

Retroviruses, Ascorbate, and Mutations, in the Evolution of *Homo sapiens*

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Abstract:

Mutations, induced by free radicals, provide a rich molecular palette that other evolutionary forces can select for or against. A recent hypothesis proposed that large numbers of free radicals were produced when, millions of years ago, Anthropoidea lost the ability to produce endogenous ascorbate, increasing the frequency of mutations and accelerating the evolution of higher primates. Recognizing that retroviruses have been active throughout the period of primate evolution, we suggest that an endogenous retrovirus or other retroviral-like element may have been involved in mutating the gene coding for gulonolactone oxidase (GLO), the terminal step in ascorbate synthesis, approximately 45 million years ago. This possibility is supported by the presence of *Alu* elements (a common primate retroelement) adjacent to the site of a missing segment of the nonfunctional GLO gene. Although *Homo sapiens* and other higher primates produce other endogenous antioxidants, including superoxide dismutase and uric acid, they do not quench the same radicals as ascorbate and cannot fully compensate for a lack of endogenous ascorbate. As a consequence, a retrovirus may have played a pivotal role in primate and *H. sapiens* evolution, and the absence of endogenous ascorbate may be continuing to accelerate the rate of *H. sapiens* and primate evolution.

Keywords: Ascorbate | Vitamin C | Free radicals | Evolution | Endogenous retroviruses | Gulonolactone oxidase | *Alu* | Reverse transcriptase

Article:

Abbreviations

DNA, deoxyribonucleic acid; GLO, gulonolactone oxidase; RT, reverse transcriptase; SINE, short interspersed repetitive element

1. Hypothesis

Free radicals reactions are well established for their ability to cause random mutations to deoxyribonucleic acid (DNA), and the origin of life and the subsequent evolution of species have

been influenced in part by these mutation-inducing reactions.[1] Unusually high mutation rates may accelerate the evolution of species and be advantageous to organisms adapting to new environments.[2, 3] A recent hypothesis proposed that large numbers of free radicals were created after Anthropoidea lost the ability to produce endogenous ascorbate millions of years ago. A high body-burden of free radicals would have increased the frequency of mutations, some of which would have been inheritable, and accelerated the evolution of Anthropoidea and the emergence of *Homo sapiens*. [4]

Plant and animal species have a variety of means to minimize free radical damage, such as through the upregulation of endogenous antioxidants and antioxidant enzymes. *H. sapiens* is one of the few animal species that does not endogenously produce ascorbate (vitamin C), a powerful antioxidant.[5] The gene that codes for the terminal step (gulonolactone oxidase, GLO) in ascorbate synthesis was damaged and stopped functioning approximately 45 million years ago.[6, 7]

The cause of this genetic damage is unknown, although it has been suggested that it was due to radiation exposure.[7] Expanding on an earlier hypothesis, it is also possible that the gene was mutated by a virus:[4] specifically, it is proposed that a retrovirus, perhaps an endogenous retrovirus, would have been capable of mutating the ascorbate-producing gene. Reverse transcriptase (RT) has been a mediator of genetic change for more than three billion years,[8] and retroviruses have influenced the evolution of Old World monkeys and hominids.[9]

One family of retroelements that has been widely dispersed in the genomes of all primates consists of *Alu* elements, a type of SINE (short interspersed repetitive element).[10, 11] The replication and insertion activity (retroposition) of *Alu* elements requires the presence of RT in the cell, which must be provided by the activity of a (usually endogenous) retrovirus, or other RT-encoding retroelement (e.g., a long interspersed repetitive element or a retrotransposon). *Alu* repeats are closely associated with genomic polymorphisms, both interspecies (e.g., the α -globin locus in Anthropoids[11]) and intraspecies (e.g., in human populations[12]). There is at least tentative evidence that speciation events have been associated with the action of transposons or retroelements, including other SINEs (e.g., in zebrafish,[13] salmonids,[14] and *Drosophila*[15]).

Inactivation of the simian GLO gene must have occurred following the divergence from prosimians (ascorbate producers), but before the divergence of New World monkeys (GLO deficient): thus, between 55 and 35 million years ago. This coincides with the period of the major amplification of *Alu* retroposons throughout simian genomes, 85% of which is believed to have occurred early in Anthropoid evolution.[10] Significantly, the sequenced fragment of the mutated human GLO gene contains several *Alu* inserts in intron regions, including two that are adjacent to an apparently missing exon (exon XI).[5] Furthermore, *Alu* inserts and *Alu*-*Alu* recombination events have been identified as a cause of various human genetic disorders,[10] including cases of Huntington's disease, hemophilia (Factor IX gene), neurofibromatosis, and adenosine deaminase deficiency. Thus, there is extensive precedent for *Alu* insertion causing a genetic disease, of which loss of GLO leading to ascorbate deficiency is perhaps the ultimate example, affecting the entire human species.[4]

This genetic defect in ascorbate production likely allowed large numbers of free radicals to remain unquenched through normal metabolic processes. Some of the resulting mutations would, because of their random occurrence, have been somatic and others inheritable. Losing the ability to manufacture ascorbate, with the subsequent increase of free radicals, would have created a palette of mutations that other evolutionary pressures could select for or against.[4] These mutations would have aided adaptation to changing environmental conditions.

Other endogenous antioxidants do not appear to fully compensate for the inability to produce endogenous ascorbate. For example, while superoxide dismutase (SOD) activity is relatively high in species lacking GLO and endogenous ascorbate, SOD cannot fully replace ascorbate, because these antioxidants function at different sites and quench different types of radicals.[16] Likewise, some higher primates, including *H. sapiens*, possess a mutated nonfunctional gene for urate oxidase, preventing the breakdown of uric acid.[17] Uric acid can function as both a prooxidant and antioxidant, but as an antioxidant it does not quench the same radicals as ascorbate. In particular, urate does not quench hydroxyl radicals, whereas ascorbate does.[18, 19] Because of a lack of endogenous ascorbate, *H. sapiens* may be continuing to undergo a relatively high rate of free radical-induced mutations and evolutionary change.

The role of free radicals in the evolution of species is supported by their role in mutations in general. For example, free radical-induced mutations appear to be involved in the etiology of some cancers and other diseases.[1, 20] It is conceivable that the incidence of these diseases may be a marker of *H. sapiens*' evolutionary diversification as a species, with a greater incidence of cancer indicative of more mutations, some of which would be inheritable. Conversely, increasing ascorbate levels slows the rate of DNA mutations,[21] and ascorbate (and other antioxidants) might be of clinical value in the treatment of cancer and other diseases.[22]

This antimutagenic effect of ascorbate would add credence to the role of free radicals and ascorbate in influencing the evolution of Anthrozoidea and *H. sapiens*. Furthermore, if *Alu* elements were involved in the primary lesion leading to inactivation of the GLO gene, then retroviruses or their cellular ancestors may have played a pivotal role in primate and human evolution.

Current dietary recommendations for vitamin C (60 mg/d) are considerably lower than the amount generally manufactured by mammals (~184.2 mg/kg/d).[23] Furthermore, the oxidative stress associated with many diseases, may increase ascorbate requirements.[24, 25] Under such circumstances, *H. sapiens* may be continuing to evolve at a faster rate relative to species producing endogenous ascorbate.

2. Conclusion

There is evidence suggesting that an endogenous retrovirus or retroviral-like element was involved in mutating the GLO gene, which codes for the terminal step in ascorbate synthesis. High endogenous production of SOD and urate in *H. sapiens* and other higher primates would not fully compensate for the lack of endogenous ascorbate.

With the loss of endogenous ascorbate production over the past 45 million years, Anthropeidea and *H. sapiens* would be predisposed to a high body burden of free radicals and oxidative stress. These free radicals would have increased the frequency of mutations, some of which would have been inheritable, accelerating the evolution of Anthropeidea and *H. sapiens*. High dietary or supplemental levels of ascorbate and other antioxidants might protect against retrovirus-induced mutations and, in doing so, might slow the evolution of *H. sapiens*. It would, however, take millions of years for that change to be noticed.

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