in a terminology that, at this stage, seems to be deeply rooted in practice. A drift from an original meaning of a concept is common in science, representing adaptability of the original ideal definition to realistic restrictions that emerge when put to practice.

We arrive at our final question: Is the geometry of nature fractal? Several key processes involving equilibrium-critical phenomena (in magnets, liquids, percolations, and phase transitions, for example) and some nonequilibrium growth models (such as aggregation) are backed by intrinsically scale-free theories and lead therefore to power-law scaling behavior on all scales. However, the majority of the data that was interpreted in terms of fractality in the surveyed *Physical Review* journals does not seem to be linked (at least in an obvious way) to existing models and, in fact, does not have theoretical backing. Most of the data represent results from nonequilibrium processes. The common situation is this: An experimentalist performs a resolution analysis and finds a limited-range power law with a value of D smaller than the embedding dimension. Without necessarily resorting to special underlying mechanistic arguments, the experimentalist then often chooses to label the object for which she or he finds this power law a "fractal." This is the fractal geometry of nature.

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VIROLOGY

Even Viruses Can Learn to Cope with Stress

Grant McFadden

More than 5 years ago, a commentary in *Science* announced that viruses engage in "Star Wars" strategies against the immune system. Some of the viral invaders make receptors (viroceptors) that imitate normal cellular receptors and so can sequester and inactivate molecules that the immune system tries to use to fight the virus (*1*). Since that time, numerous other viral subterfuges for evading or subverting host defense mechanisms have been exposed (*2–4*), and viruses now are known to use an extraordinary spectrum of proteins to target immune molecules of the host cells. One particularly effective host defense is for the infected cell to self-destruct by programmed cell death, and in fact, cell death is triggered by infection with a wide variety of viruses (*5*). In response some viruses use specific proteins to suppress the cell suicide that would normally curtail the infection (*5*, *6*). Other classes of intracellular responses have elicited their own array of viral countermeasures as well (see the table). To this growing list, we can now add reactive oxidative species (oxidative stress) as a worthy target for viral inhibition. On page 102 of this issue, Shisler *et al.* (*7*) report that molluscum contagiosum virus (MCV) encodes a novel anti-oxidant protein (MC066L) that functions as a scavenger of reactive oxygen metabolites and protects cells from ultraviolet- or peroxide-induced damage. Equally intriguing, MC066L is also the first bona fide selenoprotein expressed by a virus.

The story began last year when B. Moss and his colleagues at the National Institutes of Health sequenced the genome of MCV, a human poxvirus that causes benign tumor-like skin lesions that can become problematic in immunosuppressed patients, including those with AIDS (*8*). Given the proclivity of the larger DNA viruses to engage in widespread gene piracy, it was expected that MCV would encode a variety of host-derived proteins. But what was most unexpected was how extraordinarily different the nonessential gene repertoire of MCV was from those of previously sequenced poxviruses, particularly vaccinia and variola (*9*). Not only was MCV bereft of most of the better studied immunoregulators, such as the secreted viroceptors that precipitated the original Star Wars analogy, but 77 of the 182 predicted MCV open reading frames had no obvious viral counterparts at all. Moreover, some of these novel candidates were predicted to antagonize immune responses on the basis of their sequence similarities to other known host genes, and this list included such luminaries as a major histocompatability complex–1 heavy chain homolog, a β-chemokine, and two related death effector domain–containing proteins (*8*, *9*). Particularly notable among these host-derived candidates was a predicted

Intracellular Defense Strategies by Viruses

Host cell anti-virus mechanisms	Virus counter-strategies	Virus examples
Apoptosis (cell suicide)	Homologs of bcl-2	**BHRF1** Epstein-Barr virus; **E1B/19K** adenovirus
	Caspase inhibitors	**crmA** cowpox virus; **p35** baculovirus
	Death effector	**MC159** molluscum contagiosum virus; **E8** equine herpes-2
	Serpins	**SPI-1** rabbitpox virus
	p53 binding proteins	**T-Ag** simian virus 40; **E1B/55K** adenoviru
	Rb binding proteins	**E7** papilloma virus; **IE2** cytomegalovirus
	Ankyrin-repeat host range proteins	**CHOhr** cowpox virus; **M-T5** myxoma virus
	ER-retained protein	**M-T4** myxoma virus
Intracellular signaling	PKR inhibition	**E3L, K3L** vaccinia virus
	Tyrosine kinase modulation	**Tip** herpesvirus saimiri **LMP-2A** Epstein-Barr virus
	Receptor mimicry	**M-T2** myxoma virus
	Signal transducer protein	**LMP-1** Epstein-Barr virus; **IAP** baculovirus
Viral antigen presentation	MHC-1 suppression	**E3/19K** adenovirus; **US11** cytomegalovirus
	TAP inhibition	**ICP47** herpes simplex virus; **US6** cytomegalovirus
Oxidative stress response	**Anti-oxidant selenoprotein**	**MCO66L (molluscum contagiosum virus)**

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gene product (MC066L) that was 74% identical to human glutathione peroxidase, a major cellular scavenger of reactive and toxic oxygen metabolites and one of the few known enzymes that requires covalently bound selenium as a cofactor.

The importance of this remarkable sequence similarity was further underscored by the discovery of a predicted stem-loop selenocysteine insertion sequence (SECIS) motif within the 3′ untranslated region of MC066L. Hairpin SECIS structures in mRNA allow cellular translational machinery that makes the protein to read through an internal UGA codon that would ordinarily stop translation. By inserting a specific selenocysteine suppressor tRNA instead of stopping when the UGA occurs, the ribosome continues to the next downstream stop to make the full-length selenoprotein. Similar sequence motifs have been reported for other viruses (*10*), notably human immunodeficiency virus–1 (HIV-1) and Ebola, but actual synthesis of viral selenoproteins had never been demonstrated. The MCV gene has an in-frame UGA at codon 64, and the incorporation of ^{75}Se into expressed 30-kD MC066L protein (*7*) supported the contention that at least some of the translated viral protein resulted from readthrough all the way to the downstream stop at codon 221. Furthermore, transfection experiments in HeLa cells and immortalized HaCaT keratinocytes revealed that MC066L expression protects against cell death induced by ultraviolet treatment or hydrogen peroxide but not by either tumor necrosis factor ligand or FAS-antibody, which act by triggering programmed cell death (*7*).

So what does glutathione peroxidase actually do for MCV? Unfortunately, MCV does not grow in cultured cells, and no animal models exist to test the effects of gene deletions on viral pathogenesis. Nevertheless, certain predictions can be made from what is known about the glutathione peroxidase–reductase cycle that couples peroxide and hydroxyl radical detoxification with the oxidation of reduced glutathione. Along with catalase and superoxide dismutase, glutathione peroxidase is a major protectant against reactive oxygen metabolites, which can not only damage viral macromolecules directly, but are also potent inducers of apoptosis by virtue of their ability to trigger mitochondrial membrane permeability transitions (*11*, *12*). In fact, reduced glutathione peroxidase activity caused by selenium deficiency is associated with increased susceptibility to apoptosis (*13*) and excessive oxidant-induced cellular damage in HIV-1 infection (*14*).

Shisler *et al.* (*7*) speculate that MC066L might protect MCV—an exclusively dermatrophic virus that replicates only in suprabasal layers of differentiating keratinocytes—from intracellular peroxide toxicity or free radicals generated directly by ultraviolet light exposure. However, there is another possibility that is difficult to dismiss—that MC066L also serves as an intracellular protective mechanism against the toxic effects of diffused peroxide produced from dermal phagocytic leukocytes (*15*). Before regression, MCV lesions contain few inflammatory cells, although some tissue phagocytes may patrol below the basement membrane. Because hydrogen peroxide released during an oxidative burst by activated phagocytic cells can readily penetrate membrane barriers and produce damaging hydroxyl radicals within infected target cells, even small amounts could be significantly toxic for the relatively slow-growing MCV, particularly because virus replication likely represses the expression of all cellular anti-oxidant genes. Thus, in a manner that is analogous to how some tumor cells have hijacked the glutathione redox system to protect against peroxide cytotoxicity (*16*), active viral glutathione peroxidase could be the most effective countermeasure against phagocyte-derived peroxide for a virus-infected cell.

Taken in this light, it seems appropriate that the biological treasure-trove of the poxvirus family has not only introduced us to the extracellular Star Wars technologies, but is also the first to teach us that viruses can be equally adept at the kind of intracellular hand-to-hand combat normally associated with ground-level warfare as well.

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17. I thank the members of my laboratory for helpful discussions, B. Moss for communicating unpublished information, and M. Barry for constructive comments.

NOTE BENE: OPTICAL PHYSICS

Sweeping the Field

The payoffs for inventing new ways to compress pulses of light are substantial: data flow faster through optical fibers and all-optical switches for next-generation computers. But cleverness has a price, in that most methods require high nonlinearity—the ability of light to change the optical properties of the material it passes through—which in turn demands high optical power. One way out is to use a second optical pump wave to induce the nonlinearity and allow the weaker signal pulse to exploit it (*1*). Recently, Broderick *et al.* of the University of Southampton have demonstrated an elegant technique for molding short pulses—the "optical pushbroom" effect (*2*). They start with a useful device called a fiber Bragg grating, a resonant structure in which a lot of optical energy can be stored by a low-power continuous beam. Then they introduce a powerful but relatively long pulse that traverses the grating. As it passes through the grating, the strong pulse puts a slight "chirp" or frequency shift on the continuous beam, with some parts made higher and some lower pitch. But the Bragg grating itself is a highly dispersive medium, so the high frequency parts speed up and overtake the low frequency parts, causing a drastic pile-up of optical energy. In effect, the long pump pulse gathers up probe energy in a short spike on its leading edge, much as a broom piles up debris as it is swept along the floor. The result: a purely optical conversion of easily crafted long pulses into useful shorter ones.

–David Voss

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