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FATE OF FOOD-INGESTED DNA - A NEGLECTED TOPIC IN BIO-MEDICAL RESEARCH

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ABSTRACT

This review is based on experimental work in the author's laboratory over several decades. Food-ingested DNA provides the bulk of foreign DNA which constantly invades all organisms. Small amounts of this DNA are able to survive the gastro-intestinal passage and gain access to many organ systems via the lymphatic and blood circulatory systems. Foreign DNA entering mammalian cells can compromise the epigenetic stability of their genomes and alter their DNA methylation and transcription profiles. This occurs particularly, though not exclusively, when foreign DNA is inserted into the genomes of the recipient cells. Hence, hidden, hitherto unrecognized effects of food ingested DNA in an organism might attain unsuspected significance for many important mechanisms in biology and medicine.

KEYWORDS: DNA methylation, epigenetics, alterations of DNA methylation and transcription profiles in transgenomic cells.

Viral Genomes

Viruses are powerful instruments of nature to confer foreign genetic material into cellular organisms. Viral genomes can replicate in their specific hosts and cause a broad spectrum of diseases in plants, animals and humans. More hideously, they can insert their genomes permanently into those of the infected host cells and lead to persistent or latent infections. HIV and other retroviruses exemplify this type of virus-host interactions. Retroviruses have often been identified as tumor viruses. Frequently viruses unfold their most powerful, for the infected individual most dangerous, potential, when they succeed in expanding their host range. HIV, SARS, and Ebola are prominent cases in point. There are only speculations about the origin of viruses: RNA viruses may have arisen early in evolution. DNA viral genomes or at least some of their components could have originated from cellular genetic material. It is well established that DNA viral genomes can recombine with cellular DNA and then carry and utilize cellular genetic material to their own replicative and re-combinatorial advantage. In what way, if any, this genetic potential of viruses has contributed to evolution remains to be determined. The consequences and long-term effects of persistent viral infections on affected organisms have not been fully recognized.

Food-ingested DNA

When considering possible sources of foreign DNA other than viral, food-ingested DNA is the predominant species also in mammalian systems. Copious amounts of foreign DNA are constantly ingested by all living organisms daily and for the duration of their entire lifetimes. There is no escape or protection. Not only the quantity of foreign DNA but also its vast heterogeneity and the biochemical potential of the attached packaging material should alert the researcher to the importance of this source of foreign DNA. The inherent, but unproven, concept has prevailed that DNA, like other macromolecules in food, will be degraded while passing through the gastro-intestinal tract. My laboratory has demonstrated that small amounts of orally fed, even naked DNA transiently survive in the murine gastro-intestinal tract, though in extensively fragmented form.[1] In addition, evidence has been presented that an even smaller percentage of these DNA fragments can be traced to various organ systems in mice. In spleen cells, fragments of food-ingested DNA might become linked to cellular DNA.[1] In the offspring of eight consecutive generations of mice, which had been continuously fed soy bean leaves, even traces of the plant-specific, nucleus-encoded ribulose-1,5-bisphosphate carboxylase (Rubisco) gene could not be detected. Hence the germline appears to be shielded from contamination by food-ingested DNA.[2]

Foreign DNA Induces Epigenetic Alterations

Pursuing a completely different aspect of the fate of foreign DNA, we have investigated the genome-wide consequences of the insertion of foreign DNA into the

host genome. Mammalian cells in culture, which carried integrated adenovirus type 12 (Ad12) DNA, bacteriophage λ DNA or a 5.6 kbp bacterial plasmid were investigated for the stability of their epigenetic profiles. In an Ad12 transformed Syrian hamster (*Mesocricetus auratus*) cell line, with about 12 copies of Ad12 DNA inserted at a single chromosomal site, extensive increases in cellular DNA methylation were documented across the genome at sites remote from the chromosomal locus of Ad12 DNA integration.[3] Single copy genes as well as endogenous retroviral genomes were affected. Even after the loss of all viral transgenomes from the genomes of a revertant of the transformed cell line, the changed methylation patterns persisted. These findings indicated that the trans-effects of foreign DNA insertion on the methylation profiles of cellular DNA, once enacted, remained stably imprinted in the recipient genomes.[3] Lambda DNA as transgenomes in hamster cells similarly, though possibly to a lesser extent, led to methylation changes in the recipient cells' genomes.[4] Again, multiple copies of λ DNA were integrated at a single chromosomal locus in the recipient hamster genomes. In addition, the transcriptional patterns in both Ad12- and λ DNA-transgenomic cells were altered.[5]

Subsequently, we chose a different experimental approach and transformed human HCT116 cells with a 5.6 kbp bacterial plasmid, which carried the selection marker kanamycin as the sole actively transcribed gene [6]: In 4.7% of the 28,869 human gene segments analyzed by about 765,000 distinct probes, transcriptional activities were up- (907 segments) or downregulated (436 segments) in the transgenomic cell clones. Genome-wide profiling revealed differential methylation in 3,791 of 361,983 CpG's examined in transgenomic versus non-transgenomic control clones: Hyper-methylation was found in 1,504, hypo-methylation in 2,287 of the transgenomic clones. Many of the gene segments affected by differential transcription or altered cellular DNA methylation mapped to genes involved in signal transduction.[6] Furthermore, there is recent evidence that the productive infection of human cells with Ad12 alters cellular methylation patterns early after viral infection.[7]

These findings observed in very different experimental systems identify the insertion of foreign DNA into established mammalian genomes as a causative factor in enacting epigenetic changes in mammalian cells. It will therefore be prudent to consider epigenetic complications in experimental regimens involving manipulations of mammalian genomes. Likely, among the epigenetically affected cells there must be some with a completely different phenotype and with compromised genetic activity profiles. We pursue the possibility that the site of foreign DNA insertion might determine extent and location of these epigenetic alterations.[8]

In yet another biological system we found alterations of cellular DNA methylation patterns upon the entry of foreign DNA into human cells with integrated or episomal persistence of the transgenomes.[9] In a human genome segment upstream of the FMR1 (fragile X mental retardation 1) gene promoter (Xq27.3), a cluster of genetic signals is located. One of these is a DNA methylation boundary which lies 65-70 CpG's upstream of a CGG repeat, the latter being characteristic for this region. In fragile X syndrome (FXS) chromosomes with an expanded CGG repeat, the boundary is lost, and the promoter is inactivated by methylation spreading [10]. In FXS individuals and often in non-FXS cells transgenomic for episomal EBV (Epstein Barr Virus) DNA or for the integrated telomerase gene, the large number of normally methylated CpG's in the region far-upstream of the boundary is decreased about 4-fold.[9] We interpret this loss of CpG methylation in the far upstream region as a further example of DNA methylation changes in the wake of entry of foreign DNA into human cells, i.e. of episomal EBV genomes, of the integrated telomerase gene or of the expansion of the endogenous CGG repeat in FXS.

An Important Topic for Critical Investigation

It will be intellectually appealing and medically of high priority to intertwine the two areas of research described above and experimentally explore whether food-ingested DNA will, by intrusion into somatic cells and via the epigenetic modifications of genomes, alter cells stochastically thus that they might become origins of human disease. I am currently pursuing the following scenario:

1. Small amounts of highly abundant, food-ingested DNA survive passage through the gastro-intestinal tract in minute amounts and in fragmented form.
2. These fragments can be taken up by cells of the intestinal defense systems which are ubiquitous in the walls of the gut or in its mesentery. Food-ingested DNA can also penetrate into cells of the epithelial lining of the gut.[1]
3. Food-derived DNA fragments are then distributed via the lymph and/or blood flow throughout the organism and obtain access to many cell types, apparently with the exception of the germ line.
4. The entry of foreign DNA into cells and its probably rare integration into the genome of the invaded cells cause alterations of the transcriptional and DNA methylation profiles of the invaded cells via epigenetic dysregulation.
5. In this way, completely different cell types will be generated as compared to the phenotype of the "normal" cell before invasion by foreign DNA fragments. These events are rare, lead to stochastic changes, and only occasionally assume significant pathogenetic potential. However, the process occurs daily and during the duration of an individual's entire life. Medically relevant errors are expected to accumulate with age.
6. Since the germ line is spared, the nucleotide sequences of the large number of organisms, for which total genome sequences are available, would

not reveal foreign DNA sequences. Many of the invaded cells might be scavenged and will not survive. Moreover, if present at all, food-ingested DNA sequences would be derived from an occasional cell and might in general be difficult to detect since they would only rarely be derived from the few percent of coding sequences of the originally ingested organism. Lastly, it is doubtful whether the proposed scenario has been seriously considered, let alone investigated.

7. In view of the fact that the genetic mechanisms behind most human ailments, particular the very common ones, including tumor diseases are largely unknown, a novel approach will be worth considering.

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