Pathogenic archaebacteria: do they not exist because archaebacteria use different vitamins?

Sir,

Recently in these pages, Cavicchioli et al.[1] addressed an interesting question, namely: do pathogenic archaebacteria exist? In the main, they cite evidence to establish the following points. (1) No archaebacteria have yet been found to be agents of disease. (2) Archaebacteria are sufficiently abundant in non-extreme environments as to provide them ample opportunity to infect animals and humans. (3) Some archaebacteria interact intimately with eukaryotes as intracellular symbionts, the best-known examples being methanogens that inhabit the cytosol of eukaryotes that possess hydrogenosomes. (4) Methanogens are very commonly found as inhabitants of the human oral cavity and intestinal tract, though no clear-cut link between methanogen presence and any disease has yet emerged. (5) Some archaebacteria appear to possess toxins, although no toxicity to humans or animals is known. (6) Secretion systems associated with eubacterial pathogenicity and with pathogenicity islands seem to occur in fragmentary form among archaebacterial genomes, suggesting that the well-known mobility of these genes does not seem to have altogether missed the archaebacteria as recipients. (7) There are some human diseases to which no causative agent has been assigned, leaving the possibility open that archaebacteria might ultimately be found to be responsible. From those seven basic observations, none of which I would contend in any way, they surmise in conclusion that *"There are two possible reasons why no pathogenic archaea are known: (1) they do not exist or (2) they have not been identified." They continue "From our reasearch, there are no compelling reasons to suppose the first possibility."* However, considering the present question from an entirely different standpoint (simple biochemistry), I think that there are compelling reasons, which I wish to briefly mention here, to suppose that archaebacterial pathogens do not exist.

In a nutshell, the answer to the question of why there are no archaebacterial pathogens is probably: "cofactors" (also called "vitamins" in the context of nourishment). Archaebacteria synthesize and use in their day-to-day biochemistry a variety of cofactors that humans, animals, eukaryotes in general, and most eubacteria for that matter, neither synthesize nor require.[2–7] A few examples are methanopterin (a C1-donating cofactor with similar spectrum of functions as folic acid), coenzyme M (a methyl carrier), factor F_{430} (a nickel-containing porphyrin analogue involved in methyl transfer), factor F_{420} (a hydride carrier like riboflavin), coenzyme B (a thiol-containing cofactor involved in redox reactions), methanofuran (involved in CO_2 reduction), cobamids (corrinoids that can be viewed as anaologues of cobalamin), alternative quinones such as sulfur-containing heterocyclic benzothiophenes or methanophenazine (not a quinone at all but used by many archeabacteria instead of quinones), halocyanin (an alternative to cytochromes), and so on, and so forth.[2–7]

Vitamins are important for nourishment, they are essential components of the diet for those organisms, such as humans, that are unable to synthesize all of the vitamins (or even amino acids) that they need to survive. Pathogens, like every other organism on earth, are looking for a meal. The underlying themes of pathogen evolution among eubacteria seem to be (1) gain access to a host, (2) learn to avoid host defence and (3) undergo genome reduction by virtue of the ability to parasitize the host's biochemistry. Mesophilic archaebacteria should not have a fundamental problem with the first two steps, but arguably have an insurmountable problem with the third step. By no means do I purport to be an expert on the topic of archaebacterial cofactors, but I have read that some exist. In fairness, the papers cited here deal mainly with methanogens (one group of archaebacteria). But looking around, basic biochemistry in archaebacteria seems to be different enough to consider the suggestion that the lack, in eukaryotic cells, of what an archaebacterium would perceive as a good meal, would make eukaryotes fundamentally uninteresting as a substrate for infection and growth. As an example, consider the glycolytic pathway, familiar to most of us from textbooks, which operates without the participation of NAD (or any other niacin homologue) in some archaebacteria,[8,9] and with the help of enzymes that, in the majority, do not share common ancestry with their eubacterial and eukaryotic homologues,[9–11] notwithstanding the circumstance that relatively few archaebacteria even have an Embden–Meyerhof type glycolytic pathway.[9–11]

As a main course at dinnertime, the cell content of eukaryotes in general and humans in particular, does not provide a complete diet for archaebacteria, except for some autotrophs in those eukaryotes that have hydrogenosomes,[12] because for many archaebacterial autotrophs, H_2 is almost a complete meal. That brings us back to the universal tree,[13] according to which eukaryotes and archaebacteria should tend to use the same cofactors, which they don't. Rather, eukaryotes and eubacteria tend to use the same cofactors, probably for the simple reason that eukaryotes inherited most of their biochemistry from their mitochondrial symbiont.[11] From these considerations a simple prediction follows: if archaebacterial "pathogens" are found, they will infect other archaebacteria—not eukaryotes—and one such example seems already to have been described.[14]

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Response to William Martin's letter

Sir,

Indeed archaea do produce novel cofactors. They also are unique in producing methane, and the synthesis of a glycerol phosphate backbone for their phospholipids (G-1-P) that differs in stereospecificity from bacteria and eucaryotes (G-3-P).[1] In this regard, the novel features of archaea may serve as useful biomarkers. However, it is not clear that because archaea use different cofactors, this would prevent them from being pathogens. Pathogens can benefit in various ways from their host, not just by obtaining common vitamins and cofactors. Availability of metabolites, amino acids, nucleic acids and energy sources may also be advantageous. For viruses, part of the ''nutritional'' benefit is access to the host's replication and gene expression machinery. Evolutionary processes enable selection based on fitness. If colonising a warm, nutrient-rich, secure, gastrointestinal tract (GIT) provides a competitive advantage, then, given the opportunity, a successful candidate will emerge. Irrespective of their cofactor requirements, methanogens have evolved to thrive in the GIT. The lack of a supply of exogenous cofactors from the host (or for that matter from the GIT bacteria) has not prevented their successful colonisation. Given that they can compete and benefit from the host, the question still remains why they have not been shown to take the next step, and cause harm to their host.

The fact that methanogens must synthesise their own cofactors reflects an interesting evolution. It also provides an explanation for why they maintain the capacity to do so. Some methanogens can grow, for example, on a completely defined medium in the absence of exogenously added vitamins.

The best example of a minimalistic genome for any organism is from the archaeon, *Nanoarchaeum equitans*. Its genome was recently sequenced and found to be 490,885 bp.[2] It is either a symbiont or a parasite of its archaeal, hyperthermophilic host (*Ignicoccus*). It is interesting to consider whether its small genome reflects genome reduction or the properties of its primordial ancestor. If one assumes the former, while genome reduction may have been possible because its host is able to provide most of its genetic needs (including genes for cofactors), it would not preclude a hypothetical archaeal pathogen of a human from undergoing genome reduction—it would simply set a different minimum level of genome reduction. The focus should surely not be on the consequence of becoming a bacterial pathogen (e.g. reduced genome size), but considering the mechanisms that may enable an organism (e.g. archaeon) to be, or become a pathogen.

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