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Host-Controlled Variation in Animal Viruses

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Almost all heritable changes in animal viruses have in the past been ascribed to the occurrence of mutations equivalent to gene mutations in higher forms, selection enabling the mutants to become established within the population. Almost certainly selection of mutant forms is responsible for the appearance of a great many virus variants, although direct evidence that such changes owe their origin to mutation is usually lacking. Evidence is commonly based upon the observation that a number of passages of the virus in a new host is usually required before any change in the population is seen. Nevertheless, we do know that when the selection pressure is sufficiently intense changes in a virus population can be observed even after a single passage (*Burnet* and *Bull*, 1943; *Clarke* et al., 1958). Thus, *Burnet* and *Bull* (1943) found that a single passage of influenza A virus of human origin in cells lining the chick amniotic cavity resulted in the emergence of a variant which, unlike the original material, was able to grow in the allantois and agglutinate chick erythrocytes more readily than the human virus. But since amniotic passage at limiting infective dilution resulted in retention of the O ('original') form of the virus, the D ('derivative') form emerging only when passage was made with undiluted virus, it appeared that the O-D change was due to the appearance of a variant backed by intense selection pressure, rather than a change due to some direct modifying effect of the host.

Similar considerations to these apply to many instances of variation in bacterial viruses, in which the variants may arise by a process of random mutation; so that among the progeny of individual cells variant clones may be found (*Luria*, 1951). A study of such clones shows that the change is random rather than directed by the host. However, among the bacteriophages some variation under conditions of single passage has been shown to be under direct host control. In the cases that have been reported, such variation appears to affect host range only, and may be towards either an extension or a restriction of this range. For example, *Bertani* and *Weigle* (1953) showed that phage P2B, which

normally destroys a population of *Escherichia coli* B cells, is unable to do so after a single cycle of growth in cells of *Shigella dysenteriae*, strain Sh. Nevertheless, the modified P2B phage can have this growth restriction removed; it is able to replicate in a few exceptional cells of an *E. coli* B population (one in 10^4), so that the progeny from the latter cell-virus interaction is fully infective for the entire population. The essential feature of this phenomenon, and others of a similar kind (*Anderson* and *Felix*, 1952; *Luria*, 1953), is that the change resulting in the appearance of a variant phage form takes place during the course of a single cycle of replication. As such, it may be interpreted as being due to a direct modifying effect of the host. Variants of this kind are genetically stable—within the limits imposed by random mutation—as long as they continue to replicate within the modifying host.

The early recognition of the importance of the host cell in some cases in directing the genetic future of the phage owed much to the ease and accuracy with which quantitative experiments could be performed. Only much more recently have comparable methods become available for those studying animal virus-cell interactions. Since there is no *a priori* reason for believing that the host may not directly modify hereditary processes in animal viruses, it is worth considering some instances where such a process may be operating. Unfortunately, a survey of the literature reveals that the most important single criterion upon which any recognition of direct host control depends—the time factor—has received little attention. Nevertheless, for the reasons already indicated we can eliminate from consideration any change that does not occur during one passage of the virus in a given host.

We have seen that the O-D change in influenza cannot be explained in terms of host-controlled variation. But in many other cases of single passage change the part of the host can by no means be excluded. The YSK strain of poliovirus is pathogenic for cynomolgous monkeys, when administered either intracerebrally or orally. But *Sabin* (1955) found that after a single passage in the mouse brain *in vivo* the virus was no longer able to elicit paralysis in the monkeys after oral administration, while it still retained its intracerebral virulence. *Dick* and *Dane* and their co-workers (1957) fed monkey-attenuated strains of poliovirus to human volunteers, who later excreted in their faeces virus which had an increased virulence for monkeys. More recently, *Clarke* et al. (1958) performed a similar experiment using an attenuated Type III strain of poliovirus, and found that two patients excreted virus of increased virulence within 48 hours of feeding. While nothing is known of the growth cycle period of poliovirus in the human gut, clearly the excreted

virus must have been produced some hours earlier; so that if one is not to invoke host control to explain this observation any spontaneous variants must have been exposed to a very intense selection pressure.

Stronger evidence for host-controlled animal virus variation is provided by *Cairns*'demonstration (1951, 1954) that unadapted influenza A virus is able to undergo only a single cycle of multiplication in the mouse brain, and subsequently infect a second host system. The single cycle took place even with small inocula, so that interference by 'incomplete' virus (*von Magnus*, 1951) appeared to be ruled out as the restricting factor. Furthermore, the production of some inhibitory substance in the infected brain could not be adduced to explain the growth restriction, since challenge with fresh virus of animals in which virus growth had already taken place resulted in a further single cycle of virus multiplication. However, in spite of the failure of the virus to replicate in the mouse brain beyond one cycle the brain-propagated virus was still able to multiply in the chick allantois.

Cairns' findings differ from those cases of abortive multiplication in which inoculation of the virus leads to synthesis of new virus products which, though themselves products of normal virus replication in a fully competent system, have not been demonstrated to be infective for a second host. For example, *Henle*, *Girardi* and *Henle* (1955) have shown that Hela cells inoculated with any of several strains of influenza virus yield only non-infectious haemagglutinin and complement-fixing antigen. In this case the virus-cell interaction leads to the formation of products which are non-infective for the host cell and, therefore, exclusively derived from the cells originally infected; these substances are not known to be infective for another host. Abortive growth cycles of this kind do represent examples of modification of the virus by the host, and, since no new infective virus is produced to initiate a second cycle, are, by definition, changes brought about under single growth cycle conditions. However, the host range of the single growth cycle product in most instances has not been investigated, and enquiry might lead to results of the kind reported by *Cairns*.

It is unfortunate that *Cairns* was unable, for technical reasons, to determine whether his mouse brain-propagated influenza virus could in fact be passed to further mice, since failure of passage at high dilution would suggest more strongly that the phenomenon was one of host-controlled variation. Nevertheless, it does vary in principle from those cases of host-controlled modification known in bacterial viruses, where the modified form replicates within the host which causes the change, the modification itself representing a restriction of host range only for

a second host. More analogous to host-controlled bacteriophage variation is the behaviour of encephalomyocarditis (EMC) virus in the mouse brain, already reported (*Hoskins*, 1959). A variant of this virus, cytopathic for mouse sarcoma 180 cells *in vitro*, loses its capacity to destroy the cells after a single cycle of growth in the mouse brain.

Host-controlled variation in encephalomyocarditis (EMC) virus

Murine encephalomyocarditis (EMC) virus was used in the experiments to be described, the starting material being an infected brain suspension from the 63rd intracerebral mouse passage of the original virus isolated by *Helwig* and *Schmidt* (1945); this is referred to as mouse brain virus. The sarcoma 180 tumour used was obtained in the solid form from the Chester Beatty Research Institute, and maintained by serial sub-cutaneous transplantation in genetically heterogeneous albino mice. Monolayer cultures were prepared by trypsinizing the tumour according to standard methods, and suspending the cells so obtained in a mixture of 80% '199' (*Morgan* et al., 1950) and 20% horse serum. In later experiments an ascites form of the tumour was used; except where otherwise stated the following description applies specifically to the solid form of the tumour.

Cells of the mouse sarcoma 180 maintained *in vitro* are normally insusceptible to EMC virus of mouse brain origin. Nevertheless, starting with mouse brain virus, a variant capable of growing in and destroying sarcoma 180 cultures was isolated. The variant, designated S180 virus, presumably arose by mutation and selection. The single pool of stock S180 virus used in the experiments described below contained 2.0×10^7 plaque-forming units (PFU)/ml.

Considered as a mutant which is highly destructive for monolayer cultures of sarcoma 180 cells, it seemed likely that S180 virus would still destroy the tumour cells after growth in various host systems. However, when a small inoculum of the virus (10^2 PFU) was injected intracerebrally into mice, the suspension subsequently prepared from the brains of these animals when they became moribund a week later was no longer able to multiply in or destroy tumour cultures. Various mechanisms could account for the difference between S180 virus before and after growth in the mouse brain.

a) An infected mouse brain suspension contains a substance capable of inhibiting infection of the tumour cells by S180 virus. This would explain both the failure of EMC virus of mouse brain origin normally to infect sarcoma 180 cells, and the inability of S180 virus after growth in the mouse brain to infect the cells.

b) S180 virus is modified as a whole by growth in the mouse brain *in vivo*, to a form no longer infective for the tumour cells. This might be due to the production within the mouse brain of virus with some intrinsic defect so that it is unable to replicate subsequently in the tumour cells.

c) S180 virus mutates, either in the mouse brain or in the tumour cells *in vitro*, to a form which is not infective for sarcoma 180 cells; this mutant then overgrows and suppresses the action of S180 virus, in a way analogous to the O-D change in influenza virus (*Burnet* and *Bull*, 1943).

The presence of an inhibitor in infected brains seemed unlikely, since high dilutions of a stock suspension of mouse brain-propagated virus failed to destroy cultures of sarcoma cells. Similarly, a preparation of the same virus, purified by protamine precipitation and high-speed centrifuging (*Weil* et al., 1952), also failed to destroy the cells. Furthermore, a mixture in equal proportions of a 20% normal mouse brain suspension and undiluted S180 virus was fully destructive for similar cultures. If, therefore, an inhibitor were present, it would be a substance appearing only in infected brains, sedimenting with the virus throughout all stages of purification, and active at a dilution comparable with the virus infectivity end-point.

Possibilities *b* and *c*, above, were distinguished in the following way. Two supposed clones of S180 virus were prepared by:

1. Three limiting infective dilution passages in sarcoma 180 cells *in vitro;* such a procedure would be expected to isolate the predominant component—in this case tumour-infective—in a heterogenous virus population (*Isaacs* and *Edney*, 1950). The virus suspension from the third passage contained 1.5×10^6 PFU/ml.

2. Two successive single plaque isolations from limiting infective dilutions, the virus being plated on Krebs-2 mouse ascites tumour cells (*Sanders* et al., 1958); the second plaque, suspended in phosphate-buffered saline (*Dulbecco* and *Vogt*, 1954), contained 2.9×10^5 PFU/ml.

0.03 ml volumes of each virus clone were inoculated intracerebrally into mice, whose brains were removed at the end of one virus growth cycle. 12 hours was chosen as the growth cycle time, on the basis of *in vitro* studies with Krebs-2 cell suspension cultures (*Sanders*, 1957). 0.15 ml volumes of a 10% suspension of these brains was not destructive for sarcoma 180 cultures, although samples of the virus clone preparations with which the mice had been inoculated were fully infective for control tumour cells (Table 1). At the same time, control assays showed that the virus had multiplied normally in the mouse brain, so

Table 1

Effect of growth in mouse brain on infectivity of S180 virus

Virus	Effect on S180 cells	
	before growth in mouse brain	after growth in mouse brain
Plaque-isolated clone	cytopathic effect	nil
Tissue culture clone	cytopathic effect	nil

Table 2

Quantitative aspects of growth of S180 virus

Virus	Virus content[1] of mouse brain after		Virus content[2] of Krebs-2 cell cultures infected with mouse brain phenotype		
	1 hour	12 hours	at infection	after 1 cycle	after 2 cycles
Plaque-isolated clone	1.0×10^2	1.1×10^6	2.5×10^3	9.6×10^4	2.6×10^6
Tissue culture clone	1.1×10^3	8.4×10^6	2.1×10^4	1.1×10^6	1.4×10^7

[1] PFU/ml of 10% brain suspension

[2] PFU/ml of cell suspension supernatant fluid

that failure to multiply could not be adduced as the reason for failure of the brain-propagated virus to infect the tumour cells (Table 2).

It therefore follows that a single growth cycle of S180 virus in the mouse brain *in vivo* is sufficient to render a clonal preparation of the virus—normally destructive for sarcoma 180 cultures—non-destructive for these cells. In fact, whereas a single PFU of S180 virus is able to initiate a spreading wave of destruction in S180 cultures (*Hoskins*, unpublished), the above experiment indicates that less than one PFU in 10^5–10^6 is able to do so after growth in the mouse brain. Since the virus population as a whole appears to be changed during the course of one growth cycle only, the phenomenon is unlikely to be explicable as the emergence and selection during this period of a mutant which overgrows and suppresses the action of S180 virus. We can therefore rule out possibility *c*, above. It is probable that the phenomenon is a modification of the virus directly induced through growth in the mouse brain.

Although S180 virus loses its infectivity for sarcoma 180 cultures during mouse brain passage, the following evidence shows that the changed phenotype can reacquire its infectivity under suitable conditions. Cell suspension cultures (*Sanders*, 1957) of Krebs-2 ascites cells were inoculated with 10^3–10^4 PFU of mouse brain-modified S180 virus prepared from each of the clones described in the previous experiment.

After incubation at 37° C for 12 hours, portions of the centrifuged suspensions, containing 10^4–10^5 PFU, were inoculated into fresh Krebs-2 cell suspensions and incubated for a further growth cycle. Control assays (see Table 2) showed that virus multiplication had occurred during each period of incubation. Table 3 shows that, following growth of modified S180 virus in suspensions of Krebs-2 tumour cells, the undiluted culture fluid subsequently contained virus which was once more destructive for monolayers of sarcoma 180 cells. Moreover, this reacquired cytopathic property was inherited through a second cycle of growth in Krebs-2 cells.

Table 3

Effect of growth in Krebs-2 cells on infectivity of modified S180 virus

Origin of modified virus	Effect on S180 cells		
	before growth in Krebs-2 cells	after growth in Krebs-2 cells	
		1 cycle	2 cycles
Plaque-isolated clone ..	nil	cytopathic effect	cytopathic effect
Tissue culture clone ...	nil	cytopathic effect	cytopathic effect

This phenomenon is formally analogous to the bacteriophage modification described by *Bertani* and *Weigle* in 1953, in which these workers showed that bacteriophage λ, which normally destroys a population of *E. coli* S cells, is unable to do so after a single cycle of growth in cells of *E. coli*, strain C. However, after growth in *E. coli* C cells the phage, now called λC, can be modified again by single cycle growth in a few cells in a strain S population (one in 5×10^3) so that it reverts to the λ form and is once more able to grow in all strain S cells. It is also possible that modified S180 virus may behave in the same way as λC, and that a similar small proportion of sarcoma 180 cells may support the multiplication of modified virus. It may be that the effects of such virus growth in the tumour cultures would not be detected because of the limiting of cytopathic destruction by interference from the excess brain-modified virus always present. However, during the course of working with three genetically distinct strains of EMC virus (*Hoskins*, 1959) no evidence of interference was seen. It was therefore desirable to analyse further the quantitative aspects of the host-controlled changes observed with S180 virus. Unfortunately, for technical reasons it was not possible to do this using the tumour cell system that was employed in the experiments already described, and an ascites form of the sarcoma 180 was thus obtained. The new tumour was received, from the Sloan Kettering Institute in New York, growing in a strain of genetically heterogeneous

Table 4

Absence of host range modification of S180 virus by S180 ascites cells

Virus	PFU/ml when plated direct on	
	Krebs-2 ascites cells	S180 ascites cells
Plaque-isolated S180 virus clone	1.0×10^3	5.0×10^2
Mouse brain-passaged S180 virus clone	1.0×10^5	4.0×10^4

Table 5

Absence of host range modification of S180 virus by S180 ascites cells

Virus	Adsorbed on	Plated on	Infectious centres/No. cells plated
Mouse brain-passaged S180 virus	Krebs-2 ascites cells	Krebs-2 ascites cells	$1/6.2 \times 10^1$
		S180 ascites cells	$1/1.2 \times 10^2$
	S180 ascites cells	Krebs-2 ascites cells	$1/4.9 \times 10^1$
		S180 ascites cells	$1/2.5 \times 10^2$

albino mice, and was later maintained by intraperitoneal passage in mice from a similarly outbred colony. After washing the ascites cells, cell suspension cultures were prepared, and plating experiments carried out, as previously reported (*Sanders* et al., 1958).

When EMC virus of mouse brain origin was plated on sarcoma 180 ascites cells, the virus grew in the latter and produced characteristic plaques; this result being at complete variance with that found for the solid tumour infected as monolayer cultures. In a second experiment, S180 virus which had undergone a single growth cycle in the mouse brain was plated direct onto sarcoma 180 ascites cells, and also onto a neutral, indicator cell system, the Krebs-2 ascites carcinoma (*Hoskins*, 1959). Table 4 shows that the modified virus is equally infective for both cell types. Table 5 illustrates that when the modified virus is allowed to adsorb onto both the Krebs-2 and sarcoma 180 ascites cells, and the cells themselves plated onto each cell type, there is again no significant difference between the number of plaques produced. In fact,

it appears that the ascites form of the sarcoma 180 cannot be used to demonstrate host-controlled variation of S180 virus, and that the tumour itself may be different from the solid form. There is further evidence that the latter is the case. A number of attempts were made to convert the solid tumour into an ascites, with no success (*Craigie*, 1959). Five attempts to do so by the author confirmed the view that the sarcoma 180 is a difficult tumour to establish as an ascites, and that the ascites tumour used in the experiments described had little in common with the solid sarcoma. Moreover, after conversion of the ascites to a solid tumour by sub-cutaneous implantation in mice, its histological appearance differed markedly from that of the original solid.

Mechanisms in host-controlled variation

When bacteriophages were shown to be able to undergo host-controlled variation, the fact that reversion of the change could also be demonstrated led some investigators to believe that the phage genotype remained unaffected. However, *Hershey* and *Chase* (1952) have shown that following adsorption of the phage to the (modifying) host, deoxyribonucleic acid (DNA) is injected into the cell, leaving the empty protein shell outside. It seems unlikely that the host can act upon anything other than the phage genetic material, but the possibility cannot be excluded, since *Hershey* has more recently emphasized that up to 3% of the phage protein enters the bacterium during the injection process (*Hershey*, 1957). Working with a legume-infective strain of tobacco mosaic virus, *Bawden* (1956, 1958) has reported a modification following growth in a variety of French bean. Both serological and nucleic acid changes were observed. The change in the former implies alteration of the virus protein in some way, but there is no reason why this may not be mediated through altered genetic material. The modification was not reported to take place under single cycle conditions, but it was reversible, and, while one cannot exclude the possibility that the hosts selected variants which originated in them as the result of events equivalent to reversible mutations, the hosts themselves may have been responsible for the observed changes.

The use of infective nucleic acid preparations has enabled one to study the animal virus genome independently of its phenotype, and the following experiments suggest that the use of infective ribonucleic acid (RNA) preparations may give informative results. RNA was prepared by a phenol extraction procedure (*Schuster* et al., 1956) from the supernatant fluids of infected ascites tumour cell suspensions, harvested after a single growth cycle. The initial infection was at a calculated multiplicity

Table 6

Host range of RNA preparations made from different types of host cell infected with K2 encephalomyocarditis (EMC) virus

Virus grown in	Titre* of RNA when tested in			
	Krebs-2 Carcinoma	Sarcoma 37	Ehrlich Carcinoma	Sarcoma 180
Krebs-2 carcinoma	6×10^3	4×10^4	9×10^2	5×10^4
Sarcoma 37	trace	1×10^3	7×10^1	0
Ehrlich carcinoma.....	2×10^3	4×10^1	9×10^2	4×10^2
Sarcoma 180	1×10^3	6×10^2	3×10^3	6×10^2

* 50% MID_{50}/ml

Table 7

Host range of RNA preparations made from two types of host cell infected with different encephalomyocarditis (EMC) virus strains

Host cell	Virus strain	Titre* of RNA when tested in			
		Krebs-2 carcinoma	Sarcoma 37	Ehrlich carcinoma	Sarcoma 180
Krebs-2 carcinoma	EMC (mouse brain)	1×10^4	2×10^4	Trace	Trace
	S180	3×10^4	3×10^4	Trace	Trace
	K2	6×10^3	4×10^4	9×10^2	5×10^4
Sarcoma 37	EMC (mouse brain)	Trace	6×10^1	6×10^3	5×10^2
	S180	0	0	6×10^3	Trace
	K2	Trace	1×10^3	7×10^1	0

* 50% MID_{50}/ml

of three PFU/cell. Assays of RNA were made by preparing a mixture in equal proportions of RNA dilutions and a suspension of washed tumour cells (10^8/ml); after 30 minutes interaction at room temperature aliquots were inoculated intraperitoneally into albino mice. Mice developing specific signs of infection (absence of ascites, subsequent death) were scored as positive; those developing ascites were scored as negative.

Table 6 shows that when the K2 strain of EMC virus (*Sanders* et al., 1958) is grown in different types of mouse tumour cell *in vitro* under single growth cycle conditions, although the progeny virus has the same host range irrespective of the cell in which it is grown, infective RNA preparations made from the same materials differ widely in their host range. Furthermore, with EMC virus strains of different host range we find that infective RNA preparations derived from them are both host-determined and virus-determined in their host range (Table 7). It there-

fore appears that animal virus variation controlled by the host may be the result of processes going on at the level of the viral nucleic acid. More conclusive results would be provided by studying the nucleic acid derived from purified virus preparations. However, studies have been hampered by the finding that infective RNA could not be extracted from purified EMC virus, but only from virus-infected mouse tissues or tissue culture fluids (*Huppert* and *Sanders*, 1958).

Summary and conclusions

A strain of encephalomyocarditis (EMC) virus, designated S180 virus, has been shown to undergo a restriction of its host range following a single cycle of growth in cells of the mouse brain *in situ;* it is rendered unable to grow in monolayer cultures of a solid form of the mouse sarcoma 180, a cell system in which it is normally able to replicate. The modified virus is able to have this growth restriction removed following a further single cycle of growth in cells of a second mouse tumour, the Krebs-2 ascites carcinoma. No evidence of an inhibitor for the successful infection of sarcoma 180 cells could be detected in the mouse brain, and, since the change regularly occurred during the course of one growth cycle, the phenomenon seemed explicable only in terms of a variation directly controlled by the metabolic processes operating in the mouse brain; similar importance being attached to the removal of the growth restriction by growing the modified virus in the Krebs-2 ascites cell.

It was not possible for technical reasons to analyse in detail the quantitative aspects concerning the degree of modification taking place, and attempts to do this by using an ascites form of the sarcoma 180 were frustrated since the latter did not behave in the same way as the solid tumour. Further evidence is presented which indicates that the tumours themselves are genetically different.

Preliminary experiments suggest that in host-controlled variation with S180 virus the control may be exerted directly upon the viral nucleic acid, although further work is needed to confirm this suggestion. In bacteriophage modification one may be observing a control exerted only upon the nucleic acid, although one cannot be sure of the part played by the minority protein component which also enters the bacterium during injection; it is possible also that some protein is present in the infective ribonucleic acid preparations used in studying the genome of S180 virus.

The demonstration of host-controlled variation in an animal virus emphasizes the importance of understanding more adequately the inter-

action taking place when virus and cell come into fruitful contact; i.e., are able to yield new, infective virus. Compared with the parent strain the progeny virus may possess an increased or restricted host range; in the former case it may be towards an increase in virulence. Thus, poliovirus strains of reduced virulence for monkeys are able to revert towards the more virulent parent type during the course of a single passage through the human gut. Whether such changes in the virus are due to the direct influence of the host is entirely unknown, and it does, therefore, seem necessary to know much more about the genetic stability of virus strains; in particular, the attenuated ones which, in the case of poliovirus, are becoming increasingly implicated in human prophylaxis.

Abstract

The behaviour of a variant of murine encephalomyocarditis (EMC) virus following growth in the mouse brain has been investigated. The variant strain is normally able to elicit destructive cytopathic changes in monolayer cultures of a solid form of the mouse sarcoma 180, but this capacity is lost following a single growth cycle in the mouse brain *in situ*. Furthermore, the ability to destroy sarcoma 180 cells is reacquired following a further single cycle of growth in cells of a second mouse tumour, the Krebs-2 ascites carcinoma. Evidence is presented which indicates that this phenomenon probably represents a modification of the virus directly induced through growth in the mouse brain. It is possible, although confirmation is needed on this point, that the host may exert its control through the virus genome.

Zusammenfassung

Der Autor untersuchte das Verhalten einer auf Mäusegehirn gezüchteten Variante des murinen Encephalomyocarditis-Virus. Dieser Stamm vermag in einschichtigen Kulturen von Sarcoma solidum 180 der Maus normalerweise destruktive cytopathische Veränderungen hervorzurufen, eine Fähigkeit, die jedoch nach einem einzigen Wachstumszyklus innerhalb eines Mäusegehirnes in situ vollkommen verschwindet. Durch einen weiteren einzigen Wachstumszyklus innerhalb der Zellen eines anderen Mäusetumors des Krebs-2-Asciteskarzinoms wird die Fähigkeit der Zerstörung von Sarcoma-180-Zellen erneut erworben. Es wird gezeigt, daß dieses Phänomen wahrscheinlich eine durch das Wachstum im Mäusegehirn direkt induzierte Modifikation des Virus darstellt. Möglicherweise übt der Wirt diesen Einfluß über das Virusgenom aus; der Beweis hierfür muß jedoch erst noch geliefert werden.

Résumé

L'auteur a examiné le comportement d'une variante du virus de l'encéphalomyocardite murine (EMC), après avoir été cultivée sur le cerveau de la souris. Cette souche est d'ordinaire capable de provoquer des modifications cytopathiques destructives dans une culture en couche unique de la forme solide du sarcome 180 de la souris, mais cette faculté est perdue après un passage seulement sur le cerveau de la souris in situ. D'autre part, cette capacité de pouvoir détruire les cellules du sarcome 180 est réintégrée après un passage seulement sur les cellules d'une autre tumeur de la souris, le carcinome Krebs-2 avec ascite. Les preuves avancées semblent démontrer que ce phénomène représente vraisemblablement une modification du virus, provoquée par le passage sur le cerveau de la souris. Il est possible, mais ceci demande encore confirmation, que le porteur exerce cet effet par l'intermédiaire des gènes du virus.

Riassunto

Viene studiato il comportamento di un ceppo variante del virus dell'encefalomiocardite del ratto, ceppo che venne coltivato nel cervello di ratto. Il ceppo variante è normalmente in grado di provocare effetti citopatogeni distruttivi in culture ad un solo strato di una forma solida del sarcoma del ratto 180; tale facoltà scompare tuttavia dopo un solo ciclo di crescita nel cervello di ratto in situ. Inoltre la capacità di distruggere le cellule del sarcoma 180 è ricuperata dopo un successivo ciclo singolo di crescita nelle cellule di un secondo tumore del ratto, il carcinoma Krebs-2 ascite. Si dimostra che molto probabilmente questo fenomeno rappresenta una modificazione del virus indotta direttamente dalla crescita nel cervello del ratto. E possibile – sebbene questo punto richieda ancora conferma – che l'ospite possa esercitare il suo controllo attraverso il genoma del virus.

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Discussion:

C. Hallauer (Bern): Mr. Hoskins, have you tested S180 virus for haemagglutinating activity?

J. M. Hoskins: Yes. When comparable brain suspensions of mice infected with S180 virus and mouse brain EMC virus are tested for sheep red blood cell agglutinating activity no differences can be detected.

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