Bacteriophage Collagen

We enjoyed the Perspective by Jürgen Engel (19 Sept., p. 1785) describing the homologs of vertebrate collagen that have been characterized in invertebrates. We wish to highlight the occurrence of collagen-like repeats encoded in bacteriophage genomes. Analyses in our and others' laboratories have identified five examples of the characteristic collagen-like repeat (Gly-X-Y)$_n$ in genes encoding structural components of bacteriophage virions. These examples include coliphage 933W, with stretches of 51 and 38 repeats of the collagen motif within the same gene (*1*); actinophage fC31, with five and 10 repeats separated by four amino acids (GenBank accession number Z99661); coliphage BF23, with 12 repeats (Z50114); lactococcal phage BK5-T, with 64 repeats distributed in 11 short stretches within one gene (*2*); and coliphage PRD1, with six repeats (3). The bacteriophage collagen sequences have the bias toward proline at the second and third positions of the motif that has long been known in animal collagens.

What roles do collagen repeats play in bacteriophages? For phages fC31 and 933W, it is very likely (and possibly also true for BF23 and BK5-T) that the collagen repeat is within a tail-fiber gene. All well-characterized phage tail-fiber proteins are trimeric, including phage l fibers that share other sequence similarity with the 933W putative fiber. Thus, collagen sequences in phage tail fibers may well have the triple helical structure found in animal collagen. The PRD1 collagen sequence, in contrast, occurs in a trimeric protein that lies on the surface of the phage head (*4*).

There would seem to be four possible evolutionary explanations for the occurrence of collagen in such phylogenetically diverse locations as animals and bacteriophages: (i) collagen already existed in a common ancestor of animals and bacteriophages (or their bacterial hosts), (ii) collagen arose independently in animals and phages, (iii) collagen arose in animals and was passed horizontally to phages [a precedent of this type of transfer could be the fibronectin III domain (5)], or (iv) collagen arose in phages and was passed horizontally to animals. While there is no evidence to support any of these scenarios at present, we are particularly intrigued by the fourth possibility—that phages invented collagen to make better tail fibers and then passed it to eukaryotes, making possible the construction of animals as we now know them.

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Response: The observations by Smith *et al.* are interesting, but are made in the absence of sufficient biochemical proof of three-stranded molecules and hydroxylation of prolines. Thus, the sequence data are suggestive, but do not prove the presence of collagen triple helices. In particular, the short segments of only five adjacent Gly-Y-X repeats in lactococcal phage BK5-T could only combine to form stable triple helices after hydroxylation and other postribosomal modifications that do not show up in the DNA sequence. For the thermal stability of mammalian collagens, hydroxyprolines in the Y position are essential, and stable collagens with only five repeats are not known. It is interesting that, in mammalian collagen, exons of 54 nucleotides are common, that they correspond to six Gly-X-Y repeats, and that these repeats are combined in the protein to much longer helical domains. Phages or their host bacteria would need appropriate hydroxylases, but I am not aware of any information about this possibility.

Concerning the phylogenetic argument made by Smith *et al.*, one might note that collagens do not occur in plants. Instead, in plants and in Volvox (*1*), proteins are found in which long hydroxyproline-rich and glycosylated regions act as a kind of substitute for collagen triple helices.

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The Oldest Human

The life-span of Jeanne Calment, who died in Arles, France, on 4 August 1997, at the age of 122 years and 164 days, is the longest ever recorded in a human being, exceeding the 120 years generally acknowledged as the ultimate limit. Experts consider that the first real centenarians appeared in Western societies around the turn of the 19th century (*1*), but 10 years ago, biologists of aging still estimated that the maximum life-span of a human being was 100 years and that the observation of centenarians was a universal phenomenon, valid for all historical periods and all societies (*2*).

Because of the current explosion of the number of centenarians in the most developed countries, for example, in England and Wales, where the number of persons attaining age 100 increased from 183 in 1950 to 1971 in 1990 (*3*), biologists of aging have gradually extended the age limit attainable by humans (*4*). Today, most authors cautiously put the biblical figure of 120 years forward as the limit.

The age of Jeanne Calment was carefully verified in 1995, when she was 120 years old (*5*), and an assessment of her cognitive functions was carried out (*6*). In addition, in our research, we have identified 52 immediate ancestors of Jeanne Calment corresponding to five generations (two parents, four grandparents, eight great-grandparents, 16 great-great-grandparents, and 32 great-great-great-grandparents). We were able to validate the length of life of 55 ancestors out of these 62.

In order to appreciate the length of life of these ancestors, we found controls who had also had children. Although this is not strictly equivalent, we paired each ancestor of Jeanne Calment with an individual of the same sex married in the same municipality (the same parish before the French Revolution) and shown on the register of marriages just before him or her, or, if this was not possible, just after. Altogether, the controls constitute a reference family of the same space and time, since the beginning of the 18th century. As expected, the professions of the ancestors of Jeanne Calment and of the reference family are not very different from one another.

Jeanne Calment had a Total Immediate

Ancestral Longevity (7) of 477 compared with 289 for the sum of the ages at death of the six immediate controls of the reference family. The 55 immediate ancestors of Jeanne Calment lived to an average age of 68.2 years, versus 57.7 years for the 55 controls in the reference family.

The ancestors of Jeanne Calment included a large proportion of long-living individuals (age of death, 80 years or over): 13 out of 55 (24%) versus one in the reference family (2%). Five of her six immediate ancestors lived for more than 70 years. However, the ratio of the years lived by the ancestors of Jeanne Calment compared with the years lived by the controls decreased from her parents to her great-great-great-grandparents is as follows: 2.1 for the parents; 1.5 for the grandparents; 1.4 for the great-grandparents; 1.3 for the great-great-grandparents; and 1.0 for the great-great-great-grandparents.

We did not observe any trace of simple hereditary transmission of longevity among the ancestors of Jeanne Calment, but we did see an extraordinary concentration of long-living individuals, especially on her paternal side. The 32 great-great-grandparents are, in fact a melting pot of nongenetically related people. The probability of having such a high concentration of long-living ancestors during the 18th and 19th centuries is likely close to zero. One might hypothesize that the extraordinary longevity of Jeanne Cament is largely genetic in origin and that it is due to an exceptional genetic inheritance, randomly accumulated within the ecological niche of Arles in the 18th and 19th centuries (and, more specifically, within the social group of craftsmen and shopkeepers running prosperous businesses in the town). Her brother, who inherited the nearest genetic combination, died at the age of 97.

Genetic inheritance could be explained by the absence of alleles predisposing individuals to various life-threatening degenerative diseases or by the presence of genetic combinations, or both, particularly effective in terms of longevity. On the other hand, the parents of Jeanne Calment had lost two children in infancy before she was born. One might therefore hypothesize that Jeanne Calment lived in an environment perfectly adapted to her genetic profile (and vice versa).

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Letters to the Editor

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