in the thermal streams in Yellowstone; however, when grown in flask cultures, the cells are short rods³². Recently, the first member of a separate lineage in the *Aquificales* was isolated from deep-sea hydrothermal vents^{35,36}. This lineage is only about 80% similar in 16S rRNA sequence to all other known cultured *Aquificales*, and the deep-sea isolate is closely related (92–95%) to 16S rRNA sequences or PHYLOTYPES obtained from thermal springs in Yellowstone, Japan and Iceland^{33,34,37}.

As these organisms are deeply diverging filamentous chemolithoautotrophs, which are often associated with mineral precipitates^{33,34,37}, they could be relatives of some of the early fossils that have been described from hydrothermal deposits⁹. Furthermore, as many of these mats are dominated by a single type³⁴, this order is a good target for exploring mechanisms and regulation of mineral precipitation and microbial fossilization; studies that will help predict the types of biochemical microbial biosignatures that could form in these ecosystems. Indeed, Cady and Farmer³⁸ showed that the filamentous communities in Yellowstone's Octopus

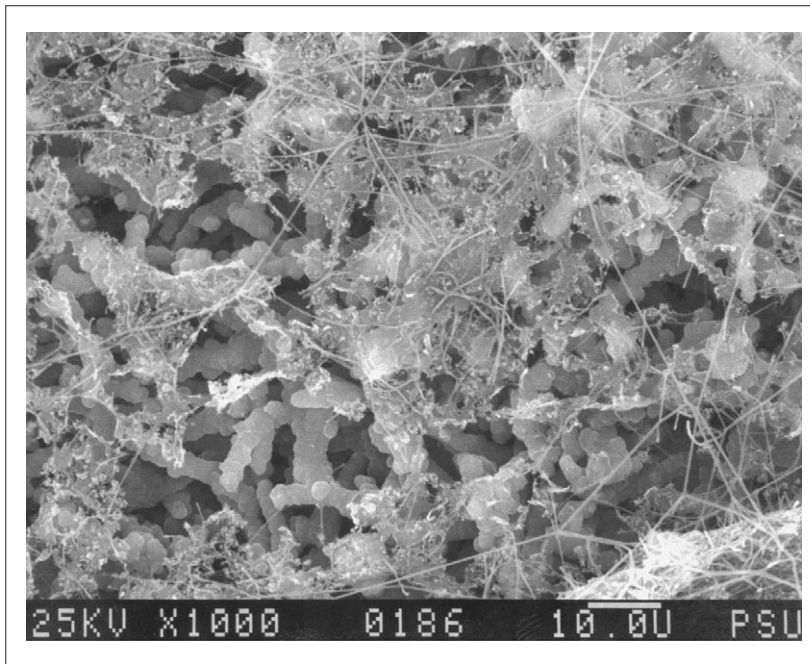


Fig. 5. Scanning electron photomicrograph illustrating the variation in microfossil size owing to silicification via encrustation of thermophilic filaments. The top layer consists of unsilicified filaments within a partially silicified biofilm matrix. The bottom layer consists of heavily silicified filaments that are much larger in diameter owing to the deposition of several layers of opaline silica. These filaments are presumably *Chloroflexus*, as the samples were obtained in areas where active viable unsilicified *Chloroflexus* was growing. Courtesy of Zach Oestreicher.

Pool sinter (where *T. ruber* resides) are sites for the nucleation of siliceous deposits. Additionally, the black filamentous communities at Calcite Springs in Yellowstone National Park and the Azores actively precipitate iron minerals within their periplasmic space and extracellularly^{9,39}. Iron mineral precipitation by microorganisms could contribute positively to their preservation by silicification^{20,40}, adding additional impetus for studying fossilization mechanisms of these organisms.

Two additional interesting rod-shaped thermophilic genera that are thus far endemic to marine vents are *Methanopyrus*, a rod-shaped methanogen⁴¹, and *Desulfurobacterium*, a sulfur-reducing obligate chemolithoautotrophic bacterium⁴². Both of these rod-shaped chemolithoautotrophs form distinct lineages within the archaeal and bacterial domains, respectively and have been isolated from the highly mineralizing environments of black sulfide chimney smokers. The role of these isolates in nucleating minerals has not been explored.

Many of the thermophilic phototrophs, such as *Chloroflexus* (Fig. 3b), are filamentous and provide the matrix for extensive photosynthetic microbial mats in terrestrial thermal springs. These mat structures have been used as analogs of biogenic STROMATOLITE formation. Additionally, Cady and Farmer³⁸ have shown that, with time, these filaments are silicified primarily by encrustation and deposition of fine laminae of opaline silica (Fig. 5). Clearly, these types of studies improve paleobiological and paleoenvironmental interpretation of ancient microfossils.

Chloroflexus is of additional interest with regard to its role in the evolution of photosynthesis⁴³. Xiong *et al.*⁴⁴ provided evidence that the photosynthetic pigments of this group, together with the purple, green sulfur and non-sulfur Bacteria, all evolved before

oxygenic phototrophs. This organism grows best as a PHOTOHETEROTROPH, with organic compounds as carbon sources. As an autotroph, it has a very unusual mode of carbon fixation, using the 3-hydroxypropionate cycle. It has recently been demonstrated that organic matter in mats dominated by *Chloroflexus* spp. has a high ¹³C content, as do their lipids. These results suggest that heavier isotopes could have a biological origin, which is contrary to reports that suggested isotopically heavier organic carbon in ancient rocks is the result of the alteration of organic carbon by thermal metamorphism⁴⁵.

Diversity of some mesophilic chemolithoautotrophs

Although mesophilic filamentous iron- and sulfur oxidizers have been described from deep-sea vents^{30,46}, their role in low-temperature terrestrial hydrothermal systems is overshadowed by phototrophs. The iron oxidizers can be sheathed and encrusted by iron minerals and are therefore also good models for fossilization^{47,48}. Many of the sulfur-oxidizers are large filamentous cells similar to *Beggiatoa* and *Thiothrix*⁴⁹ and form extensive mats at deep-sea vents⁵⁰. The *Beggiatoa*-dominated mats are often associated with thin filamentous flexibacteria (2.0–2.6 μm in width and 6–10 μm in length)⁴⁹, reminiscent of filamentous microorganisms depicted in Fig. 3. Clearly, if these mats are mineralized and if their cell structural integrity is maintained, they will provide important biosignatures of these microbial communities. Filaments with sheathed structures preserved in organic-rich siliceous rocks in the Miocene Monterey Formation, have been attributed to *Beggiatoa*-like sulfur-oxidizing bacteria⁵¹. These fossils could be useful in interpreting how such filaments are fossilized in the deep-sea. Additionally, from soft mineral crusts obtained from rock samples collected near active deep-sea vents, Fortin *et al.*⁴⁸ have shown that bacteria and their associated exopolymers do serve as nucleation surfaces for iron oxide and iron silicate precipitation in these environments.

Filamentous mesophiles occupy many other niches in deep-sea vents, for example, as epibionts of macrofauna^{52,53}. But perhaps one of the most significant recent findings regarding mesophilic diversity at deep-sea hydrothermal vents was the discovery of microorganisms that produce copious amounts of inorganic filaments of sulfur⁵⁴. The *Arcobacter*-like isolates are able to produce filamentous sulfur in high fluid-flow H₂S–O₂ environments and it has been suggested that the sulfur precipitation is a strategy for vibroid organisms to remain in place in the turbulent environment. These epsilon proteobacteria are probably responsible for the white flocculent material that covers fresh basalt within weeks following an eruption, and are also probably associated with white flocculant mats at shallow marine hydrothermal

systems⁵⁵. Whether and how this extensive biological production of sulfur is preserved in the rock record is unknown. However, it is likely to be distinguished by a biologically fractionated sulfur isotope biosignature if it is not completely recrystallized during diagenesis.

Although this review has focused on thermophilic rods and filaments, as mentioned above there are also many mesophilic rods and filaments, making interpretation of fossils based on morphology alone potentially misleading. With recent developments in compound-specific isotope analysis and ion microprobes, more detailed understanding of isotopic fractionation in extant and fossil microorganisms is possible. Clearly, isotopic analysis of organically preserved fossils in hydrothermal deposits, along with a more detailed understanding of isotopic fractionation by chemolithoautotrophs will lead to additional insights into the nature of the evolution of life on earth.

Concluding thoughts

Filamentous and sheathed organisms are abundant in terrestrial and marine hydrothermal systems. This morphology could be an advantage over cocci, enabling complex microbial mat formation and retainment of filaments in a fast-flowing fluid environment. Prevalent iron, sulfur and calcite mineral precipitates coat many of these communities. Furthermore, many of the remaining microfossils in ancient hydrothermal systems are of organism-like filaments and sheaths encrusted by secondary minerals such as pyrite (Fig. 3c), reminiscent of present-day thermophiles. Although Schopf⁵⁶ and others²⁵ have developed convincing arguments about the nature of these early microfossils, other interpretations might still exist as we learn more about life on earth today. The challenge for microbiologists and paleobiologists alike is to improve our understanding of the early evolution of life using modern and highly evolved analogs.

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Hijacking and exploitation of IL-10 by intracellular pathogens

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Macrophages play a central role in infections, as a target for pathogens and in activation of the immune system. Interleukin-10 (IL-10), a cytokine produced by macrophages, is a potent immunosuppressive factor. Some intracellular pathogens specifically target macrophages for infection and use IL-10 to dampen the host immune response and stall their elimination from the host. Certain viruses induce production of cellular IL-10 by macrophages, whereas other viruses encode their own viral IL-10 homologs. Additionally, specific bacteria, including several *Mycobacteria* spp. and *Listeria monocytogenes*, can survive and replicate in macrophages while inducing cellular IL-10, highlighting a potential role for IL-10 of macrophage origin in the immunosuppressive etiology of these pathogens. Thus, the exploitation of IL-10 appears to be a common mechanism of immunosuppression by a diverse group of intracellular pathogens that can infect macrophages.

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Interleukin-10 (IL-10) can have potent anti-inflammatory and immunosuppressive effects on the functions of haematopoietic cells. This cytokine is secreted by macrophages, T cells, B cells, mast cells and keratinocytes, is normally produced late in the immune response to a pathogen compared with other cytokines and serves to dampen the response by the suppression of inflammatory cytokines¹. IL-10 can inhibit the production of many cytokines including interleukin (IL)-2, interferon gamma (IFN- γ), tumor necrosis factor alpha (TNF- α), IL-4, IL-3, IL-1 and granulocyte–monocyte colony stimulating factor (GM-CSF), and has thus been called the 'macrophage deactivation factor'. Various surface molecules are downregulated by IL-10, including major histocompatibility complex class II (MHC class II)

proteins and co-stimulatory molecules (B7.2 or CD86), and the production of reactive oxygen and nitrogen intermediates in activated macrophages, and macrophage-dependent T cell proliferation is also inhibited¹. IL-10 can also stimulate the production of the IL-1 receptor antagonist (IL-1ra), another anti-inflammatory agent produced by monocytes and polymorphonuclear leukocytes. IL-1ra can modify the of IL-1 and TNF- α activity¹. In addition to its immunosuppressive effects, cellular IL-10 can also act as a growth factor for mast cells, is a potent growth and differentiation factor for B cells, and can stimulate proliferation of CD8⁺ T cells¹.

Soluble IL-10 mediates its action by binding to the cellular IL-10 receptor (IL-10R). IL-10R is composed of two subunits, the ligand-binding IL-10R α chain and the accessory subunit CRF2-4 (Ref. 2). IL-10R α binds IL-10 with high affinity and, in the presence of IL-10, associates with CRF2-4. Both subunits are required for signal transduction³. IL-10R signaling in monocytes and T cells involves the tyrosine phosphorylation of signal transducers and activators of transcription (STAT) -1 and -3 (Ref. 4) and the kinases Jak1 and Tyk2 (Ref. 5). Because IL-10 is known to have different effects on different cell types, it is possible that alternative signal-transduction pathways are present in different cell types, although these have not yet been identified.

Initiation of *IL-10* gene transcription and protein synthesis involves multiple levels of control. The *IL-10*