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Review Article

Hypothesis - Origin of Parietal Cells: Transfer of the H^+K^+-ATPase Gene from Parasitic Microorganisms to Cnidaria ?

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Abstract

Parietal cells present in the stomach and terminal ileum secrete a highly-concentrated hydrochloric acid into the lumen. The cells are characterized by the enzyme P-type H^+K^+-ATPase, which has an α-subunit with a high homology (>85%) for the amino acid sequences of frog, mouse and pig stomachs. Gastric H^+K^+-ATPase also exhibits a high homology to H^+-ATPase in yeast and Na^+K^+-ATPase in many tissues, suggesting origination from a common ancestral ATPase. It is known that parietal cells first appeared in fish and were later expressed in evolutionarily-higher organisms. Primitive organisms, such as Cnidaria and Ctenophora, that possessed digestive organs, but not parietal cells, were abundant in the ocean more than 600 million years ago (Pre-Cambrian period). The author thus hypothesized that the genes of either H^+-ATPase or H^+K^+-ATPase that were present in parasitic microorganisms, such as yeast, were transferred to the interstitial cells of host organisms, such as Cnidaria, eventually leading to the evolution of parietal cells. It appears that although parietal cells in the stomach developed by chance, such cells have greatly contributed to the evolution of advanced organisms, including humans, by affording safe ingestion of a large volume of various foods.

Key Words: parietal cells, H^+-ATPase, gastric H^+K^+-ATPase, yeast, symbiosis, gene transfer

Introduction

Of the approximately 200 odd cellular phenotypes within the human body, parietal cells in the gastric mucosa represent very characteristic, unusual cells from the viewpoint of location (the stomach and ileum), morphology (intracellular canaliculus, abundant mitochondria, and life span of >120 days), and function (secretion of a highly-concentrated hydrochloric acid via H^+K^+-ATPase) (Figure 1). In addition, it has been noted that parietal cells belong to one of the few cell types that do not become cancerous. Since Prout discovered the presence of parietal cells in the stomach (Figure 2), there has been a vast amount of research performed concerning both the function of the cells as acid secretors and their relationship to peptic ulcer diseases (1-4). Despite the unusual features of parietal cells, no attention has been paid to either the elucidation of

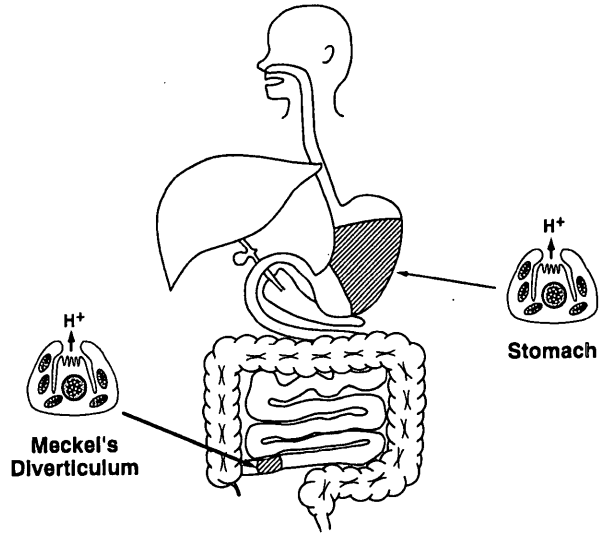

Fig. 1. Localization of parietal cells in the stomach and the terminal ileum.

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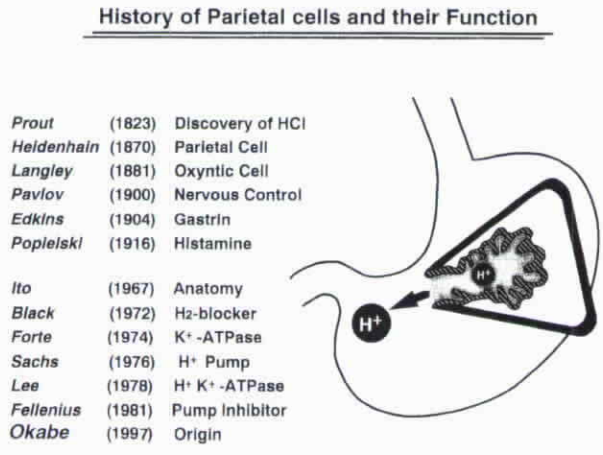

Fig. 2. Historical overview of studies of the function of parietal cells.

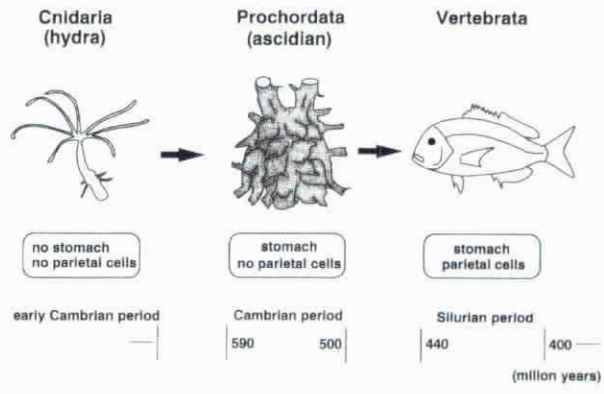

Fig. 3. Evolutional process from Cnidaria to Vertebrata in relation to the development of parietal cells.

the origin of parietal cells or the necessity of parietal cells. The reason for such a lack of attention appears to derive from the general belief that the 200 odd cells in the human body simply differentiated from one unique eukaryote. It should be questioned, however, if such an assumption is indeed correct.

In the human body there are many organic acids, such as lactic acid, acetic acid, pyruvic acid, butylic acid, and citric acid, which are all derived from the metabolism of organic substances. The author thus found it puzzling that, instead of a more commonly-produced organic acid, parietal cells secrete the inorganic acid HCl at an amount and concentration sufficient to dissolve stainless steel. At present, it is commonly accepted that parietal cells are not found in organisms of a lower level than fish (Figure 3). This implies that the origin of the cells that eventually evolved into parietal cells remains unknown.

As reported in an earlier work, the author hypothesized that parietal cells, characterized by the presence of H^+K^+-ATPase, evolved through a transfer of the H^+-ATPase or H^+K^+-ATPase gene from a microorganism to a stem cell in the gastro-intestinal mucosa of a primitive organism (5, 6). It was proposed that this transmission occurred during the Pre-Cambrian era in Prochordate, which existed before the development of fish. Nevertheless, the author would like to suggest a more suitable target organism as the recipient of the ATPase gene, namely, a more primitive organism, evolutionarily speaking, than Prochordate. In particular, Cnidaria, the phylum containing such organisms as hydra, might be more compatible with the original hypothesis, as is depicted in Figure 4 of the author's previous manuscript (5). The three reasons that lead to the suggestion of Cnidaria are described below. In addition, other topics that are also addressed include: the homology of amino acid sequences among gastric H^+K^+-ATPase,

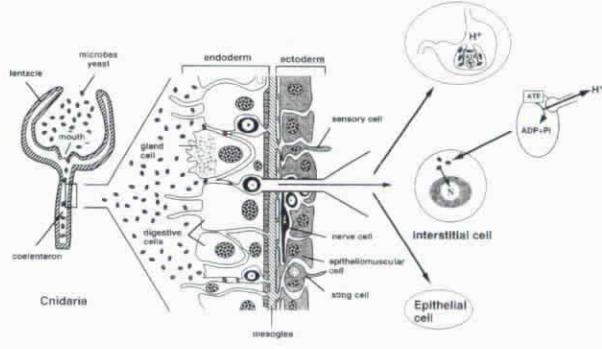

Fig. 4. A H^+-ATPase or H^+K^+-ATPase gene of microorganisms in symbiosis with host organisms, such as Cnidaria or Cnidaria-like organisms, transferred to the interstitial cells. The epithelial cells that were provided with such genes evolved into parietal cells in fish.

H^+-ATP in yeast, and Na^+K^+-ATPase in various tissues, potential gene transfer, and the evolutional benefits of parietal cells.

Cnidaria: a Potential Host Organism

The first reason that leads to the suggestion of Cnidaria follows from the chronology of evolutionary events. According to the fossil record, a variety of organisms suddenly appeared during the early Cambrian era (circa 600-700 million years ago) (7). The simultaneous appearance of such a vast number of organisms, including a linear antecedent of vertebrates, is generally known as the 'Cambrian Explosion.' Ohno (8) suggests that all organisms of the early Cambrian period were endowed with nearly-identical genomes (The Cambrian Pananimalia Genome) and that differential usage of the same set of genes accounts for the extreme diversity of body forms. The phyla of Cnidaria and Ctenophora (formerly classified as branches of Coelenterata)

contain the most primitive multicellular organisms, such as hydra. The structure (endoderm and ectoderm) and function of the species form a primitive prototype for more advanced organisms. It is thus conceivable that hydra and/or hydra-like organisms were one of the organisms on the evolutional path to humans. Notably, it is thought that both Cnidaria and Ctenophora (Ediacara fauna) were widespread in the oceans far before the Cambrian Explosion. If the transfer of the H^+-ATPase or H^+K^+-ATPase gene occurred in such organisms, then the gene could easily have been propagated to the multitudinous organisms of the Cambrian Explosion through the Pananimalia Genome.

The author would thus like to suggest that the gene transfer of the H^+-ATPase or H^+K^+-ATPase gene occurred during the early Cambrian era, when Cnidaria and/or Ctenophora were abundant in the oceans (Figure 4). The genome DNA of Cnidaria and/or Ctenophora, including the newly-incorporated H^+-ATPase or H^+K^+-ATPase gene, could then have been passed down to the many organisms that suddenly appeared during the Cambrian era.

Obviously, Cnidaria and/or Ctenophora did not possess parietal cells, but, rather, fish were the first organisms to express parietal cells with H^+K^+-ATPase. Accordingly, in organisms such as Chordata and Cyclostomata, which might have received the H^+K^+-ATPase or H^+-ATPase gene through the Pananimalia Genome, it follows that such genes remained dormant until the evolutionary step towards fish. Presently, it remains unknown whether or not a microorganism possessing H^+K^+-ATPase existed during the era of this gene transfer to the target organism. Nonetheless, it certainly is possible that the H^+-ATPase gene (which was abundant in microorganisms at the time) was first incorporated into the DNA genome of Cnidaria and/or Ctenophora, and then simply adapted into H^+K^+-ATPase in parallel with the increase of K^+ ions in the ocean. On this point, the presence or absence of parietal cells in organisms more primitive than fish, such as Protochordate, remains unstudied. The author and his colleagues (C.J. Pbeiffer) recently confirmed via a TEM study that there were no parietal cells in the stomachs of Ciona intestinalis (Urochordate). In addition, H^+K^+-ATPase was not detected by immunostaining with mouse H^+K^+-ATPase antibodies in the upper intestine of Ciona intestinalis and Myxine garmani (hag fish).

The second reason that leads to the suggestion of Cnidaria follows from the fact that the organism has a coelenteron, a unique digestive cavity surrounded by the endoderm. Upon ingestion of food into the coelenteron, the food is digested by enzymes secreted from gland cells. The partially-digested food is subsequently endocytosed into the digestive cells,

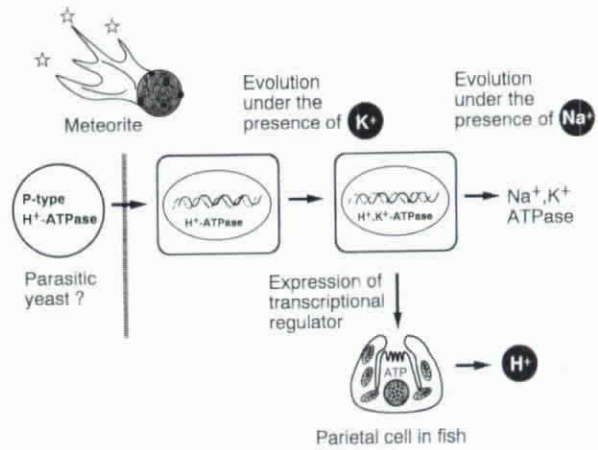

Fig. 5. Suggested evolutional process of parietal cells (see text for further details). Gene transfer appears to have been induced following unusual circumstances, such as a meteorite shower.

where digestion is completed. Alternatively, undigested food can also be incorporated into the digestive cells by endocytosis and then intracellularly digested. Various kinds of microorganisms can assume a state of parasitism in the coelenteron of Cnidaria, a phenomenon that has been witnessed in other species. It is also well known that the ocean has often experienced sudden, drastic changes during its history of 3 to 4 billion years. It has been postulized that frequent unusual fluctuations in the ocean temperature occurred, potentially due to meteorite activity. Furthermore, ion concentrations have gradually changed over time; e.g., a steady increase in K^+ and Na^+ ions in the ocean has occurred. Perhaps such unusual and volatile conditions provided an environment wherein parasitic microbes could be incorporated into the interstitial or digestive cells of Cnidaria by endocytosis. Eventually such incorporation might have resulted in the transfer of the genes of the parasites to the nuclei of the cells in the host organism (Figure 5). Such a gene transfer might have spontaneously occurred over a period of many years, although a more sudden transfer, through the agency of a virus, plasmid or transposon, remains an equally-probable hypothesis. The interstitial cells of Cnidaria, also known as progenitor cells, are diffusely situated at the base of the endoderm and ectoderm, where they can differentiate into various cells (digestive and gland cells from the endoderm, and sensory nerve, epitheliomuscular, and sting cells from the ectoderm). Through this mechanism, the affected interstitial cells might have differentiated both into mucus-secreting epithelial cells and possibly, at a later stage in evolution, into parietal cells.

The third reason that leads to the selection of Cnidaria is based upon the phylum's biphasic

reproductive system, namely both asexual and sexual, which depends on the temperature of the surrounding environment (7). In the case of hot temperatures, Cnidaria reproduce by spouting projections from their body, which eventually detach as progeny. In the case of cold temperatures, however, the organism produces gamete that conjugate and grow into adult Cnidaria when the temperature rises. If the above-hypothesized gene transfer occurred in Cnidaria, the Cnidarian reproductive system makes for an extremely-feasible target organism for the propagation of a gene to subsequent generations. In the case of sexual reproduction, an alteration in a DNA genome must be passed to reproductive cells if the alteration is to be propagated to progeny. Due to the asexual reproductive phase of Cnidaria, the trait could be passed with a much higher probability.

If the H^+K^+-ATPase gene was to be propagated in organisms with sexual reproductive systems, such as Chordata, then the gene must be transferred to not only digestive cells, but also cells responsible for reproduction. Considering that parietal cells are mainly localized in the stomach and ileum (Meckel's diverticulum) in humans, it becomes difficult to postulate that the gene transfer occurred in organisms with a sexual reproductive system. Furthermore, in the case of a gene transfer to an organism with a sexual reproductive system, it could be presumed that parietal cells (together with H^+K^+-ATPase) would be expressed in many locations, rather than simply being focused in the gastrointestinal tract. Recent research has demonstrated that H^+K^+-ATPase is also found in the colon, gall bladder and kidneys (9-12). It is thus possible that the H^+K^+-ATPase in these organs also received the H^+K^+-ATPase gene during the same evolutionary time period. In contrast to gastric H^+K^+-ATPase, however, the activity of such non-gastric H^+K^+-ATPase enzymes is not inhibited by gastric H^+K^+-ATPase inhibitors, such as omeprazole.

It is also reasonable to suggest that the gene translocation might have occurred in a species that developed after Cnidaria, e.g. Echinodermata (star fish, urchins, sea slugs, etc.), when species had already developed digestive organs. Generally speaking, any species had the potential to accept such a translocation, as long as interstitial cells, which could later evolve into a gastrointestinal tract with parietal cells, were present in the endoderm. Nonetheless, it is unlikely that Echinodermata contained compatible target organisms, since, similar to Chordata, the organisms of this phylum utilize a sexual reproductive system. It follows that it is logical to focus on Cnidaria as the target organism that received the genes for parietal cells, due to the asexual phase of the reproductive system.

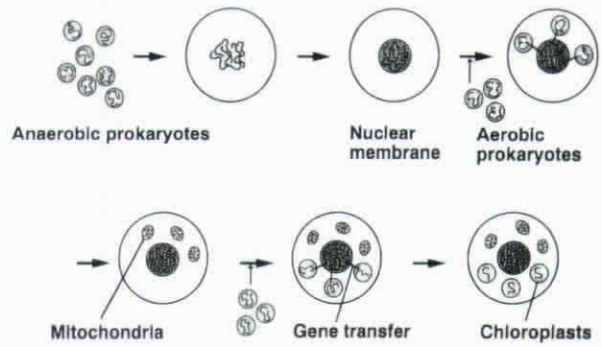

Fig. 6. Evolution of eukaryotic cells (Goksoyr 1967).

Did the First Eukaryotic Cells Contain H^+-ATPase or H^+K^+-ATPase Upon Development?

In 1967, Goskoyr (13) hypothesized that the first eukaryote evolved from the contact of a number of prokaryotic cells lacking intervening cell walls (designated as the coenocytic relationship). Such eukaryotes subsequently evolved into more advanced eukaryotes by further contact with other, distinct prokaryotes (Figure 6). According to such a hypothesis, the puzzling parallels existing between groups of eukaryotes and prokaryotes are readily explained. In short, the most advanced eukaryotic organism, i.e. humans, developed from a patchwork of various prokaryotic cells. Based upon Goksoyr's hypothesis, through symbiosis with various prokaryotes that expressed H^+-ATPase or H^+K^+-ATPase, it remains possible that the gene encoding for H^+-ATPase or H^+K^+-ATPase was already established within the genome DNA at a stage as early as the development of the first eukaryotic cells. If such was the case, then H^+-ATPase or H^+K^+-ATPase-encoding genes might have been present in the interstitial cells of Cnidaria or Cnidaria-like organisms, from which both endoderm and ectoderm developed prior to the early Cambrian era. The question remains as to why the H^+-ATPase or H^+K^+-ATPase gene was only expressed in the endoderm, from which parietal cells subsequently developed. It might be postulated that such genes were present even in the ectoderm, from which nerve or muscle cells later developed, but such was clearly not the case. If the first eukaryotes possessed H^+-ATPase or H^+K^+-ATPase genes in the genome DNA at the time of development, parietal-like cells might have appeared in brain, liver, or muscle tissue, etc., resulting in the death of such organisms. There should exist a concrete reason that parietal cells, which are able to secrete hydrochloric acid, only developed in the gastrointestinal tract facing the lumen.

If the first eukaryotic cells did not develop from a prokaryote expressing an H^+-ATPase gene, then it

Table 1. Amino Acid Identity of Gastric H^+K^+-ATPase α-Subunits from Different Species (Mathews et al., 1995)

	Xenopus gastric α H-K	Murine gastric α H-K	Pig gastric α H-K	Rat colonic α H-K	Bufo bladder α H-K	Xenopus α1 Na-K
Xenopus gastric α H-K	100.0	85.0	84.7	64.4	67.9	62.5
Murine gastric α H-K	85.0	100.0	97.3	64.0	65.6	63.4
Pig gastric α H-K	84.7	97.3	100.0	64.1	65.2	62.5
Rat colonic α H-K	64.4	64.0	64.1	100.0	75.0	64.7
Bufo bladder α H-K	67.9	65.6	65.2	75.0	100.0	67.0
Xenopus α1, Na-K	62.5	63.4	62.5	64.7	67.0	100.0

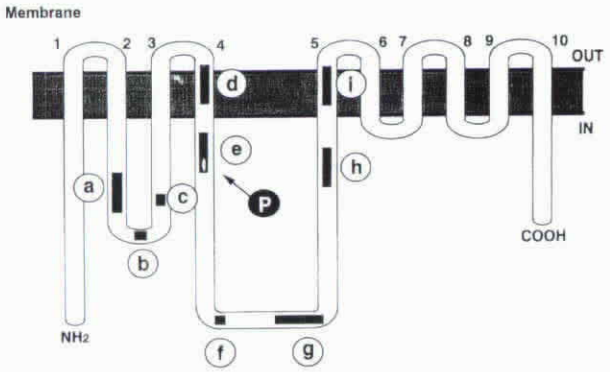

Fig. 7. Transmembrane topology of yeast H^+-ATPase (Serrano et al., 1986). Note that there is a strong homology between the amino acid sequences of yeast H^+-ATPase and those of Na^+K^+-ATPase, K^+-ATPase and Ca^{2+}-ATPase, as shown by the shaded areas (a to i).

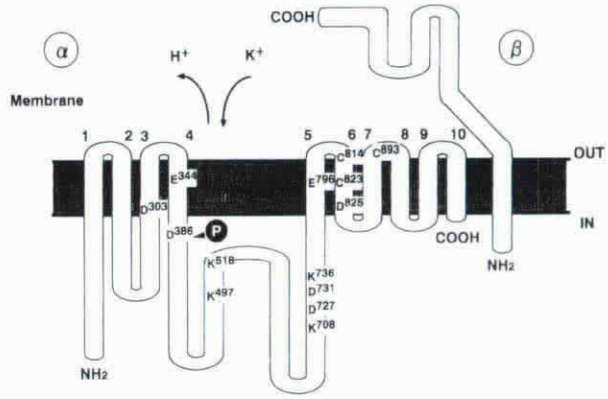

Fig. 8. Transmembrance topology of porcine H^+K^+-ATPase (Maeda et al., 1995).

might be more logical to consider the possibility of a transfer of the H^+-ATPase gene from prokaryotes to primitive eukaryotic organisms, such as Cnidaria. It should be noted that the transfer of an ongogene was postulated to have occurred approximately 500-600 million years ago, namely at the same time of the author's proposed transfer of the H^+-ATPase gene.

Homology of P-type ATPase in Microorganisms and Advanced Organisms

Dame and Scarborough (14) hypothesized that the ATPase that operates as an H^+ pump in the plasma membrane of Neurospora evolved the ability to transport Na^+, K^+ and Ca^{2+} after its initial development. Serrano et al. (15) have demonstrated that an H^+-ATPase expressed in yeast cells has a high homology to sheep renal Na^+K^+-ATPase, cardiac muscle SR Ca^{2+}-ATPase, and K^+-ATPase of E. coli (Figures 7, 8). Based on the findings of their study, Serrano et al. suggested that the family of cation pumps may have evolved from a common ancestral ATPase. In addition, Maeda et al. (16-18) reported that there exists a high homology (63%) for the amino acid sequences of gastric H^+K^+-ATPase and Na^+K^+-ATPase in exon/intron organization. It is even more interesting that Mathews et al. (19) demonstrated a high amino acid homology for the gastric H^+K^+-ATPase α-subunits of frogs (Xenopus), mice and pigs (Table 1). It was found that there was only a 15% difference between frog and mouse gastric H^+K^+-ATPase. Rodents, including mice, are assumed to have developed approximately 300 million years after the appearance of amphibians, suggesting that such an amino acid sequence has been well conserved over time. The amino acid sequences of the gastric H^+K^+-ATPase in fish have not yet been elucidated. Nonetheless, it can be predicted that there exists a high homology for the H^+K^+-ATPase of fish and amphibians, as it is widely accepted that fish developed approximately 100 million years before the appearance of amphibians. Although a mere speculation, quite possibly the structure of gastric H^+K^+-ATPase in fish lies in between the structures of yeast H^+-ATPase and gastric H^+K^+-ATPase in amphibians.

Gene Transfer of H^+-ATPase or H^+K^+-ATPase

Yeast cells, a parasitic organism, are present

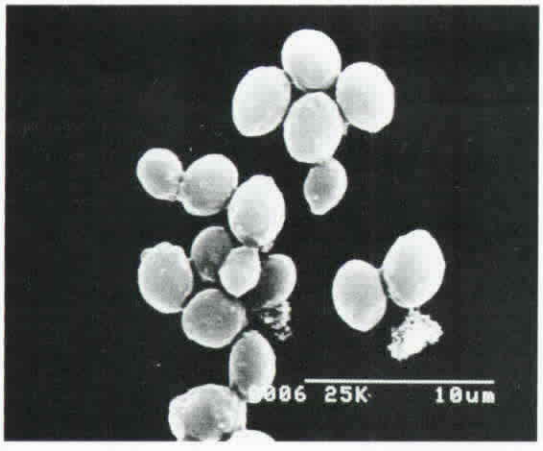

Fig. 9. Scanning electron microphotograph of yeast cells (×50,00).

with abundance in the intestines of humans and other animals (Figure 9). The ingestion of food by digestive cells in primitive organisms, such as hydra, is a typical, simplified model for the supply of nutrients to an organism. Accordingly, there exists the intriguing possibility that yeast cells in symbiosis in the coelenteron were endocytosed both into the digestive cells of the endoderm and into the interstitial cells as well. Under unusual circumstances, the H^+-ATPase or H^+K^+-ATPase gene might have been transferred to the nuclei of interstitial cells. Such a gene transfer of a primitive H^+-ATPase or H^+K^+-ATPase to the interstitial cells scattered in the gastrointestinal tracts of host multicellular organisms appears to represent a more plausible hypothesis for the evolution of parietal cells.

It should be noted that the presence of oncogenes has been demonstrated even in yeast. Similar to H^+K^+-ATPase genes, it is possible to postulate that oncogenes present in yeast were also endocytosed into the interstitial cells at the level of Cnidaria or Cnidaria-like organisms, eventually developing into a part of the human genome. It should be noted that Mathews et al. (16) succeeded in expressing, via molecular biological techniques, the gastric H^+K^+-ATPase α-subunit of both Xenopus and mice and the gastric H^+K^+-ATPase β-subunit of rabbits in Xenopus oocytes by a cRNA injection. As a result of such procedures, Matthews successfully demonstrated the assembly of the α/β complex. In addition, Matthews also proved the presence of K^+-transporting H^+K^+-ATPase in the plasma membrane of oocytes by observing $86Rb^+$ uptake. Moreover, it was revealed that K^+ uptake mediated by the H^+K^+-ATPase was inhibited by the gastric H^+K^+-ATPase inhibitor Sch-28080, but not by ouabain. The combination of such findings strongly suggests that the gene transfer of H^+-ATPase or H^+K^+-ATPase to the nuclei of interstitial cells made possible the expression of these enzymes in the gastric mucosal cells, leading to the evolution of parietal cells.

The Role of Parietal Cells in Evolution

It is conceivable that the expression of parietal cells in the stomach of an organism secured survival of the organism and thus led to the passing down of such a trait through evolution over the course of time. Such a hypothesis follows from the fact that although organisms equipped with a mouth ingest various nutritional substances, this ingestion is highly non-selective, thus leading to the occasional ingestion of virulent bacteria. If the stomachs of an organism should have no parietal cells, i.e. no hydrochloric acid secretion, then the survival rate of such an organism might be greatly reduced due to the ingestion of hazardous materials or microorganisms. For example, certain land-based organisms ate corpses of other organisms, which inherently contained a number of microbes. It follows that organisms expressing parietal cells in their stomachs could ingest a wider variety of nutrients in greater amounts, due to the ability to eradicate virulent microorganisms. Survival of an organism and propagation of its traits is guaranteed by a supply of sufficient nutrition through a secure system of food ingestion.

Howden and Hunt (20) postulated that, in addition to assisting with digestion, organisms developed parietal cells to sterilize the stomach following introduction of both pathogenic bacteria present in ingested food and parabiosed bacteria regurgitated from the lower parts of the intestines. Yet, such a postulation implies that a trait developed by logical intention, whereby an organism consciously chose to start expressing parietal cells for its protection. It is hard to believe that fish in the ocean developed the incredibly-complicated parietal cell with the pre-conceived intention to eliminate harmful bacteria in the stomach. This is especially true since there should be no virulent bacteria in the ocean due to a high concentration of salts. To the best of the author's knowledge, the salt concentration in the ocean of the early Cambrian period is nearly the same as that of the current concentration. If the salt concentration was not high enough to kill virulent bacteria at the time of the development of fish, it would have been necessary to develop parietal cells for survival. Nonetheless, the questions remain as to how and why fish developed such parietal cells for the secretion of hydrochloric acid in their stomachs. Furthermore, it should also be asked why mammals require parietal cells that secrete hydrochloric acid at a concentration that dissolves stainless steel.

Intrinsic Factors Involved in Parietal Cells

In addition to hydrochloric acid, an intrinsic factor is secreted mainly from parietal cells (human) and chief cells (mouse and rat) (21-23). As previously proposed by the author, although parietal cells seemingly evolved by a chance gene transfer from symbiotic microorganisms with the H^+ATPase or H^+K^+-ATPase gene, parietal cells have come to play an important role for the evolutional advance of organisms. Certainly, the intrinsic factor is also crucial for the survival of organisms, particularly mammals, due to its role in the intestinal absorption of vitamin B_{12}. Without this factor, secreted from either parietal or chief cells, megaloblastic anemia and a demyelinating disorder of the nervous system develop (24, 25). It remains unknown when parietal cells developed the property to secrete such an intrinsic factor protein in addition to hydrochloric acid. Parietal cells, as well as chief cells, might have originally differentiated from stem cells expressing the genes for the intrinsic factor. At some instance during the course of evolution, the H^+K^+-ATPase gene might have been incorporated into the nuclei of the stem cells that developed into parietal cells.

Organ Protection by Bacterial Symbiosis

The uterus is the most vital component for fetal development. Accordingly, it must remain well protected from infectious diseases. An infected uterus can both endanger fetal survival and potentially prevent spermatid from reaching the ovum. The uterus remains at a continual risk for bacterial, or even viral infection, due to both the monthly inflammation caused by menstruation and the anatomical location, proximal to the anus. Lactobacilli is frequently found in the mouth, intestine, and vaginas of both humans and lower animals. In the case of the vagina, symbiosis with Doderlein's bacillus, which secretes lactic acid, acidifies the vaginal area and thus protects the uterus against infection. The above indicates that humans have developed bacterial symbiosis for the self-defense of reproductive organs. It is therefore possible that the stomachs of primitive organisms might also have contained symbiotic lactobacilli, or other bacteria, which secreted lactic acid or hydrochloric acid for protection against infectious microbes. Nevertheless, certain bacteria with a proton pump may have been accidentally incorporated, transferring their genes to the interstitial cells through a virus or a plasmid. Eventually, parietal cells developed, and the symbiosis of bacteria in the stomach became unnecessary for protection against infectious organisms. Yet, in order to transfer a gene to animals with reproductive systems, the gene must be transferred to the reproductive cells of these organisms. As reproductive organs developed during the time of the Cambrian explosion, local transfer of genes in animals with reproductive systems became impossible. Such a condition explains the inability of organisms to develop cells resembling parietal cells in the vagina. It is of note that *Helicobacter pylori*, a bacteria that resists the stomach's acidic condition by producing ammonia, is found in the stomach. In contrast to lactobacilli in the vagina, the presence of such bacteria can lead to numerous detrimental stomach conditions, inducing gastritis, ulcers, and even cancer.

Conclusion

In summary, the evolutionary path leading to parietal cells may have been initiated by a simple, chance transfer of the H^+-ATPase or H^+K^+-ATPase gene of prokaryotes or eukaryotes to other advanced organisms with digestive organs. Nevertheless, the chance evolution of parietal cells in fish or amphibians became a prerequisite for organisms on the evolutionary pathway towards humans. The evolutionary pathway from monocellular organisms to humans, passing through innumerable primitive polycellular organisms, remains unclarified due to the many missing links between species. The search for the origin of parietal cells, focusing on H^+K^+-ATPase present in various species, might also provide a clue in defining the ancestral roots of mankind.

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