most definitive evidence to date that recently formed, dissolved organic molecules are being mixed rapidly into the upper ocean. This means that labile DOC may be an important source of food deeper in the ocean than was previously thought, and that synthetic organic compounds also could penetrate rapidly and deeply into the sea.

Second, DOC in the deep ocean has a mean age of roughly 6,000 years (approximately twice the previously suggested value[7]), which shows how unreactive this material is and refines significantly the global carbon cycle. This more precise radiocarbon measurement indicates that organic molecules dissolved in the deep sea on average survive approximately six exposures to concentrated light and life at the ocean surface during global circulation and are even more refractory than previously indicated. In addition, it is now clear that the amount of carbon that must enter or leave the ocean DOC pool per year ($10^{14}$ grams of carbon; ref. 1) is much less than 1 per cent of the organic matter synthesized annually by marine plankton and only half the mass of DOC discharged into the ocean annually by rivers.

This result, together with the estimate that the amount of organic matter deposited in marine sediments does not exceed a quarter of the DOC input from rivers, indicates that most of the DOC entering the ocean from land, and most of it cycling within the ocean itself, must be destroyed by oxidation to $CO_2$. This implication, supported by the observation that the organic materials in all three reservoirs are compositionally dissimilar[4,7-10], is surprising because both riverine and deep-ocean DOC are relatively resistant to biodegraduation[10]. Ironically, Williams and Druffel's measurements[1] not only indicate that deep-ocean DOC is more refractory than previously thought, but also point towards an as-yet undiscovered process by which the sea eventually recycles this huge reservoir of recalcitrant organic molecules back to inorganic carbon. □

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## Virology

# Vector-directed interleukin expression and infection

Brigitte A. Askonas

THERE is a continued need to develop vaccines against serous infections that do not permit the use of attenuated infective particles. Purified components of pathogens are often poorly immunogenic and in most cases do not induce relevant responses of cytotoxic T cells. One approach to vaccine development is to insert genes encoding single viral antigens into vaccinia virus[1,2], and an interesting novel variant of this method has now been developed by Ramshaw and colleagues, who reported their results in Nature last month[3], and by Flexner et al., who report their results on page 259 of this issue[4].

In the standard approach[1,2], the inserted gene as well as vaccinia virus (VV) proteins are expressed by the infected cells in vivo or in vitro to mimic antigen presentation in a normal virus infection. The recombinant VV proteins are good inducers of antibodies and different T-cell responses, and are excellent tools to study the T-cell repertoire for viral components (for example, influenza or respiratory syncytial virus components; refs 5, 6). But vaccination using such constructs can lead to disseminated vaccinia infections in immunosuppressed hosts. In their new work, Ramshaw et al. and Flexner et al. insert the gene encoding human or murine interleukin-2 (IL-2) into vaccinia virus that can contain additional viral genes such as influenza haemagglutinin (HA) or nucleoprotein (NP). IL-2 amplifies T-cell responses and also acts on B cells of the immune system. Ramshaw et al.[3], using athymic nude mice as a model of an immunodeficient host, demonstrate that infection (local or intravenous) of IL-2/HA/VV causes clearance of vaccinia virus by day 11, whereas HA/VV leads to persistent vaccinia infection. In normal mice, inclusion of the IL-2 gene in recombinant VV does not influence the rate of virus clearance.

Flexner et al. in this issue[4] present more extensive data in a model of disseminated VV infection. Inbred athymic nude mice die within a few days following intraperitoneal infection with recombinant vaccinia virus constructs. Inclusion of the IL-2 gene in the vaccinia virus vector results in survival for more than 60 days. It is of particular interest that evidence for IL-2 production in host mice could be obtained even 6 days after infection. This raises the question as to which cell types are able to produce IL-2 following vaccination, because athymic mice have no functional T cells. It is possible that T-precursor cells are activated to differentiate into lymphokine-activated killer cells, with dramatic results: although vaccinia infection is not totally prevented, VV titres in affected tissues are strikingly low.

In normal host mice of the BALB/c strain, infection by recombinant vaccinia virus with inserted influenza HA or NP genes results in complete or partial protection, respectively, against lethal challenge with the homologous influenza virus. Co-expression of IL-2 in these vectors does not enhance partial protection nor does it overcome lack of protection by NP/VV in mice of the B10.A(5R) strain. The latter strain shows no NP-specific cytotoxic T cells as it expresses only NP non-responder class I alleles of the major histocompatibility complex[7].

The preliminary data of Flexner et al.[4] show variable effects on antiviral antibody formation by the IL-2/HA/VV vector, depending on the mouse strain and route of infection. The immunological effects of including the IL-2 gene in the recombinant vaccinia virus need to be studied, and particularly the long-term priming of B- and T-memory cells, the main aim of vaccination to protect against exposure to natural infection.

The concept of using recombinant vaccinia virus for clinical applications remains questionable, but it should be possible to develop additional vectors for the expression of desired growth or differentiation factors for possible clinical use. The observations by Flexner et al., that IL-2 is produced for several days in vivo, is encouraging, because IL-2 and many interleukins or interferon-$\gamma$ have very short half-lives when administered directly in vivo. Thus, continued production of a growth factor in vivo may modulate responses in severe immune disorders. The next step is to analyse the immunological effects induced by co-expression of IL-2 in recombinant vaccinia in athymic or other immunodeficient or immunosuppressed hosts. □

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