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# TYPE C INFLUENZA VIRUS

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*Summary.* — According to the morphology, type and function of its structural components the segmented genome of type C influenza virus is similar to that of influenza viruses A and B. However, type C influenza virus differs from them by the reticular structure of virion surface, absence of the surface glycoprotein neuraminidase, the presence of unusual for *Orthomyxoviridae* cell receptors and the ability to induce an essentially moderate respiratory illness.

*Key words: type C influenza virus; morphological characteristics; biological properties*

During the influenza epidemic in 1947 a respiratory virus (strain 1233), antigenically unrelated to at that time known influenza viruses A and B was isolated (Taylor, 1949). In 1950, another strain (JJ) was isolated, which appeared antigenically related to the strain 1233 (Francis *et al.*, 1950). Based on the clinical, epidemiological and serological data, they were classified as type C influenza viruses (Francis *et al.*, 1950; Taylor, 1951).

The attempts to propagate type C viruses in cell culture had been long unsuccessful, significantly delaying the study of their biology. The methods of cultivation of type C influenza viruses have been mastered only recently using cells of variable origin (Labodinska, 1972; Chakraverty, 1974; Compans *et al.*, 1977; O'Callaghan *et al.*, 1977; Austin *et al.*, 1978; Meier-Ewert *et al.*, 1978; Nerome and Ishida, 1978; Petri *et al.*, 1979*a*, *b*, *c*) which provided more information presented in this study.

*Type C influenza virions*

Type C influenza virions are somewhat larger than A and B virions. They are morphologically heterogeneous. Virions from the allantoic fluid are generally roughly spherical, with a diameter of 75—100 nm, including the layer of surface spikes of about 10 nm. Virions grown in chick fibroblasts are predominantly filamentous and have the same diameter. The filamenents are about 7 μm long (Apostolov *et al.*, 1970; Compans *et al.*, 1977). A characteristic feature of laboratory strains of type C influenza virus is the arrangement of its spikes, which form a pattern of a hexagonal structure network

(Flewett and Apostolov, 1967; Compans *et al.*, 1977). It is hold together due to lateral interaction of glycoprotein subunits and remains intact on their removal from the membrane after protease-treatment (Herrler *et al.*, 1981). Type C virions are distinguished from type A and B virions by their hexagonal surface structure. According to Martin *et al.*, (1977) however, the marked hexagonal surface structure appears only after 406 passages in chick embryo allantoic fluid. These authors detected many filamentous particles among spherical virions at each passage.

*The genome structure*

The genome of type C influenza virus consists of 7 fragments of single--stranded (ss) RNA (Petri *et al.*, 1980). The nine RNA fragments detected in some experiments (Petri *et al.*, 1979*c*) might be due to the presence of interfering particles with additional RNA segments. The size of the segments varies from $0.23 \times 10^6$ to $0.94 \times 10^6$ daltons (Ritchey *et al.*, 1976; Petri *et al.*, 1979*a*, *b*, *c*). The total molecular mass of the genome of type C influenza virus ($5-6 \times 10^6$) is close to that of influenza A virus (Compans *et al.*, 1977).

Nucleotide composition of influenza C virus RNA is similar to that of A and B influenza viruses: G-C/A-U ratios for the strains C/CL/1167/54, A/PR/ /8/34 (H1N1) and B/Lee/40 are 1.38, 1.23 and 1.25, respectively (Ritchey *et al.*, 1976). Although hybridization analysis of viral RNA sequences with complementary DNA failed to reveal a significant homology between A, B and C influenza virus genomes (Elliott and Palese, 1980), highly conservative 3′-and 5′-terminal nucleotide sequences of the three types of influenza viruses (Desselberger *et al.*, 1980) seem to indicate to their common evolutionary origin.

Alike to other influenza viruses, genetic recombination is a property of type C influenza virus. However, the absence of genetic markes had long prevented the demonstration of recombinations between type C influenza viruses. Racaniello and Palese (1979) showed that recombination was possible with strains C/JJ/50 and C/JHG/66. All the known strains of influenza virus, except of C/JHG/66, form clear distinct plaques in MDCK cells. The plaques formed by C/JHG/66 virus are opaque, hardly distinguishable. Mixed infection of MDCK cells with C/JHG/66 and UV-inactivated C/JJ/50 viruses allowed to isolate clear plaques, which turned out to be formed by recombinants. Oligonucleotide analysis has shown that the recombinant clone has inherited most likely the fragments from C/JJ/50 virus. So far, it is not clear whether a recombination is possible between all RNA fragments of type C influenza virus.

Protein composition of influenza C virions is mainly similar to that of other type influenza virions. They consist of 6 structural polypeptides: nucleoprotein (NP), membrane protein (M), proteins P1 (PB2), P2 (PB1), P3 (PA) and the glycoprotein gp88 (Kendal, 1975; Meier-Ewert *et al.*, 1978; Herrler *et al.*, 1979; Herrler *et al.*, 1979; Petri *et al.*, 1979*a*, *b*, *c*, 1980). Triton X-100-treated virions are able to synthesize RNA in vitro (Meier-Ewert *et al.*, 1981*a*). RNA-polymerase activity similarly as in influenza A virus is

likely to be related to P proteins. In the course of virus replication, 2 nonstructural proteins could be detected ($NS_1$ and $NS_2$).

*Replication and protein synthesis*

The replication cycle of influenza C virus is longer than that of A or B influenza viruses (Petri *et al.*, 1979*c*). It was shown that addition of actinomycin D (0.3 μg/ml) into the medium of chick kidney cells infected with the strain C/JHB/I/66 decreased the yield of infectious particles 100-fold. Introduction of actinomycin D within the first 5 hr after infection entirely suppressed the synthesis of structural polypeptides gp88, NP and M, as well as of nonstructural proteins (Petri *et al.*, 1979*b*). The presence of actinomycin D at later intervals hardly affected protein synthesis. The actinomycin-sensitive phase of the replication cycle seems consistent with the period of sensitivity to the inhibitor of viral protein synthesis. UV-treatment of chick kidney cells significantly decreased the virus yield (Petri *et al.*, 1978*b*).

The optimal replication remperature of the type C influenza virus in chick embryos as well as in vitro is 32—33 °C (Kilbourne, 1975). Chemical mutagens allowed to obtain the first temperature-sensitive (ts) mutants of type C influenza virus (D'Amico *et al.*, 1980).

SDS-PAGE under reducing conditions of type C influenza viruses grown in chick embryos revelaled three glycoproteins with $M_r$ of about 88,000, 65,000 and 30,000 (gp88. gp65 and gp30) (Kendal, 1975; Compans *et al.*, 1977), while under nonreducing conditions only the polypeptide gp88 was found. The three types of influenza C virus glycoproteins differ from the influenza A virus (strain S/WSN) by the electrophoretic mobility of 3 main proteins (Compans *et al.*, 1977). It has been demonstrated that each of the three glycoproteins of influenza C virus contains N-acetylneuraminic (sialic) acid. Qualitative and quantitative differences have been established between the types of oligosaccharides of influenza A and C virus glycoproteins, grown in the same cell system (Nakamura *et al.*, 1979).

Glycoproteins gp65 and gp30 are cleavage products of gp88, which, in turn, is formed by cleavage of a larger precursor at later stages of virion „assembly" (Herrler *et al.*, 1979). The subunit gp65 is located at the N-terminal, while the subunit gp30 at the C-terminal of the gp88 polypeptide (Herrler *et al.*, 1981). Glycoproteins gp65 and gp30 are linked by disulphide bond and resemble $HA_1$ and $HA_2$ of influenza A virus (Meier-Ewert *et al.*, 1978). Cleavage of gp88 is likely to take place at the internal part of the molecule and requires at least 2 breaks (Herrler *et al.*, 1979) unlike to haemagglutinins of influenza A and B viruses, in which only one break is needed.

The cleavage of gp88 into subunits gp65 and gp30 is associated with a noticeable increase in virus infectivity, more significant than in influenza A or B viruses (Sugawara *et al.*, 1981). The virus infectivity can be increased by the cleavage of gp88 with trypsin or elastase. In such case, the virions induce cell fusion. Chymotrypsin and thermolysin fail to produce this effect (Sugawara *et al.*, 1981; Kitame *et al.*, 1982). The degree of proteolytic cleavage

of type C influenza virus glycoproteins depends on the host cell (Herrler *et al.*, 1979).

By analogy with influenza A and B viruses, it can be suggested that it is gp30, being a less glycosylated subunit, similarly to N-terminal of polypeptide $HA_2$ of A or B influenza viruses, contains conservative sequences, rich in hydrophobic residues (Herrler *et al.*, 1981): however, unlike these, it is devoid of N-terminal glycine. The absence of glycine at the N-terminal was also found in polypeptide F1 of paramyxoviruses (Gething *et al.*, 1978).

*Biological properties*

At 37 °C and acid pH (at optimal pH 5.0) type C influenza virus can cause haemolysis and intensive fusion of membranes of murine red blood cells (Ohuchi *et al.*, 1982). A very slight haemolysis of human and chick red blood cells under the same conditions is likely due to a much smaller number of receptors on their surface.

Type C influenza virus agglutinates red blood cells and elutes from them at room temperature. Haemagglutinating activity is most likely related to the glycoprotein gp88 and to its subunits (Ohuchi *et al.*, 1982). The presence of lipid is needed for manifesting this activity. According to Herrler *et al.* (1981), influenza C virus HA, separated from internal nonglycosylated proteins by Triton X-100, fails to induce haemagglutination. Haemagglutination is determined by glycoprotein purified by octylglycoside treatment, which does not affect the lipids. The haemagglutination reaction is not inhibited by soluble glycoproteins, active with respect to type A influenza viruses. Different strains of type C influenza viruses are distinguished by their ability to agglutinate the red blood cells of different animal species, to absorb to rat and fowl red blood cells, by the rate of their elution from the cells by the heat-resistance of their haemagglutinating activity (O'Callaghan *et al.*, 1977; Chakraverty, 1978; Govorkova *et al.*, 1983). These dissimilarities do not correlate with antigenic activity of the strains.

The elution of the virus from red blood cells is related to the receptor--destroying activity (RDA), specifically inherent in the virion; the activity does not disappear after purification of the virus by centrifugation in sucrose density gradient (Kendal, 1975). So far, it is unclear, whether RDA is related to one of the main glycoproteins or it is inherent in a minor, as yet unknown protein. The latter, however,is hardly likely, taking into account the small (7) number of RNA fragments and the amount of identified virus-specific proteins (8). The absence of RDA in purified glycoproteins can be determined by conformational changes in the process of their isolation (Herrler *et al.*, 1981).

Receptor-destroying activity of type C influenza virus has turned out ineffective with respet to influenza A and B virus receptors, i.e. influenza C viruses need their own receptors on the cell surface, different from those of influenza A and B viruses (Hirst, 1950; Kendal, 1975; Meier-Ewert *et al.*, 1978; Nakamura and Compans, 1978; O'Callaghan and Labat, 1983). Treatment with concetrated purified neuraminidase fails to inactivate them,

whereas the same treatment destroys influenza A and B virus receptors (Kendal, 1975). It has been found that influenza C virus cannot destroy the receptors, containing N-acetylneuraminic (sialic) acid. During the incubation of influenza C virus with substrates containing sialic acid, in particular with fetuin, the acid is not split off (Kendal, 1975). The lack of neuraminidase (NA) activity is related neither to thermostability of the enzyme, nor to the presence of neuraminic acid aldolase in the virion. Since influenza C virus can destroy its own receptors, the lack of NA activity cannot be attributed to a mutation responsible for the loss of activity of the given enzyme. This indicates that influenza C virus does not contain NA as confidently established in a number of experiments (Kendal, 1975; Nerome *et al.*, 1976; Compans *et al.*, 1977; Chakraverty, 1978). The virus destroys its rceptors probably by the help of another specific enzyme.

Direct evidence has been gained, that influenza C virions contain sialic acid as a component of glycoproteins (Nakamura *et al.*, 1979), and therefore, can serve as receptors for the agglutination with influenza A virus which results in the formation of mixed virus aggregates. The treatment with influenza C virus inhibits haemagglutinating activity of influenza A and B viruses. Pretreatment of influenza C virions with purified NA almost entirely deprives influenza C virus of its ability to inhibit the haemagglutination of influenza A and B viruses (Nerome *et al.*, 1976; Meier-Ewert *et al.*, 1978).

The virus envelope does not seem to contain host-cell structures (Nakamura *et al.*, 1979). The presence of some cell components in the purified virion can be probably accounted for by their high affinity to the virus. Comprehensive study of these components may bring us closer to the elucidation of the nature of virus receptor.

*Circulation in human population*

Epidemiological information about type C influenza is very scarce, as compared to influenza A and B. Epidemics of influenza C are unknown. Occasional epidemic outbreaks have been observed in groups, especially those of children (Minuse *et al.*, 1954; Styk, 1955; Zhdanov, 1959; Dykes *et al.*, 1980). Clinically, this disease does not differ from the light form of influenza A. In children, the disease can be more severe (Styk, 1955; Zhdanov, 1959). Because of the mild subclinical course, the virus is often isolated in association with other respiratory infections, in particular, with those induced by influenza A or B viruses.

Type C influenza viruses are ubiquitous. Their wide distribution in nature has been confirmed by the fact that HI antibodies to influenza C virus are present in rather high titres in serum of healthy adults (Andrews and McDonald, 1955; Jenning, 1968; Homma *et al.*, 1982). Homma *et al.* (1982) detected maternal antibodies to influenza C virus in infants, which disappeared essentially by the age of 6 months. Since the age of 1 year the percentage of seropositive individuals gradually increased reaching its maximum by 20—30 years. Similar data were obtained in the U.S.A. (Minuse *et al.*, 1954; Dykes

*et al.*, 1980), England (Andrews and McDonald, 1955), F.R.G. (Gerth *et al.*, 1975) and Jamaica (Jennings, 1968) indicating the epidemiological consistency in different regions. In England the proportion of adults seropositive to influenza C is about 80%, in the U.S.A. 60—90%. According to Japanese investigators, by 10 years of age essentially all children have antibodies to influenza C virus (Homma *et al.*, 1982).

The permanent circulation of type C influenza virus is confirmed by the maintenance of antibody titres in adults at the approximately same level. The decrease of the antibody titres in humans over 65 years reported by a number of authors (Minuse *et al.*, 1954) can be probably accounted for a lower activity of antibodies in elderly humans. According to Jennings (1968), the percentage of sera positive in HI-reaction increased with age even in this age group. Based on data obtained in Japan, Homma *et al.* (1982) consider that the man is exposed to infection by influenza C virus no less than once a year. The incidence of infection varies from year to year. Thus for instance, among population of the U.S. the incidence of influenza C infection in the period from autumn 1976 to autumn 1978 was estimated 7.8%, all cases falling on winter 1976—1977 (Troisi and Monto, 1981). The majority of patients were children of 5—9 years.

It was long thought that for influenza C virus, as well as for influenza B virus, the man was the only natural host. However, in 1983 it was reported that in China there were isolated 15 strains of influenza C virus from domestic pigs (Guo *et al.*, 1983). Cross-testing demonstrated the similarity between all strains and the human strain C/NJ/I/76. Seasonal activity and the possibility of virus transfer from animal to animal were observed in experimental infection. There is also indirect evidence for probable circulation of influenza virus among roes and sheep (Pfeil-Putzien and Meier-Ewert, 1980).

*Antigenic variability of influenza C virus*

Influenza C viruses seem to be genetically more stable, as compared to influenza A and B viruses (Palese, Young, 1982). Variations among influenza C viruses, in particular, slight antigenic differences between American and Japanese strains (Homma *et al.*, 1982), can be attributed to antigenic drift (Atsumi *et al.*, 1966; Pereira, 1969; Czekalowski and Prasad, 1973). Nevertheless, analysing 7 strains of influenza C virus in HI test, Chakraverty (1978) observed some antigenic variation, though less marked than in influenza A.

The results of Meier-Ewert *et al.* (1981*b*) obtained by the analysis in HI test of 5 strains of influenza C virus isolated in different regions of the world over 32 years, have shown that the antigenic variability of the C strains was lower as compared to isolates of influenza A virus (H3N2), isolated within 5 years period only (1968—1973). Oligonucleotide analysis of the recently (1966—1979) isolated strains C/JHG/I/66. C/JHB/67, C/Japan/64 and C/Bavaria/79 which were indistinguishable in HI test, allowed to detect only minimal dissimilarities between these strains in positions of 1—2 oligonucleotides. The dissimilarities (9 oligonucleotides) between these isolates and strain C/Taylor/1233, isolated in 1947, are more significant.

It is of interest that antibodies to strain C/Taylor/1233/47 occur in titres 1/40 and higher in high percentage of sera of all age groups, except children under 5, indicating recent activity of this virus (Chakraverty, 1978).

Thus, alongside with quite a number of common basic charecteristics of immunological types A and B influenza viruses, type C influenza virus has also several significant specific features concerning both, the pathogenesis of the related disease and the biology of the virus. Intensive molecular biological study of type C influenza virus will be helpful in providing its ultimate taxonomical identification. Presently available data suggest that type C influenza virus could be attributed to a probable separate genus of family *Orthomyxoviridae* (Matthews, 1982).

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