encode products involved in controlling the cell division cycle or cancer progression. This supports the hypothesis that disruption of these genes by proviral insertion promotes growth or persistence of the host cell (13). Maldarelli *et al.* and Wagner *et al.* identify the host gene encoding the basic leucine zipper transcription factor 2 (BACH2) as a frequent site of HIV integration. BACH2 is a transcriptional regulator that controls CD4⁺ T cell senescence and cytokine homeostasis (14). Thus, the new findings suggest a link between the persistence of latently infected cells and proviral integration in genes related to cell proliferation and cancer.

"... findings suggest a link between the persistence of latently infected cells and proviral integration in genes related to cell proliferation ..."

Further experiments should strengthen these ideas. There is as yet no molecular evidence that such integrations of HIV-1 lead directly to the proliferation of latently infected cells, but it should be possible to engineer viral integration into specific sites of the host cell genome and demonstrate cell proliferation. In addition, there is as yet no proof that the proviruses encode for replication-competent HIV genomes. Maldarelli et al. did carry out the Herculean task of single-genome amplification and sequencing tiny amounts of HIV RNA recovered from the plasma of some patients studied. This verified a close similarity of circulating viral envelope sequences to those found in integrated proviral genomes in expanded clones. However, like prior studies (11), such sequencing is limited to a small portion of the HIV genome, and cannot eliminate the possibility of inactivating mutations in other parts of the proviral genome, making the virus incompetent to replicate. Given that the cells harboring quiescent HIV-1 are only a tiny minority of the total CD4+ T cell population examined by Maldarelli et al. or Wagner et al., and that years of ART have allowed for years of selection, alternative interpretations of the data are possible. For example, it is not yet ruled out that the expanded T cell clones detected could be expanding for other reasons (e.g., in response to stimulation by a specific antigen). There may be other reasons for preferential viral integration into the genes described as well. There may also be "survivor bias" in the detection of replication-incompetent genomes.

Indeed, given the model, it is puzzling that no increase in the total number of HIV DNA-positive cells was observed.

The findings of Maldarelli et al. and Wagner et al. raise additional issues. Lentiviral vectors are used extensively in therapeutic gene transfer, so monitoring for related events of proliferation-promoting integration with these vectors during gene therapy is important. Indeed, clonal expansion was observed in the case of a lentiviral-based gene correction of the blood disorder betathalassemia in which integration at the site of a proto-oncogene increased cell proliferation (15). In this case, the host gene encoding high-mobility group AT-hook 2 (HMGA2) produced a truncated mRNA due to vector insertion within the gene. HMGA2 is a transcription regulatory protein. The truncated mRNA removed a binding site for a microRNA that negatively controls HMGA2 expression. The result was increased accumulation of HMG2A mRNA and protein. HMGA2 was not an integration target in the cells studied by Maldarelli et al. or Wagner et al., raising questions about the differences between latent HIV infections and beta-thalassemia gene therapy.

Both studies also mention the concern that HIV integration could contribute to the development of cancers by insertional mutagenesis. However most HIV-related malignancies are not T cell cancers, and even most HIV-related lymphomas are of B cell origin. HIV cancers are not thought to harbor integrated HIV DNA, although this could be reinvestigated.

If blocking proliferation of latently infected cells proves to be necessary, it will complicate efforts to clear the latent reservoir. But clearance of this reservoir is crucial to achieve a cure of HIV infection. ■

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Microplastics in the seas

Concern is rising about widespread contamination of the marine environment by microplastics

By Kara Lavender Law¹ and Richard C. Thompson²

lastic debris in the marine environment is more than just an unsightly problem. Images of beach litter and large floating debris may first come to mind, but much recent concern about plastic pollution has focused on microplastic particles too small to be easily detected by eye (see the figure). Microplastics are likely the most numerically abundant items of plastic debris in the ocean today, and quantities will inevitably increase, in part because large, single plastic items ultimately degrade into millions of microplastic pieces. Microplastics are of environmental concern because their size (millimeters or smaller) renders them accessible to a wide range of organisms at least as small as zooplankton, with potential for physical and toxicological harm.

Since its introduction in the published literature in 2004 (1), the term microplastic has been widely used to describe plastic fragments in the marine environment. Typically considered to be smaller than 5 mm in diameter, microplastics are ill defined by size, with ranges that vary between studies. In most open-water studies, microplastics are measured with plankton nets, and particles smaller than the net mesh (typically ~0.33 mm) can evade capture. In marine sediment, bulk sampling can retain particles of all sizes; however, efficient identification is a serious challenge in quantifying microplastic loads, especially with decreasing size. Spectroscopic analysis has identified individual fragments of common plastics as small as 20 μm in diameter.

The sources of microplastic include fragmentation of larger items entering by rivers, runoff, tides, winds, and catastrophic events, together with at-sea sources, including lost cargo and fishing and aquaculture gear. There are also direct inputs of microplastics as micrometer-sized particles, such as cosmetic beads and clothing fibers

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that pass through wastewater treatment into the environment. Although the sources are well known, knowledge of their relative contribution and geographic distribution is limited.

Once in the ocean, floating microplastics are transported passively by complex twoand three-dimensional physical flows, resulting in very large variability in surface concentrations that makes detection of long-term trends difficult even in the heavily sampled western North Atlantic (2) and eastern North Pacific Oceans (3). Oceanographic models [including (4)] and environmental observations find very high concentrations (up to 10⁶ pieces km⁻²) of floating microplastic in subtropical ocean gyres, far from land-based sources. In these gyres, converging surface currents trap and retain floating debris. Similarly high concentrations have been observed in enclosed basins such as the Mediterranean Sea (5).

In coastal sediments around the world, microplastics also appear to be ubiquitous, with quantities typically ranging from 2 to 30 particles per 250 ml of sediment (6). Arctic sea ice is the most recently identified reservoir of microplastics (7). With the exception of localized spills, the relationship between microplastic concentration and its sources is poorly understood because of complex transport mechanisms and unknown fragmentation rates.

Because of their size, microplastics may have different effects from larger items of debris. For example, floating microplastics in open ocean gyres provide habitats for diverse communities of microorganisms, with assemblages that differ from those in surrounding seawater and that vary with polymer type (8). Furthermore, microplastics may be ingested by many diverse organisms, and some animals such as mussels can retain particles after ingestion (9); ingestion of small quantities of microplastics can disrupt physiological processes in marine worms, compromising their ability to store energy (10).

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Microplastics everywhere. Microplastics collected from seawater, shorelines, or marine sediments are typically defined as particles with a diameter of 5 mm or less. Sources include larger deteriorating plastic items, as well as microbeads used in the cosmetics industry. The microplastics in the photo were collected in the North Pacific subtropical gyre with a surface plankton net.

Plastic debris readily accumulates harmful chemicals such as dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs) from seawater worldwide (11), increasing their concentration by orders of magnitude. This process is reversible, with microplastics releasing contaminants upon ingestion (12) and laboratory evidence of uptake in marine worms (13) and fish (14). Transfer depends on the polymer, contaminant, and conditions in the organism, particularly pH and temperature. These interactions are specific but not yet fully predictable (15). There is also concern that plastic debris might release monomers and potentially toxic additives such as plasticizers, flame retardants, and antimicrobial agents that are incorporated into plastics during manufacture.

This emerging evidence of harm comes primarily from laboratory studies. It is unclear whether microplastics in the environment transport chemicals to biota in concentrations high enough to cause substantial damage. The potential for harm from microplastics could increase with decreasing particle size, but size distributions and generation and degradation rates are essentially unknown, and the resulting effects on natural populations are difficult to ascertain. Nevertheless, ingestion of microplastics by mammals, fish, birds, and invertebrates is now well documented. Although quantities can be low, the widespread incidence in some natural populations together with evidence of potentially harmful effects is cause for concern.

Major questions remain about the risks from microplastics to marine organisms and ecosystems, as well as to food safety and public health. Research is urgently needed on the behavior of different polymers in the environment, including fragmentation, chemical release, degradation, transport, and accumulation; the rate at which organisms encounter microplastics, based on particle size and degradation time; and the physical, chemical, and interactive risks to organisms from these encounters, including possible magnification with increasing trophic level (biomagnification).

Given the concerns over microplastics, the temptation

may be to "clean up the mess," but substantial removal of microplastic debris from the environment is not feasible. Identification and elimination of some of the major inputs of plastic waste is a more promising route, as is reduced consumption and the recognition of plastic waste as a resource. With the rapidly increasing human population, the need for greater resource efficiency could have a secondary benefit in reducing the quantities of debris entering the environment. ■

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