conservation applications, for example, regenerative energy capture during the stopping of a hybrid city transit bus, may require more than 1 million charge/discharge cycles during their operational life. A storage system can be replaced several times or "supersized" to reduce the depth of discharge in each cycle and increase cycle life, practices commonly used for battery technologies. However, both approaches mean that the storage system will have higher cost. ECs, by contrast, rely on physical rather than chemical storage and do not suffer from limitations of cycle life. They effectively can be "right-sized" at the start and last the entire life of a given application. In short, cycle life can impart great value to an energy storage technology.

Storage system shape is another factor that may have high value in some applications. Energy density advantages generally can be best achieved with shapes approaching a cube, whereas power density advantages can be best achieved with thin, large-area designs. A given energy storage technology may lend itself to either one of these extremes. Besides offering power advantages, very thin energy storage devices may enable a broad range of new applications. If these devices have mechanical flexibility, then there are even more potential applications. One example is a fabric EC that is charged by piezoelectric transducers that harvest and store body-movement energy. This would allow the creation of "smart" garments for making fashion statements or to power flexible electronics that may be embedded in a military uniform (see the figure). Other examples include energy storage for use in camouflage, for car interiors, and to make electronic wall paper.

An interesting feature of the conversion process reported by El-Kady *et al*. is that graphene patterns can be "laser scribed" directly onto very thin graphene oxide deposits (*10*). As one example, interdigitated planar structures of graphene can be created, which after receiving an electrolyte overcoat become planar ECs. This route for producing extremely thin and highly flexible energy storage structures is quite exciting and shows great promise.

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AIDS/HIV

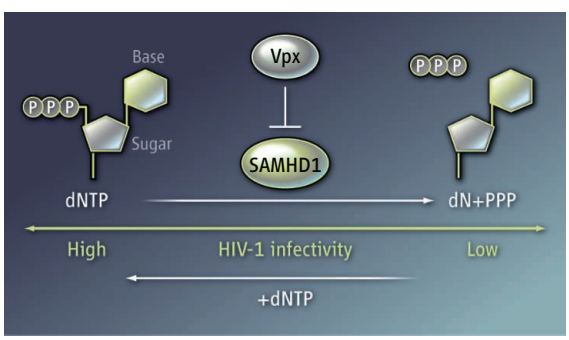
HIV Interplay with SAMHD1

A protein that controls nucleic acid metabolism affects the balance between HIV infection and immune responses.

Torsten Schaller, Caroline Goujon, Michael H. Malim

New insights into the complex interplay between human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) and their primate hosts are being gleaned from studies of viral accessory proteins. It is now apparent that these proteins (which are often dispensable for replication in cell culture) frequently antagonize host innate and adaptive immune responses. In several cases, accessory proteins repress specific host cell inhibitors of infection known as restriction factors (*1*). That the genes encoding restriction factors have been subjected to Darwinian selection pressure suggests the evolutionary importance of their function (*2*, *3*). These general themes have recently been reprised through studies on the Vpx accessory protein of HIV-2/SIV_{smm} and the discovery of its host cell target called sterile alpha motif (SAM) and histidine/aspartic acid (HD) domain–containing protein 1 (SAMHD1).

Cells of myeloid origin (including dendritic cells and monocytes) are often poorly permissive for HIV-1 infection compared to activated $CD4^+$ T cells. HIV-1 infectivity can be increased by introduction of the Vpx protein of HIV-2 and some SIV strains (*4*). Similarly, Vpx-deficient strains of HIV-2/SIV_{smm} are much less infectious in myeloid cells than wild-type viruses. The Vpx-mediated enhancement of infectivity correlates with the increased accumulation of viral cDNAs (*4*), key intermediates in the replication of retroviruses.



Restricting HIV infection. SAMHD1 regulates dNTP concentrations and HIV-1 infection in myeloid cells. The viral accessory protein Vpx blocks SAMHD1, targeting it for destruction by proteasomes. PPP, triphosphate

The *vpx* gene most likely originated by recombination or duplication of *vpr*, a related gene in primate lentiviruses whose contribution to HIV-1 replication and pathogenesis remains uncertain. Vpx and Vpr engage cellular ubiquitin ligase complexes (which modify proteins, among other activities, for destruction by proteasome), providing the rationale for seeking cellular Vpx/Vpr binding partners as candidate regulators of HIV and SIV replication. Last year, SAMHD1 was defined as a target for Vpx: As predicted, SAMHD1 is degraded by the proteasome in the presence of Vpx, and its depletion from myeloid cells promotes more efficient HIV-1 infection (*5*, *6*).

More recently, in vitro enzymatic assays demonstrated that the dimeric SAMHD1 core domain has 2′-deoxyguanosine 5′-triphosphate (dGTP)–stimulated deoxynucleoside triphosphate (dNTP) triphosphohydrolase activity and converts dNTPs to deoxynucleotides (dNs) and triphosphate (*7*, *8*). By showing that Vpx expression or SAMHD1 depletion each increases the amount of dNTPs in macrophages, and that the extracellular addition of dNs to macrophages enhances HIV-1 infection (*9*), a model has emerged in which SAMHD1 inhibits HIV and SIV infection of myeloid cells by elimi-

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nating the dNTP substrates required for viral cDNA production (a step in the genome replication process involving reverse transcription) (see the figure).

The assignment of SAMHD1 as a viral restriction factor is not the first time this protein has been associated with innate immunity. Mutations in *SAMHD1* can cause Aicardi-Goutières syndrome (AGS), a rare autoimmune disease resembling congenital infections, in which excessive production of the cytokine interferon-α (IFN-α) and detrimental immune activation are prominent. Importantly, monocytes of AGS patients that harbor nonfunctional SAMHD1 protein are susceptible to infection by HIV-1 ex vivo, whereas cells from healthy donors are not (*10*).

In addition to *SAMHD1*, mutations in four other genes have been linked to AGS: *TREX1*, *RNAseH2A*, *RNAseH2B*, and *RNAseH2C*. Intriguingly, two of these factors (TREX1 and RNAseH2A) stimulate HIV-1 replication, the opposite of SAMHD1's effect in myeloid cells (*11*, *12*). TREX1, a 3′→5′ deoxyribonuclease (DNase) involved in removing endogenous retrotransposon-derived cDNA, may also degrade surplus HIV-1 cDNAs thereby averting an IFN response and the induced expression of antiviral genes (*11*). Elucidating the role of SAMHD1 in dNTP metabolism and viral cDNA synthesis provokes questions regarding the natural functions of SAMHD1, and the molecular pathogenesis of AGS. For instance, do inactivating *SAMHD1* mutations lead to abnormal levels of cDNAs encoded by retroelements (or other templates), as observed in the absence of TREX1? If this is the case, is this confined to myeloid and/or postmitotic cells, and is elevated dNTP concentration the underlying mechanism? Importantly, there are AGS patients who do not have mutations in *SAMHD1*, *TREX1*, *RNAseH2A*, *RNAseH2B*, or *RNAseH2C*: This suggests that additional protein(s) acting at the interface of cellular nucleic acid metabolism and innate immunity may affect HIV-1 biology.

Unlike the Vpr proteins of some SIVs (*2*), HIV-1 Vpr does not antagonize SAMHD1, at least for the strains studied so far. One possibility is that other viral elements may compensate and perform this function. Alternatively, infections of myeloid cells may have a limited role in the spread and pathogenesis of pandemic HIV-1 strains, potentially because these viruses replicate efficiently in $CD4^+$ T cells. Indeed, forcing HIV-1 to infect dendritic cells by providing Vpx in *trans* triggers an IFN response (*13*), perhaps suggesting that SAMHD1 may promote overall replication in vivo by perturbing aspects of the human immune response to HIV-1. Possibly corroborating this notion are observations that HIV-2, whose Vpx protein inhibits SAMHD1, is generally less pathogenic than HIV-1; likewise, SIV_{mnd1} seems to be a more pathogenic virus than SIV_{mnd2}, and only SIV_{mnd2} encodes a Vpx protein that antagonizes SAMHD1. Further analyses will be needed to test these ideas, and it will be interesting to examine the N-, O-, and P-groups of HIV-1 that have not efficiently established themselves in humans. Moreover, nonprimate lentiviruses that preferentially infect myeloid cells, such as maedi-visna or caprine arthritis–encephalitis virus, do not encode obvious Vpx/Vpr proteins: Have these viruses evolved other ways to counteract SAMHD1?

Demonstrating that SAMHD1 inhibits HIV-1 infection at an early step of replication after entry of virus into the cell reinforces the view that this phase of the virus life-cycle is exquisitely vulnerable to suppression by host restriction factors. When operative, the actions of restriction factors, including apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3 (APOBEC3) proteins, and tripartite motif–containing protein 5 alpha (TRIM5α), are also manifested as the inability of HIV and SIV to produce functional reverse transcripts (*1*). However, in contrast to APOBEC3 and TRIM5α, where pharmacologic induction of their antiviral functions are desirable, the enhancement of SAMHD1 action could be contraindicated because this restriction factor may impede the elaboration of effective innate and adaptive immunity. On the other hand, there is the exciting prospect that judicious blockade of SAMHD1 (or TREX1) may evoke improved immune responses, and that agents with this property could be developed as a new class of antiretroviral drugs.

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CHEMISTRY

Getting Molecular Electrons into Motion

Markus Gühr

A method based on correlated measurements of electrons and ions shows that electrons of large molecules can be set into motion by strong laser fields.

The valence electrons of a molecule are responsible for making chemical bonds, and their interactions with one another determine whether processes such as electron transfer between molecular groups in light harvesting occur. Electrons are so light that their motion within molecules is described on time scales of attoseconds (1 as = 10^{-18} s). The promise of attoscience is to use ultrafast laser pulses to excite processes in atoms and molecules that occur on these time scales and thereby probe electron interactions. So far, attosecond time-resolved experiments have only been accomplished for isolated atoms and very small molecules. On page 1336 of this issue, Boguslavskiy *et al.* (*1*) now show that electrons of larger and more complex molecules can also be set into attosecond motion through ionization processes induced with strong electric fields generated by laser pulses.

Attosecond time-resolved experiments are done in a perturb-and-observe manner: An initial laser pulse takes one electron out of the molecule (ionization), and a second laser pulse probes the reaction of the remaining electrons to that loss. Boguslavskiy *et al.* concentrate on the ionization step to set the electrons into motion. They used an infrared laser

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