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The Consequences of integration between bacterial DNA and eukaryotic DNA

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Review article

Abstract

The transport of DNA between several organisms is referred to as lateral gene transfer (LGT), LGTs between bacteria and larger multicellular creatures are interesting. The Consequences of integration between bacterial DNA and eukaryotic DNA may be mutagenic and associated with non-inherited genetic diseases like cancer from *Acinetobacter spp.* in samples of leukemia and from *Pseudomonas spp* in stomach cancer samples.

Keywords: LGT, Endosymbionts, Non inherited genetic diseases, DNA transfer

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Introduction

The transport of DNA between several organisms is referred to as lateral gene transfer (LGT). In the scientific literature, LGT is identical to horizontal gene transfer, and the two concepts are frequently used alternately. Although LGT has long been known to exist inside the bacterial domain of life, more and more inter-domain LGTs are being described. Because they disprove the long-held belief that such transfers could only take place in closely related, single-celled organisms, LGTs between bacteria and larger multicellular creatures are interesting [1].

Lateral gene transfer has resulted in the incorporation of microbial DNA into several eukaryotic chromosomes. Directed DNA transfer from Agrobacterium tumefaciens is an

example of this, which causes the plant disease crown gall and has been exploited to produce transgenic crops. Following unauthorized recombination with the plant chromosome, the DNA that is produced by the Ti plasmid, also known as T-DNA, is transported to the nucleus. and transcription from eukaryotic promoters occurs there [2]. LGT events can take place between bacteria and animals as well as between microorganisms and plants. By investigating the possibility of LGT from bacterial genomes to those of somatic cells of human: (a) (a) Insertional mutagenesis in the human genome, (b) LGT in animals with a focus on bacteria-animal LGT, and (c) the contribution of microorganisms to oncogenesis. Then, two theories about these integrations and their possible significance in bacterial-related chronic human diseases like cancer are presented, outlining current research and directions for the future [3].

Since they would not be inherited, such transfers in the genome of humans may have gone unnoticed in the past, and up until recently, the majority of research of LGT has solely concentrated on the consensus genome that was inherited. Important mutations, however, are not just found in the genome that vertically inherited. For instance, Latest research has demonstrated that the somatic genome can harbor important new disease-causing mutations [4].

Literature review

Gene Transfer

There are two ways that genes are passed down through families: vertically, from parent to offspring, and horizontally, across members of the same or other species. The former ensures that a species' integrity is maintained, whereas the latter is a driving force that actively contributes to developmental and adaption mechanisms [5].

Gene transfer mechanism

Griffiths and his colleagues [6] mentioned conjugation, transformation, and viral transduction are three ways that genes can be transferred between bacteria. One crucial characteristic unites generalized transduction, the conjugative transfer of DNA by Hfr strains, and the transformation of donor chromosomal segments to spread genetic markers. Each procedure delivers a fragment of DNA into the recipient cell; for the fragment to be incorporated into the genome of the recipient and then passed down through inheritance, a double-crossover event must occur. Unincorporated fractions are dispersed out of the group of daughter cells because they are unable to reproduce.

The conjugative transfer of F′ factors that transport bacterial genes and the specialized transduction of particular genetic markers are methods that effectively introduce a small

number of bacterial genes into the recipient cell. As opposed to the inheritance of DNA fragments, inheritance does not involve common recombination. Following the F′ transfer, the F′ factor multiplies on its own in the bacterial cytoplasm. A recombination machinery unique to that phage combines the specialized transducing phage DNA with the bacterial chromosome. Because each mechanism permits the inheritability of both the gene that was transmitted and its equivalent in the recipient, a partial diploid arises in both situations. The chromosome can be mapped through gene transfer. To initially pinpoint a mutation to a specific chromosome region, Hfr crosses are employed. Then, generalized transduction offers a more precise localization.

Lateral gene transfer (LGT)

Lateral gene transfer (LGT) from bacteria to animals was underappreciated before the advent of genome sequencing. Using a bioinformatics technique, LGT from bacterial Wolbachia endosymbionts was discovered in around thirty-three percent of sequenced genomes of arthropod in the year 2007 [7].

Nowadays it is believed that LGT between Wolbachia and their hosts is quite common, and many other instances of LGT between bacteria and animals have been described. According to Nikoh and Nakabachi [8], LGT may be more frequently connected with endosymbionts that infiltrate germ cells and germ stem cells in insects. One example of this would be Wolbachia endosymbionts.

The LGT can take place in bacteria as well as in a wide range of eukaryotic organisms; however, it will only become vertically inherited if it takes place in germ cells. As a result, LGT might take very often in somatic cells but would never become hereditary in the population as a whole. The inability to pass on such alterations to subsequent generations significantly reduces our capacity to identify them. This type of noninhibited integration of bacterial DNA into chromosomes in the somatic cells of humans could, in a way akin to mobile elements and viral integrations, generate changes that could lead to cancer or autoimmune disorders [9].

Consequences of LGT between bacteria

Multiple genetic characteristics can be disseminated via HGT, most significantly antibiotic resistance [10], and plays a key role in bacteria's ability to successfully adapt to novel environments [11]. In addition, horizontal gene transfer raises a fascinating query when one considers the fact that prokaryotic mobile genetic elements (MGE) not only affect the way bacteria live but also the evolution of eukaryotic organisms that are more complicated. This

is because there is emerging evidence that genes can be transferred from bacteria to eukaryotes [12].

It is commonly believed that the primary mediators of antibiotic resistance are the mechanisms that allow for the horizontal transfer of genes across different bacterial strains or species. However, mutational resistance has proven to be extremely useful in the study of bacterial genetics. It is also of primary clinical importance in certain species of bacteria, such as *M. tuberculosis* and *H. pylori*, or when thinking about resistance to specific antibiotics, especially man-made antibiotics like oxazolidinones and fluoroquinolones [13].

Additionally, the mutation is necessary for the ongoing genetic evolution of acquired resistance. As an example, it has resulted in the development of over one hundred different varieties of the TEM family of beta-lactamases. Increased rates of mutation are observed in hypermutator strains of bacteria. These strains carry mutations in genes that are responsible for DNA repair and replication fidelity [14].

LGT between bacteria and animals

Bacteria-to-animal HGTs can be classified into two distinct categories: those that originate from free-living microbes and those that are endosymbiont descendants. Because of the close and consistent closeness of the cells from both organisms, the endosymbiont-to-animal HGT process is probably more common than it would otherwise be. These types of transfers are expected to occur even more frequently in endosymbionts since they reside in germ cells, which makes it more probable that they will be passed on to subsequent generations [15].

One such example is provided by mitochondria and chloroplasts, which are found in all cells. Both the alpha-proteobacteria and the cyanobacteria endosymbionts contributed to the development of these organelles. Reproductive cells may contain both of these organelles, and germ cells transmit them to the next generation. Regular DNA transfers take place between the genomes of these organelles and the genome of the nucleus. These kinds of organelle transfers have been responsible for some of the most crucial steps in the evolution of eukaryotes [16].

The transfer of 75% of the nucleus mitochondrial insert to chromosome 2 centromere of the Arabidopsis thaliana is an outstanding example of (an organelle to eukaryote transfer). The fact that the chromosomal sequence and the mitochondrial genome are 99% similar provides evidence that the transfer occurred relatively recently [17].

It is theorized that HGT is an essential stage in the transformation of endosymbionts into organelles, which occurs when the nucleus of the "host" cell starts to encode organelle proteins. It has been hypothesized that an HGT ratchet is responsible for the accumulation

of nuclear genes that originate in organelles. It has been suggested that the transmission of genetic information between bacteria and the unicellular eukaryotes that eat them occurs by a ratchet mechanism that is very similar to this [18]. These ratchets might apply to all instances of repeated HGT in situations in which two species have an ongoing and close interaction with one another. Bacteria-animal of HGT is not restricted to interactions between endosymbionts. Hydra are uncomplicated animals that live in freshwater and reproduce asexually through the process of budding. According to Chapman [19], the genome of the Hydra magnipapillata has (71 candidates) for HGT that demonstrate more closely related to genes of bacteria than they do to metazoan genes. Seventy percent of these candidates have support from ESTs. Because these 71 genes only exist in bacteria, many of them are strong candidates for horizontal gene transfer.

According to Gladyshev [20] bacterial, fungal, and plant DNA appear to be concentrated in telomere together with genetic elements that are mobile in bdelloid rotifers, which are similarly small asexually reproducing animals that live in freshwater. Even if some of the genes that were created because of HGT are not functional, others have been transcribed. The transcription of 2 genes necessary for peptidoglycan production in bacteria involves the introns splicing that are not found in bacteria. In *E. coli* overexpression of these proteins led to the discovery of a functioning enzyme in one of the proteins [21].

LGT between bacteria and Human

The bacterial LGT in mammals and humans is hardly defined, even though it occurs often between microbes and animals in invertebrates. The segregation of gametes presents a challenge to the transmission of LGT in human families. The human germline, in contrast to the germ lines of insects and plants, is well protected from germs on both a physical and immunological level. Despite this, in the human body, there are ten times more cells belonging to bacteria than there are cells belonging to humans. Thus, the somatic cells of humans have the potential to be in contact with bacteria and have a high risk of becoming cancerous as a result of long-term exposure to bacterial DNA via LGT [22].

An LGT of this kind will not be passed on to the human's progeny, but it may be passed on from one generation to the next inside an individual if the cell in question is capable of going through the process of clonal expansion. Therefore, it is possible that LGT acts as mutagenic to somatic tissues, and plays a significant role in bacteria-associated disorders such as inflammatory diseases, cancer, and autoimmune diseases. In this hypothetical situation, somatic LGT events would not make it possible for an organism to adapt to a new niche; rather, they would have the capacity to disturb the regular gene function of the

organism. It is conceivable that our DNA could become intertwined with that of other organisms through the consumption of certain foods [23].

Pattern recognition receptors, also known as PRRs, are utilized by the innate immune system to identify PAMPs. Some examples of PAMPs include lipopolysaccharide (LPS), flagellin, lipoteichoic acid, lipoproteins, and peptidoglycan. PRRs are responsible for protecting human cells against germs. In human beings, microbial DNA and mRNA are both considered to be PAMPs, although a portion of microbe's rRNA does not provoke immunity [24] Previous research has investigated horizontal (LGT) from bacteria to humans, which could lead to vertical inheritance. Initial sequencing and analysis of the human genome revealed 113 proteins that were thought to have arisen from bacterial LGT. These proteins were initially identified [23].

It has also been demonstrated that the bacteria Bartonella henselae can convert human cells in vitro. The opportunistic human pathogen known as Bartonella henselae is responsible for the sickness known as cat scratch fever. According to Koehler [24] the only known bacteria that can cause bacillary angiomatosis, often known as the growth of benign tumors in blood vessels, are the bacteria B. henselae and B. quintana. Through its type IV secretion system, Bartonella henselae was shown in a recent study to be capable of integrating its plasmid into human cells in vitro [25].

As a result of this, we may anticipate that human somatic genomes are more susceptible to being mutated as a result of exposure to bacterial rRNA. When taking into consideration the fact that some mobile components in animals have rRNA as their origin and are moved by the LINE-1 machinery, this is a particularly interesting idea. Additionally, the bacterial rRNA has the potential to integrate into the human somatic genome and cause disease through the process of random mutagenesis. This would be analogous to the way that other insertion-creating mutagens, such as viruses and mobile elements, cause disease. This DNA should become integrated into a gene and mutate it, either by causing deregulation or by causing the coding area to become disrupted, the possible implications might be quite serious. Such insertional mutagenesis, for instance, has been linked to cancer and has been attributed to mobile elements and viruses [26].

Mechanisms Of Bacterium-To-Eukaryote HGT

It is essential to recognize that the presence of bacterial HGT signals in eukaryotic genomes is not entirely dependent on the bacteria capacity to transfer DNA into the host cells. This is one of the most important takeaways from this line of research. Instead, there are four additional significant prerequisites that need to be satisfied. First, the DNA that is being transferred needs to become a part of the genome of the host. Second, it is imperative that

the foreign sequence be preserved amongst the reorganization of the genome that occurs throughout succeeding cell divisions. Thirdly, in the case of multicellular eukaryotes, the transformed cell must either be fixed in the germline in order to carry out genetic alteration of animal and plant germlines, or it must regenerate into a viable creature if asexual reproduction is possible, as is the case in plants through the process of cell dedifferentiation. In conclusion, the integrated sequence must be maintained throughout the period of evolution. Other, more distantly related eukaryotes, such as yeast [27] and many other fungi [28] as well as human and arachnid cultured cells, are amenable to Agrobacterium-mediated transformation. This is in addition to numerous species of plant, which can be transformed by Agrobacterium either naturally or in the laboratory. In addition, DNA transfer via mechanisms analogous to conjugation is conceivable under laboratory settings between other bacteria, such as E. coli, and various kinds of eukaryotic organisms, including human cells. According to Machado-Ferreira [29] the fact that several bacterial species can cause genetic changes in the cells of almost all eukaryotes lends credence to the hypothesis that horizontal gene transfer is a prevalent driving force in evolutionary processes [29].

Consequences of LGT between bacteria and human

Induction Oncogenic Mutations

Evidence for bacteria-to-human LGT is supported by recent publications that analyzed data deposited in public databases of human normal and tumor genome sequences and found a high frequency of detection of bacterial DNA integrated in human DNA. Importantly, these studies also revealed a significantly higher frequency of bacterial DNA in human cancer samples (e.g., acute myeloid leukemia, gastric cancers) compared to DNA from healthy subjects, suggesting that the sequences of bacteria may be directly or indirectly involved in the cancer development, either through direct encoding of carcinogenic protein/enzyme products or through epigenetic changes that set the way for cancer [30].

The phiC31 integrase has been used to generate bacterial plasmids that can integrate autonomously into vertebrate genomes. Integrase phiC31 was initially shown to integrate into human cells in vitro at a pseudo-attP site that does not interfere with normal gene activities [31]. In addition to rescuing a mouse knockout phenotype by appropriate protein expression, the plasmid integrates into mice in vivo following hydrodynamic tail-vein injection [32].

As seen with Crown gall disease which is caused by Agrobacterium, such integrations may emerge via a guided manner. On the other hand, the nucleic acids released of after the lysis of bacteria could be responsible for these integrations. As with mobile elements, integrations may occur only at certain sites, but they may also happen at random, like alterations caused

by exposure to ultraviolet radiation and tobacco smoke as carcinogens. Because the human immune system can identify bacterial DNA and mRNA [33]

When bacterial DNA is integrated into the genome of a new host, there is a greater chance that the gene function will be altered than that the transferred genes will be expressed by the new host. On the other hand, after the integration of DNA of bacteria there is a possibility that a gene from the bacterium will become transcribed, and either a protein or peptide will be produced. It's possible that intestinal cells would benefit from the expression of certain bacterial genes, such the gene responsible for vitamin K biosynthesis. On the other hand, the production of a protein or peptide that has a specific bacterial pathogenicity epitope may cause an unfavorable immunological reaction in cells of human. A further immunological reaction to human epitopes is possible once such a reaction has taken place. This, in conjunction with the well-known mechanism of incomplete elimination of autoreactive cells, has the potential to result in an autoimmune response and even an autoimmune illness [34]

Conclusion

Instances of LGT between (bacteria and animals), and even more specifically between (endosymbionts and the animals) that host them, have been documented. Recent LGT may have a special connection to endosymbionts that specifically target the host's germ cells and germ stem cells. It appears that LGT between bacteria and animals may occur more frequently than previously thought, as evidenced by the extensive LGT found between *Wolbachia endosymbionts* and their invertebrate hosts. Although the immune system and the segregation of gametes in vertebrates may make it unlikely that transfers like those found in invertebrates could occur, transfers to the somatic genome of vertebrates have not been recognised and need to be further investigated. Bacterial DNA integration may be a mutagen associated with noninherited genetic diseases like cancer, as suggested by a recent study that confirmed LGT from Acinetobacter spp. in samples of leukemia and from *Pseudomonas spp*. in stomach cancer samples. This finding was published in a report that summarized the study.

Recommendation

1- Investigate the relationship between certain human and animal diseases with gut microbial.
2- Publish studies explain how the LGT mechanism occurs between prokaryotic and eurokyarote.

Abbreviations

Not applicable

Declarations

Ethics approval and consent to participate

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Competing Interests

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References

1. Sieber KB, Bromley RE, Hotopp JCD. Lateral gene transfer between prokaryotes and eukaryotes. Experimental cell research. 2017; 358(2):421-426.
2. Gelvin SB. Agrobacterium and plant genes involved in T-DNA transfer and integration. Annu Rev Plant Physiol Plant Mol Biol. 2000; 51:223–256.
3. Skaar EP, Seifert HS. The misidentification of bacterial genes as human cDNAs: was the human D-1 tumor antigen gene acquired from bacteria? Genomics. 2002; 79:625–627.
4. Sung WK, Zheng H, Li S, Chen R, Liu X, et al. Genome-wide survey of recurrent HBV integration in hepatocellular carcinoma. Nat Genet. 2012; 44:765–769.
5. Syvanen M. Evolutionary implications of horizontal gene transfer. Ann. Rev. Genet. 2012; 46:341–358.
6. Griffiths A J, Miller J H, Suzuki DT, Lewontin RC, Gelbart WM. Mendel's experiments. In An Introduction to Genetic Analysis. 7th edition, 2000.
7. Fenn K, Conlon C, Jones M, et al. Phylogenetic relationships of the Wolbachia of nematodes and arthropods. PLoS Pathog. 2006; 2:94.
8. Benjamin IA, Higashi T, Hrelia S. Potential role of DNA repair in myocardial injury following ischemia and reperfusion. American Journal of BioMedicine. 2016; 4(11):466-479.
9. Robinson KM, Sieber KB, Dunning Hotopp JC. A review of bacteria-animal lateral gene transfer may inform our understanding of diseases like cancer. PLoS genetics. 2013; 9(10):e1003877.
10. Smillie C, Garcillan-Barcia MP, Francia MV, Rocha EPC, de la Cruz F. Mobility of plasmids. Microbiol. Mol. Biol. Rev. 2010; 74:434–452.
11. Wozniak RAF, Waldor MK. Integrative and conjugative elements: mosaic mobile genetic elements enabling dynamic lateral gene flow. Nat. Rev. Microbiol. 2010; 8:552–563.
12. Lacroix B, Citovsky V. Transfer of DNA from bacteria to eukaryotes. Mbio. 2016; 7.
13. CW Ford, GE Zurenko, MR Barbachyn.The discovery of linezolid, the first oxazolidinone antibacterial agent Curr Drug Targets Infect Dis. 2001; 1:181-199.
14. Woodford N, Ellington MJ. The emergence of antibiotic resistance by mutation. Clinical Microbiology and Infection. 2007;13(1): 5-18.

15. Gray MW, et al. The Origin and Early Evolution of Mitochondria. Genome Biol. 2001;2: 1018.
16. Richly E, Leister D. Numts in Sequenced Eukaryotic Genomes. Mol Biol Evol. 2004; 21:1081–1084.
17. Lin X, et al. Sequence and Analysis of Chromosome 2 of the Plant Arabidopsis thaliana. Nature. 1999; 402:761–768.
18. Doolittle WF. You Are What You Eat: A Gene Transfer Ratchet Could Account for Bacterial Genes in Eukaryotic Nuclear Genomes. Trends Genet. 1998;14:307–311.
19. Chapman JA, et al. The Dynamic Genome of Hydra. Nature. 2010; 464:592–596.
20. Gladyshev EA, et al. Massive Horizontal Gene Transfer in Bdelloid Rotifers. Science. 2008; 320:1210–1213.
21. Hotopp JCD. Horizontal gene transfer between bacteria and animals. Trends in genetics. 2011; 27(4):157-163.
22. Danchin EGJ, et al. Multiple Lateral Gene Transfers and Duplications Have Promoted Plant Parasitism Ability in Nematodes. Proc Natl Acad Sci USA. 2010; 107:17651–17656.
23. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, et al. Initial sequencing and analysis of the human genome. Nature. 2001; 409:860–921.
24. Koehler JE, Sanchez MA, Garrido CS, Whitfeld MJ, Chen FM, et al. Molecular epidemiology of Bartonella infections in patients with bacillary angiomatosis-peliosis. N Engl J Med.1997; 337:1876–1883.
25. Schroder G, Schuelein R, Quebatte M, Dehio C. Conjugative DNA transfer into human cells by the VirB/VirD4 type IV secretion system of the bacterial pathogen Bartonella henselae . Proc Natl Acad Sci U S A. 2011; 108:14643–14648.
26. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics. 2009; 25:1754–1760.
27. Bundock P, Hooykaas PJ. Integration of Agrobacterium tumefaciens T-DNA in the Saccharomyces cerevisiae genome by illegitimate recombination. Proc Natl Acad Sci U S A. 1996; 93:15272–15275.
28. Michielse CB, Hooykaas PJ, van den Hondel CA, Ram AF. Agrobacterium-mediated transformation as a tool for functional genomics in fungi. Curr Genet. 2005; 48:1–17.
29. Machado-Ferreira E, Balsemão-Pires E, Dietrich G, Hojgaard A, et al. Transgene expression in tick cells using Agrobacterium tumefaciens. Exp Appl Acarol. 2015; 67:269–287.
30. Abril AG, Lanzi PG, Notario V. Implications of Lateral or Horizontal Gene Transfer from Bacteria to the Human Gastrointestinal System for Cancer Development and Treatment. In Horizontal Gene Transfer. 2019; 377-397.
31. Groth AC, Olivares EC, Thyagarajan B, Calos MP. A phage integrase directs efficient site-specific integration in human cells. Proc Natl Acad Sci U S A. 2000; 97:5995–6000.
32. Keravala A, Chavez CL, Hu G, Woodard LE, Monahan PE, et al. Long-term phenotypic correction in factor IX knockout mice by using PhiC31 integrase-mediated gene therapy. Gene Ther.2011; 18:842–848.
33. Riley DR, Sieber KB, Robinson KM, White JR, Ganesan A, Nourbakhsh S, Dunning Hotopp JC. Bacteria-human somatic cell lateral gene transfer is enriched in cancer samples. PLoS computational biology. 2013; 9(6):e1003107.
34. Salinas GF, Braza F, Brouard S, Tak PP, Baeten D. The role of B lymphocytes in the progression from autoimmunity to autoimmune disease. Clin Immunol. 2013; 146:34–45.