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Deadly "paleoviruses": a bioweapon Pandora's box?

We would like to comment on a recent study reporting the recreation of the 1918 influenza "paleovirus".[1] Beyond this scientific tour de force, these experiments raise huge ethical concerns.[2]

The medical justifications for such an exercise are open to debate. First, it is not certain that a better understanding of the virus' pathogenesis in a mouse model would be helpful for treating influenza infections in human beings. Second, the predicted efficacy of neuraminidase inhibitors and immunogenicity of H1N1-derived vaccines have already been demonstrated in recombinant influenza A viruses bearing the appropriate H1 and N1 genes.[3,4] Third, to have a pandemic flu vaccine available on the market in the shortest possible time, the European Agency for the Evaluation of Medicinal Products encourages manufacturers to work on a core dossier using a mock-up strain.[5] However, because of the danger that the virulent 1918 flu strain presents, the strain will never be distributed worldwide for such a purpose.

By contrast, the risks of such an exercise are real. First, it is astonishing that this virus has been manipulated in a biosafety level (BSL) 3 laboratory and not at a higher level of containment. Severe acute respiratory syndrome virus escapes from BSL3 labs were reported.[6] In addition, the H2N2 1957 pandemic strain was accidentally sent to 3700 reference laboratories in 2005.[7] The 1918 flu virus poses a high risk of life-threatening disease, with high spreading aerosol transmission and without enough therapeutic stocks of antivirals available for mass treatment, and thus should have been classified as a BSL4 agent, and even contained in a special high security facility—as in the case of variola virus[8]—until its expected destruction.

Furthermore, the reconstruction of the 1918 pandemic flu virus could be viewed as research with potential for dual use (ie, for civil and military gains) and could even be interpreted as an intentional reinforcement of a highly pathogenic virus, which is forbidden by the Biological Weapons Convention that was agreed in 1972.[9]

In addition, the complete publication of the influenza paleovirus genome paves the way for the replication of the work and could be hijacked by rogue states or terrorist organisations to produce biological weapons.

It is not the first time that controversy has followed potentially harmful experiments with viruses. Unsuccessful Russian attempts to dig up live variola virus from cadavers buried in the Siberian permafrost were reported.[10] After, the publication of data describing the increased pathogenicity of ectromelia virus expressing interleukin 4,[11] genetic engineering of interleukin 4-expressing vaccinia or cowpox viruses to check the efficiency of smallpox vaccines was forbidden by French ethical committees.

For transparency, and to prevent any suspicion of state interests in dual-use research activities, responsible scientists should now submit to, and comply with, ethical evaluation of their projects at a supranational level for compliance with arms control laws, using either existing international organisations—eg, WHO, the UN—or non-governmental international scientific societies—eg, the Nobel institution.

James King-Holmes/Science Photo Library

Lung tissue samples from 1918

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Cytotoxic T-cell immunity as a target for influenza vaccines

Current vaccines against influenza virus are predominantly "killed" vaccines, where the infectivity of a virus preparation is inactivated by chemical treatment.[1] They function almost exclusively by inducing virus-neutralising antibody. However, due to the frequent antigenic drift and shift of influenza viruses, antibody-based vaccines elicit limited or no protective immunity against newly arising strains—eg, H5N1. The possible beneficial effects of vaccination-induced cytotoxic T (Tc) cell-mediated immunity in ameliorating disease severity of influenza in human beings has been largely ignored. The Tc cell response, in combination with antibodies, is thought to be important in recovery from primary infections with influenza A strains.[2,3] Although memory Tc cells cannot provide sterile immunity or prevent infection with a heterologous virus, they may reduce disease severity by lowering the viral burden early after infection, as has been demonstrated in birds challenged with the H5N1 strain.[4] The antigenic determinants giving rise to Tc cell immunity are generally not subject to immune evasion by the virus and, in the case of influenza A viruses, are broadly cross-reactive.[5] Furthermore, Tc cell immunity is, at least in mice, long-lived.[6] Consequently, the ability to induce Tc cell memory is a highly desirable property of a vaccine candidate.

The generation of Tc cell immunity generally requires infection with a live virus. Intriguingly, γ-ray-inactivated (sterile) virus preparations retain the ability to prime Tc cell immunity, which protects against lethal challenge with heterologous influenza A strains.[7] This phenomenon has also been observed with alphaviruses and bunyaviruses.[8,9] Our original observation of the cross-protective value of γ-ray-inactivated influenza A virus has been confirmed by others, although the authors did not distinguish between the contribution of humoral and cellular immunity.[10,11] γ-ray irradiation inactivates virus infectivity by generating strand breaks in the viral genome and, by contrast with chemical treatment with formalin or α-propriolactone (currently used in the production of inactivated influenza virus vaccines), γ-ray irradiation has little impact on the antigenic structure and biological integrity of proteins.[12] Thus, the haemagglutinating activity of influenza virus is retained following γ-ray irradiation.[11] It has the further advantage of high penetration into biological materials.[12]

We envisage two (not exclusive) mechanisms for the efficient induction of Tc cell responses by γ-ray-inactivated virus. First, given that the functional domains of the viral surface proteins remain intact, efficient uptake into cells and uncoating of the γ-ray-irradiated virus is likely to take place. This uptake may provide sufficient viral antigen into the cytoplasm of antigen presenting cells for induction of Tc cell immunity. Second, abortive translation of fragmented genomic viral RNA may occur, allowing the priming of virus-specific Tc cell immunity. Defective ribosomal products (prematurely terminated and misfolded gene products) are considered a dominant source of viral antigen for MHC class I antigen presentation.[13] In addition to inducing virus-immune Tc cells, γ-ray-inactivated virus may also elicit improved humoral immunity, given that the antigenic structure of γ-irradiated virus remains largely intact.

Although induction of heterotypic immunity by γ-ray-inactivated virus has, so far, only been