

Host nutritional status: the neglected virulence factor

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The emergence of new infectious diseases and old diseases with new pathogenic properties is a burgeoning worldwide problem. Severe acute respiratory syndrome (SARS) and acquired immune deficiency syndrome (AIDS) are just two of the most widely reported recent emerging infectious diseases. What are the factors that contribute to the rapid evolution of viral species? Various hypotheses have been proposed, all involving opportunities for virus spread (for example, agricultural practices, climate changes, rainforest clearing or air travel). However, the nutritional status of the host, until recently, has not been considered a contributing factor to the emergence of infectious disease. In this review, we show that host nutritional status can influence not only the host response to the pathogen, but can also influence the genetic make-up of the viral genome. This latter finding markedly changes our concept of host–pathogen interactions and creates a new paradigm for the study of such phenomena.

The unexpected and sudden emergence of human immunodeficiency virus (HIV) is the most widespread recent example of the ability of viruses to continue to cause a great deal of morbidity and mortality in human populations. Recently, the outbreak of severe acute respiratory syndrome (SARS) has again demonstrated our continuing vulnerability to newly emergent viruses. It is important to understand the underlying mechanisms involved in the emergence of new viral pathogens with altered pathogenic potential. Understanding how emergence occurs will assist in recognizing conditions of risk for new viral outbreaks and also in developing therapeutic strategies to prevent or limit them. Data from our laboratory [1–3] and others [4,5] have demonstrated that one driving force for the emergence of new viral variants is the nutritional status of the host. Using two very different viruses (coxsackievirus and influenza virus) as model systems we have shown that a host deficiency in either selenium (Se) or vitamin E, or an excess of iron, results in a change in the viral genome. In other words, specific, stable and reproducible viral mutations occur in the genome when nutritionally compromised animals are infected with these viruses; these mutations result in increased virulence of both coxsackievirus and

influenza virus [1,2]. Once these mutations occur, even hosts with normal nutritional status are susceptible to the newly virulent virus. This work represents a new area of research into the interaction of host nutrition and emerging infectious disease.

Coxsackievirus and Keshan disease: the nutrition–virus nexus

In 1935, a severe outbreak of an endemic cardiomyopathy that afflicted mainly infants, children and women of child-bearing age occurred in Keshan County, Heilongjiang Province, China [6]. Within a number of years, Keshan disease (as the condition came to be known) affected thousands of people and it became the top disease priority of the Chinese Ministry of Public Health. Several hypotheses were proposed to explain the cause of the disease, but it was not until 1979 that a connection was established between nutritional Se deficiency and Keshan disease. The amount of evidence that supported this hypothesis was impressive. Epidemiological surveys showed that Se levels in the soils, foods and people residing in highly endemic areas were very low compared with levels in control regions free of the disease [7]. Moreover, Chinese scientists carried out a large intervention trial that demonstrated quite conclusively that supplementation of individuals with nutritional amounts of sodium selenite effectively prevented the disease [8]. Widespread use of Se supplements in the endemic Keshan disease areas led to a drastic decline in the number of cardiomyopathies observed in these areas.

Despite the great success of the ‘selenium hypothesis’ in explaining multiple features of Keshan disease, it became apparent that nutritional Se deficiency in itself could not account for all the characteristics of the disease. For example, Keshan disease exhibits wide swings in prevalence from one year to another and even from one season to another. Such behavior is more consistent with an infectious disease than with a nutritional deficiency. The Chinese scientists realized this and were able to demonstrate that certain enteroviruses, particularly a coxsackievirus B4 isolated from a Keshan disease victim from Chuxiong County in Yunnan Province, were able to induce heart lesions with greater severity in mice fed a diet low in Se than in mice fed the same diet supplemented with Se [9].

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More recently, it has been possible to show that enterovirus isolates from patients with heart muscle disease in a Se-deficient area of China were predominantly coxsackievirus group B serotypes in the region in which Keshan disease is endemic. Thus, these viruses might contribute to the pathology of Keshan disease, as coxsackie B viruses are known etiological agents of myocarditis [10].

Coxsackievirus B3 and Se deficiency: animal models

To understand the relationship between host nutritional status and virus infection, we used our well-characterized murine model of coxsackievirus-induced myocarditis. Coxsackievirus B3 (CVB3) infection of mice can cause myocarditis, similar to that found in human populations. However, infection of mice with an avirulent strain of CVB3 (designated CVB3/0) does not lead to myocarditis, although replicating virus can be isolated from the hearts of infected mice. For our model, we divided mice into two groups and fed one group a normal diet and the other group a diet deficient in Se. After four weeks, all mice were infected with the benign strain CVB3/0. As expected, the infected mice fed the Se-sufficient diet did not develop any cardiac inflammation. However, the Se-deficient mice developed moderate to severe myocarditis [11]. To determine if the increase in virulence was due to host factors alone, or a result of alterations in the virus, we isolated virus from the hearts of Se-deficient mice and passed it back into Se-adequate mice. If host factors alone were the cause of the increase in virulence, then the Se-adequate mice infected with virus isolated from Se-deficient mice should not develop disease. However, the infected mice did develop myocarditis, suggesting that the virus itself had been altered [11].

Sequencing of the viral genomic RNA obtained from infected Se-adequate and Se-deficient mice confirmed that a viral genome change had occurred (Table 1). Out of the ten nucleotide positions that were reported to co-vary with cardiovirulence in CVB3 strains [12], six reverted to the virulent genotype in those virions that replicated in Se-deficient mice [1]. No nucleotide changes were found in viral genomes isolated from Se-adequate control mice. The mutations persisted after the now virulent virus was passed into naive Se-adequate mice, producing pathology (Figure 1). Therefore, replication in a Se-deficient host led

to specific viral mutations, which changed an avirulent virus into a virulent one. Once these mutations occurred, even Se-adequate mice were susceptible to the newly pathogenic virus.

CVB3 mutations and oxidative stress

One of the functions of Se is that it acts as an antioxidant, primarily through its association with the antioxidant enzyme glutathione peroxidase (GPX). GPX incorporates Se as selenocysteine (a novel 21st amino acid in addition to the 20 commonly recognized ones). When Se is limiting in the diet the activity of GPX declines. Se is also incorporated into more than 20 other proteins, some of which have functions other than antioxidant protection. To determine if a decrease in GPX activity was a crucial step in Se-associated change in virulence, we infected GPX-1 knockout mice with CVB3/0. These mice, similar to Se-deficient mice, developed myocarditis, whereas infected wild-type mice did not. Sequencing of the viral genome demonstrated mutation to the cardiovirulent genotype at seven nucleotide positions, of which six were identical to the mutations found in the virus isolated from Se-deficient mice [13] (Table 1).

Because vitamin E also acts as an antioxidant, although it works by a very different mechanism to Se, we wanted to determine if a lack of vitamin E would also affect the viral genome. As was found for the Se-deficient mice, mice fed a diet deficient in vitamin E and infected with CVB3/0 developed myocarditis [14]. Sequencing of the virus revealed that the same mutations occurred in the virus isolated from vitamin E-deficient mice as were found for Se-deficient mice. All of the experimental data led to the conclusion that oxidative stress is the common mechanism for the viral genome changes.

CVB3, vitamin E, excess iron and HIV

The redox-active ferrous ion is known to exert a powerful pro-oxidant effect *in vivo* as a result of its reaction with hydrogen peroxide to produce the extremely reactive hydroxyl free radical. In this way, excess dietary iron can damage a variety of cellular components, including lipids, nucleic acids and proteins [15]. Therefore, it was of interest to determine the effect of dietary iron overload on the ability of CVB3/0 to cause cardiopathology in our mouse model. Mice were fed either a diet containing a

Table 1. Comparison of nucleotide sequences of coxsackievirus B3 isolated from Se-adequate, Se-deficient and GPX-1 knockout mice^a

Nucleotide position (genome region)	Infecting virus: CVB3 ₀		Virus isolated from							Cardiovirulent virus: CVB3 ₂₀	
	Nt	AA	Se+	Se+	Se+	Se-	Se-	Se-	GPx-1 KO	Nt	AA
234 (5' ntr)	C	(nc)	C	C	C	T	T	T	T	T	(nc)
788 (VP4)	G	Gly	G	G	G	A	A	A	A	A	Arg
2271 (VP3)	A	Tyr	A	A	A	T	T	T	T	T	Phe
2438 (VP3)	G	Glu	G	G	G	C	C	C	C	C	Gln
2690 (VP1)	G	Glu	G	G	G	G	G	G	A	A	Lys
3324 (2A)	C	Ala	C	C	C	T	T	T	T	T	Val
7334 (3' ntr)	C	(nc)	C	C	C	T	T	T	T	T	(nc)

^aAbbreviations: AA, amino acid; GPX-1 KO, glutathione peroxidase-1 knockout mice (n=3); nc, non-coding; Nt, nucleotide; ntr, non-translated region; Se+, selenium-adequate (control) mouse; Se-, selenium-deficient mouse.

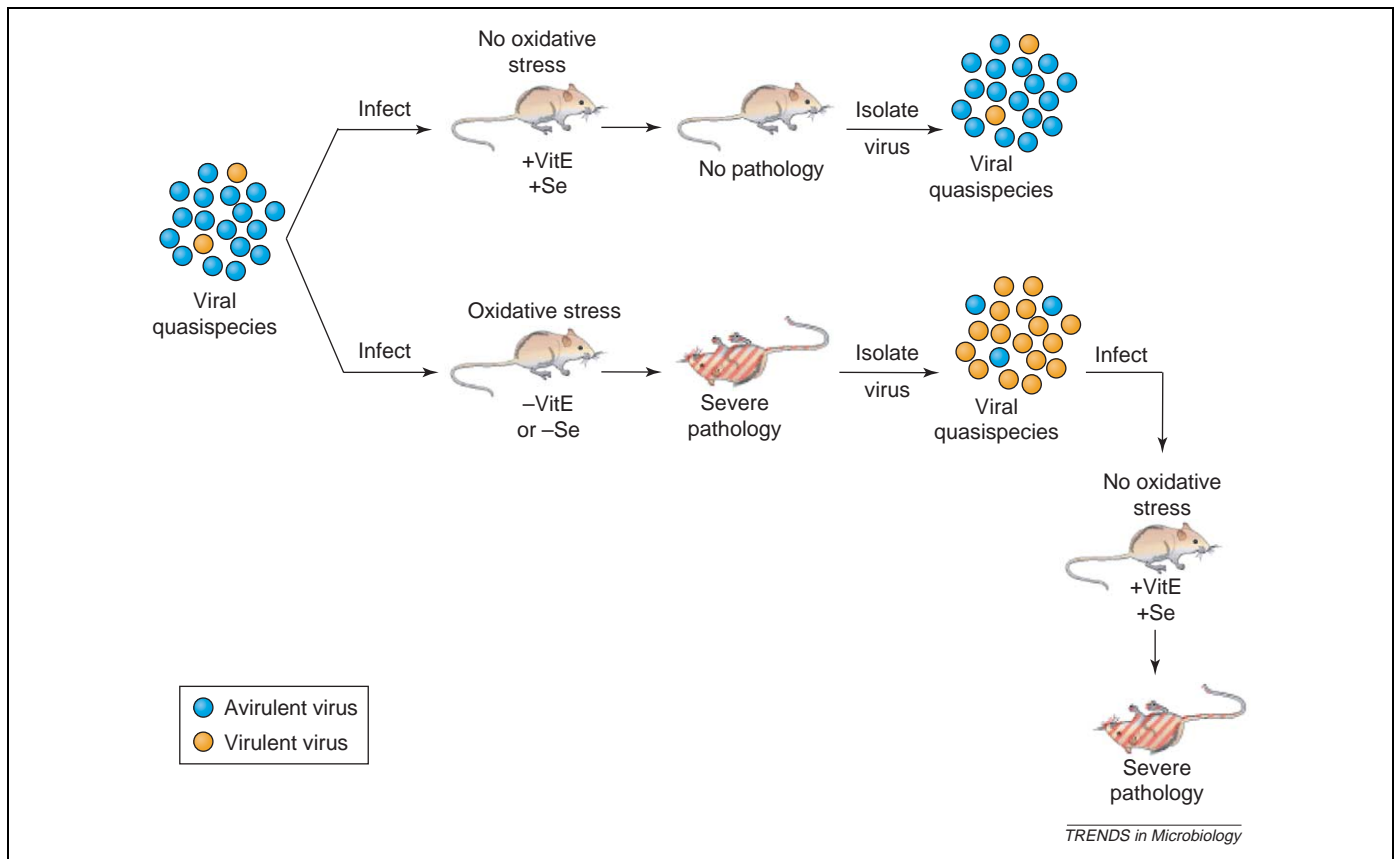


Figure 1. Selection of new viral quasispecies with increased virulence in a nutritionally stressed host. A viral quasispecies is used to infect two different populations of mice: nutritionally adequate or nutritionally deficient. Note that the consensus sequence of the viral quasispecies is avirulent (blue circles) although a virulent genotype (orange circles) is present in the mix in a very small amount and is not detectable by sequencing. Nutritionally adequate mice infected with the viral quasispecies do not develop pathology and sequencing of the virus genome confirms that the virus remains the avirulent genotype. Nutritionally deficient mice infected with viral quasispecies develop severe pathology. Isolation and sequencing of virus recovered from the nutritionally deficient host demonstrates selection of a new consensus sequence with a virulent genotype (orange circles). Once the virulent genotype becomes dominant in the viral quasispecies, even nutritionally adequate mice will develop severe pathology.

normal level of iron (35 parts per million or ppm) or an iron overload diet containing 1050 ppm of iron. At each level of dietary iron, half the mice received the same diet lacking vitamin E. After consuming their assigned diets for four weeks, the mice were infected with CVB3/0 (the amyocarditic strain of CVB3). In those mice that received the vitamin E-supplemented diets, consumption of the high iron diet resulted in elevated viral titers and increased heart damage versus the normal iron controls [16]. Consumption of the high iron diet that lacked vitamin E resulted in further increases in viral titers and heart damage. Therefore, here we have another example of how nutritional manipulation of host oxidative stress status can have an impact on viral pathogenesis, such that an amyocarditic form of the virus was converted into a myocarditic one.

It has been reported that the clinical course of some HIV patients might be unfavorably affected by elevated iron status [17]. In pregnant Zimbabwean women, for example, there was a positive association reported between HIV-1 viral load and serum ferritin levels [18]. However, this positive association between HIV progression and iron status is not universally observed [19,20], and therefore the correlation is controversial [21,22]. Needless to say, any damaging effect of iron in HIV infection would have important public health implications because of the general use of iron supplements to

prevent or cure anemia. Because of the strong combined effect of iron excess and vitamin E deficiency observed during infection with CVB3/0, it might be useful to assess vitamin E nutritional status in HIV patients who are given iron supplements.

Host nutritional status and influenza virus infection

The results observed during coxsackievirus infection suggested that viruses other than CVB3 might be susceptible to host nutritional stresses. To test this hypothesis, Se-deficient and Se-adequate mice were infected with influenza A/Bangkok/1/79, which normally induces only a mild pneumonitis in mice. Mice that were Se-deficient were found to develop severe lung pathology post-infection, whereas the Se-adequate mice developed only mild pathology [23].

Influenza virus contains a single-stranded segmented RNA genome, a lipid bilayer, which is of host derivation, and a matrix protein that lies underneath the lipid layer. The viral genome consists of eight RNA segments containing genes that encode different viral proteins, including the hemagglutinin (HA) and neuraminidase (NA) proteins (required for entry into and exit from the infected host cell, respectively), matrix proteins (M1 and M2), polymerase proteins and nucleoproteins. Viruses recovered from both Se-deficient and Se-adequate mice have been sequenced [2]. Consistent mutations in the M gene were recovered

from Se-deficient mice (Table 2). Three separate isolates from three individual Se-deficient mice all had identical mutations in 29 positions. One of the three isolates had an additional five mutations, with one additional amino acid change. Therefore, similar to what was found for coxsackievirus B3, host deficiency in Se leads to increased viral mutations in the influenza virus genome, resulting in a more virulent phenotype.

How do changes in the M protein lead to increased virulence of the influenza virus? The M1 protein has been shown to influence virulence by increasing viral replication due to rapid uncoating from the viral ribonucleoproteins. Therefore, the faster the uncoating occurs, the quicker viral replication can begin [24,25]. Consequently, mutations in the M region of the genome might lead to increased viral replication of the mutant virus. Increased viral titers in turn might lead to increased lung pathology, and hence increased pathogenicity of the virus. In support of this hypothesis, viral titers of the mutant virus were higher in infected mice compared with wild-type virus [23].

Poliovirus and Se in humans

Poliovirus, similar to the coxsackieviruses, is a human enterovirus and a member of the *Picornaviridae* family. But in contrast to coxsackievirus, poliovirus cannot be

studied using the usual mouse models, because rodents do not normally carry the human poliovirus receptor. However, it is possible to generate transgenic mice that express poliovirus receptors, thereby making them suitable for investigating numerous properties of poliovirus, including neurovirulence, attenuation and tissue tropism. Another experimental approach, of course, would be to study poliovirus in human subjects rather than in animal models. Broome *et al.* [4] supplemented three groups of healthy people (22 members, including 11 males and 11 females in each group) with 0, 50 or 100 µg of Se (as sodium selenite) per day for 15 weeks (for a discussion of what constitutes a nutritionally relevant dose of Se, see Ref. [26]). All subjects were judged to be of relatively low initial Se status as indicated by plasma Se concentrations <1.2 µmol/L. After six weeks of supplementation, all subjects were given an oral live attenuated poliomyelitis vaccine. Supplementation continued uninterrupted after vaccination for a further nine weeks.

Supplementation with Se increased several indices of Se status in these subjects, including plasma Se concentrations and lymphocyte glutathione peroxidase activities. Supplementation also enhanced certain aspects of the cellular immune response, such as increased interferon (IFN)-gamma production, earlier peak T-cell proliferation,

Table 2. Influenza A/Bangkok/1/79 M1 gene of the infecting virus and of virus isolated from selenium (Se)-deficient and Se-adequate mice^a

Nucleotide position	Infecting virus	Virus isolated from						AA ^b change
		Se+	Se+	Se+	Se-	Se-	Se-	
136	A	A	A	A	C	C	C	None
205	G	G	G	G	A	A	A	None
238	G	G	G	G	G	G	A	None
309	G	G	G	G	A	A	A	R to K
322	A	A	A	A	G	G	G	None
325	C	C	C	C	T	T	T	None
328	A	A	A	A	G	G	G	None
331	A	A	A	A	G	G	G	None
334	T	T	T	T	C	C	C	None
370	A	A	A	A	C	C	C	None
371	G	G	G	G	T	T	T	A to S
406	C	C	C	C	T	T	T	None
439	A	A	A	A	G	G	G	None
454	C	C	C	C	A	A	A	None
455	C	C	C	C	C	C	A	None
502	C	C	C	C	T	T	T	None
503	A	A	A	A	C	C	C	None
524	G	G	G	G	A	A	A	None
525	G	G	G	G	G	G	A	T to A
544	A	A	A	A	C	C	C	None
566	C	C	C	C	T	T	T	None
567	C	C	C	C	C	C	T	None
568	G	G	G	G	A	A	A	None
610	A	A	A	A	G	G	G	None
619	G	G	G	G	A	A	A	None
652	C	C	C	C	T	T	T	None
655	G	G	G	G	A	A	A	None
667	G	G	G	G	A	A	A	A to T
669	G	G	G	G	G	G	A	None
670	A	A	A	A	G	G	G	None
677	G	G	G	G	A	A	A	A to T
712	A	A	A	A	G	G	G	None
716	G	G	G	G	A	A	A	D to N
740	A	A	A	A	G	G	G	T to A

^aData represent sequenced isolates from lungs of six individual mice.

^bAbbreviations: AA, amino acid.

and increased number of T-helper cells. Humoral immune responses were not affected. However, perhaps the most intriguing observation was the fact that individuals receiving Se exhibited a more rapid clearance of the poliovirus. Moreover, poliovirus RT-PCR products isolated from the feces of supplemented subjects had fewer mutations.

The Broome study [4] presents for the first time direct evidence for the involvement of Se status in determining viral replication and mutation rates in people. These data confirm in humans what Beck and colleagues [3] have been saying on the basis of their mouse models for several years, namely that Se (and vitamin E) exerts a powerful control over viral replication and mutation rates *in vivo*, such that a nutritional deficiency of either of these two dietary antioxidants enables RNA viruses to convert to more virulent strains. Additional study of the influence of Se and/or vitamin E on the evolution of viruses in large population groups appears warranted.

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) in viral infection

Previous work has shown that ROS and RNS play a crucial role in the development of influenza-induced pathogenesis in the lung [27–29]. Akaike *et al.* [5] reported increased rates of mutation of an RNA (Sendai) virus that had been exposed to reactive nitrogen species (RNS), such as nitric oxide (NO) and peroxynitrite (ONOO⁻). Both NO and O₂⁻ have been shown to increase the pathogenesis of an influenza virus infection in laboratory experiments [27,30,31]. Notably, an inducible form of NOS (nitric oxide synthetase or iNOS) is strongly activated by a variety of pathogens, including neurotropic, cardiotropic and pneumotropic viruses (e.g. coxsackievirus or influenza virus), causing an overproduction of NO in infected tissues [28]. Importantly, inhibition or elimination (knockout) of iNOS activity significantly reduces pathological consequences of various viral infections [28], including pneumonitis caused by influenza virus in mice [27]. The work of these groups with RNS and of our group with Se and vitamin E deficiency strongly suggests that oxidative and/or nitrosative stress in the host tissues significantly contributes to the modification of viral RNA during virus replication. Therefore, a nutritional deficiency of an antioxidant that leads to increased production of ROS and/or RNS is probably responsible for viral mutations.

Host nutrition and viral genome changes: possible mechanism(s)

RNA viruses have adapted to fill all available host niches – from bacteria to plants, fish, birds, reptiles, amphibians and mammals. One method that viruses use to exploit a wide range of hosts is that of genetic diversity. A population of viruses exists as a large number of closely related mutants, rather than a single fixed sequence, and is therefore known as a ‘quasispecies’. This variation occurs because of the error-prone replication of RNA viruses, lack of viral proofreading enzymes and short generation times. During viral replication, the quasispecies will reach equilibrium and a consensus, or dominant sequence, will emerge. It has been suggested that maintaining a diverse quasispecies

provides an evolutionary advantage to the virus and enables rapid adaptation to changing host environmental conditions.

Within the quasispecies structure, a variety of sub-populations can coexist; and by adjusting their numbers, the population as a whole can move rapidly through ‘sequence space’ from one ‘fitness peak’ to another. Thus, determination of the ‘genomic sequence,’ even for a carefully cloned population, is really an assessment of the dominant (or consensus) sequence. The dominant genotype might shift gradually, or it could change suddenly if environmental pressures are imposed [32]. Most variant sequences, however, are present as tiny minorities within the overall population; nevertheless, it has been shown that a given sequence that once had a selective advantage might persist through many replicative cycles, unobserved by phenotype or consensus sequencing, and might re-emerge rapidly when it is again favored by selective pressure. This phenomenon has been termed the ‘memory’ of viral quasispecies [33].

We hypothesize that increased oxidative stress in the host, induced by dietary deficiencies in antioxidants or by increased consumption of pro-oxidant nutrients, might provide a selective environment by which the more virulent genotype (already present in the viral quasispecies) is able to outcompete the original consensus sequence. Consequently, a new genotype becomes dominant, which has a more pathogenic phenotype.

How does the nutritionally induced oxidative stress status of the host contribute to the selection of a new viral quasispecies? One possibility is an altered immune response. Our own work [3,11,23,34], and the work of many others [35–37], has demonstrated that host nutritional deficiency leads to impaired immune function. For example, a deficiency in Se can lead to decreased T cell function, impaired neutrophil chemotaxis and decreased antibody production [38]. An impaired immune response might permit a more virulent viral quasispecies, normally kept in check, to escape elimination by the immune response and therefore replace the previously dominant less-virulent genotype.

It is also possible that a shift of the intracellular redox balance toward oxidation permits faster viral replication, consequently increasing the size of the quasispecies population and permitting selection of rare variants. Nencioni *et al.* [39] reported that lower intracellular concentrations of reduced glutathione permitted influenza virus replication to higher titers in several cell lines, apparently by inhibiting expression of late viral proteins, including HA and M.

A third possibility is that an increase in nutritionally induced oxidative stress could lead to a new viral quasispecies by direct oxidative damage to the viral RNA, thus accelerating the mutation rate. In addition, the oxidative damage to cell membranes and enzymes of the replication complex might also accelerate the viral mutation rate, thus leading to a new dominant viral quasispecies with altered pathogenicity.

To date, the precise mechanisms for selection of new viral variants in a host under nutritionally induced oxidative stress are not known. However, we would propose

that several mechanisms are operating together to influence the outcome. Thus, both immune dysfunction and oxidative damage to the viral RNA might be occurring together to drive the selection of a new viral quasispecies.

Figure 1 presents a schematic of the hypothesis put forward by our data. The viral quasispecies (in which the consensus or dominant genotype is avirulent) is inoculated into either a nutritionally adequate or nutritionally deficient host. However, within the quasispecies is a small minority population of virus with pathogenic potential. Replication of the viral quasispecies within a nutritionally adequate animal (not oxidatively stressed) results in the dominant consensus genotype remaining dominant and therefore no disease is induced. However, replication of the viral quasispecies within a nutritionally deficient host (oxidatively stressed) leads to a much different outcome. The previous minority genotype is now able to outcompete and replace the previously dominant genotype. This might be due to impaired immune function as a result of the nutritional deficiencies, enabling the minority genotype to escape immune clearance. In addition, oxidative damage to intracellular structures might favor the replication of the minority genotype, again enabling the expression of a new viral variant, which now replaces the previous consensus sequence. Further, the mutation rate might be increased by direct damage to viral RNA, resulting in faster emergence of new genotypes. These mechanisms are not mutually exclusive and might work together.

Concluding remarks

The old nutritional adage 'You are what you eat!' appears to have found novel application in our work relating host diet to viral virulence. By using relatively simple nutritional manipulations we and others were able to increase the oxidative stress in our host animals either by withholding crucial cellular antioxidants from their diets (e.g. selenium or vitamin E) or by feeding with excess amounts of a pro-oxidant nutrient (e.g. iron). All techniques tested to increase oxidative stress in host animals led to the common outcome of increased viral virulence with reproducible genome mutations found in two RNA viruses: coxsackievirus and influenza. The demonstration that this phenomenon occurs within two different viral RNA families suggests that host nutritional deficiencies can have an effect on several different viral infections. These results represent a new paradigm for the interaction between host nutritional status and the emergence of new viral diseases in the human population. Widespread nutritional deficiencies occur in many developing countries, which are frequently the site of emergence of new viral diseases as well as old viral diseases with new pathogenic properties. We suggest that host nutritional status be considered when studying the causes for viral emergence, and that adequate nutrition of the population is an important form of protection against the emergence of new viral pathogens.

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Possible role for bacteria in the evolution of animal cell–cell signalling?

Researchers from the National Institutes of Health (<http://www.nih.gov>) have proposed that most of the genes encoding for enzymes involved in the synthesis of cell signalling molecules in animals may have in fact originated from bacteria [1].

Cell signalling molecules are important because they allow cells to send messages to each other enabling them to communicate.

The team conducted a search of the National Library of Medicine's (NLM; <http://www.nlm.nih.gov/>) genetic databases and discovered that, out of 17 major enzymes dedicated to messenger metabolism, only two were ubiquitous within eukaryotes and bacteria. The remaining enzymes were shared by only one or two eukaryotic lineages and bacteria.

The search was prompted by the group's earlier observation that the enzyme arylalkylamine N-acetyltransferase (AANAT) is present in animals, bacteria and yeast, but in no other living organisms. AANAT is present in the human brain where it is used to make melatonin, a hormone that regulates the body's cycles of sleeping and waking. They speculated that the evolution of AANAT might have involved horizontal gene transfer (HGT) from bacteria to an ancestral eukaryote.

HGT from bacteria to animals has, up until recently, been considered to be a rare if not an impossible event. However, during the analysis of the human genome sequence, over 100 genes showed a greater sequence similarity to bacterial genes than to genes from other eukaryotic phyla; a situation that most likely arose from HGT. The alternative explanation would be that all living organisms once possessed the genes now found only in bacteria and animals but most lost them. The authors point out that the latter scenario is unlikely as it would be surprising to find that such a large group of organisms could have lost so many genes.

Lakshminarayan Iyer, Research Fellow at the NLM and first author on the paper hopes that, "By studying these enzymes in bacteria, we may be able to get a better idea of how they work in human beings". AANAT, for example, is not only present in the brain but also in the retina of human beings and other primates where it does not produce melatonin. Enzymes such as AANAT may be important to bacteria because they provide a detoxification function and David Klein, a co-author on the paper, suspects that retinal AANAT may play a role in neutralizing and eliminating toxic substances. If this is the case it could lead to the discovery of novel functions for other enzymes found within humans.

News story by Anthony Li (A.Li@elsevier.com)

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