# Shattering the Genome

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*The following is a slight revision of one of the recent articles in a growing collection of news updates and commentaries that are part of our "Toward a Biology Worthy of Life" project. This article and all others in the collection are available at RediscoveringLife.org.*

A dose of ionizing radiation equal to 10 grays (a measure of absorbed radiation) is lethal to the human body. Most bacteria cannot survive 200 grays. But then there is the bacterium known as *Deinococcus radiodurans*: it can endure over 17,000 grays and do quite well, thank you. Never mind that its genome is thoroughly shattered by the assault.

Here's what happens. Ionizing radiation can damage DNA in various ways, perhaps worst of all by causing double-strand breaks. These are breaks across both strands of the DNA double helix. The familiar bacterium, *E. coli,* not at all untypically, dies when it suffers about four double-strand breaks per each of its four-to-eight circular DNA molecules. *Deinococcus radiodurans,* by contrast, can survive over a thousand double-strand breaks. This means that it continues life after its genome is broken into hundreds of small fragments. It does so by proceeding to put its genome back together again when living conditions improve — a daunting task, to say the least.

*Deinococcus radiodurans* is one of a small class of single-celled organisms with extreme radiation tolerance. Actually, it tolerates various other extreme conditions as well — some of which, such as dessication, likewise reduce its DNA to genomic shards. It can, for example, survive in a waterless desert for years. When moistened again — perhaps after winds have lifted it in a cloud of dust from the Sahara, high into the atmosphere (where it is exposed to damaging ultraviolet radiation 100 to 1000 times that on earth's surface), and across the Atlantic ocean to the South American jungles. *D. radiodurans* can be found on Antarctic ice, on dry frozen marble, and in the farthest depths of the sea.

Biologists have been intrigued by this peculiar survivor (along with some of its kin) for several decades, and of late they have clarified its story considerably. A central feature of that story is striking, because it points toward a truth about organisms in general, not merely those with extreme survival capabilities. The key finding is this: damage to DNA is not, in the most direct sense, what proves lethal about radiation. The primary issue, instead, is damage to proteins. As long as its proteins remain functional, a cell can reassemble even a badly fractured genome; but with damaged proteins, a cell is done for, with or without a working genome.

The secret of *D. radiodurans* lies not in an especially stable genome, and not even in highly original proteins for DNA break repair. Rather, the bacterium employs a number of strategies for preserving its rather commonplace "proteome", or total supply of proteins. These strategies include (1) preventing the oxidative damage that results from radiation, a goal it achieves in good part by means of an especially rich supply of antioxidants; (2) eliminating, before they can cause mischief, any proteins that do get damaged, while recyling their constituents; (3) scavenging amino acids and peptides (protein components) from the local environment, a capability that, together with the recycling, (4) supports new synthesis of any proteins that need replenishing.

The proteome thus preserved is then able to go about the task of reconstructing a shattered genome — a task whose complexity at the molecular level is stunning, but one that nevertheless goes on in the cells of all organisms. What distinguishes *D. radiodurans* is its ability to carry out this task to an exceptional degree by maintaining its store of proteins intact under extreme duress.

In sum, according to Anita Krisko and Miroslav Radman, researchers at the Mediterranean Institute for Life Sciences who have been studying *D. radiodurans,* "biological responses to genomic insults depend primarily on the integrity of the proteome ... This conclusion is the consequence of the fact that dedicated proteins repair DNA, and not vice versa." Moreover, "this paradigm is fundamental in its obviousness (no living cell can function correctly with an oxidized proteome) and, if it is true, must be universal, that is, hold also for human cells."

All this says something powerful about the longstanding genocentric (gene-centered) bias of biologists. Krisko and Radman delicately hint at the issue when they write in their recent paper:

> The science of molecular biology was dominated by the notion of information, its storage, transmission, and

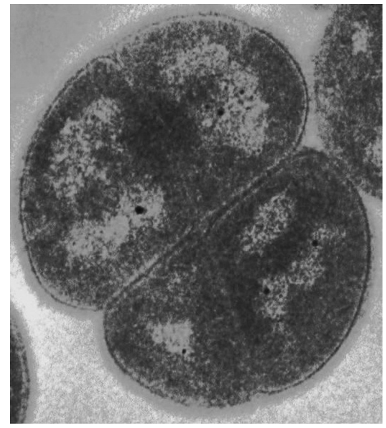
evolution as encrypted in the nucleotide sequence of nucleic acids [constituting DNA and RNA]. But the biological information is relevant to life only to the extent of its translation into useful biological functions performed, directly or indirectly, by proteins ...

This truth, as they also point out, applies to our understanding of cancer and its treatment, which has long been focused on DNA abnormalities. But instead, "an effective cancer therapy by tumor cell killing should target the proteome, or both the proteome and genome, rather than the genome alone."

It was always a strange thing when biologists, attempting to penetrate the thickly matted tapestry of cellular activity at one point or another and disentangle the threads for analysis, decided that one type of element — the gene or DNA sequence — was the place where all the activity logically begins and from where it is controlled. There is in fact no starting place and no part acting as controller, and the very attempt to think in such terms while keeping a picture of cellular behavior in mind immediately brings one up against absurdity. *D. radiodurans* no more shows proteins to be the "controlling" elements than it does DNA. There is an infinite range of ways a cell can shape its thoroughly interwoven processes, and while any given organism may bring one aspect or another to the fore in a particular context, the finely differentiated whole remains integral and irreducible.

If there was one reason for imagining DNA to be the desired starting point, it was the idea that DNA carried the "controlling information" or "computational program" for directing everything else. But this never made any sense. Among other things, it glorified a linear string of statically encoded *information* while ignoring the much more profoundly informed *performances* we observe in the behavior, for example, of those many molecules that coordinate and collaborate in transcribing DNA into RNA — or, for that matter, in repairing damaged DNA.

The molecular complexes carrying out these processes are not simply bumping into each other and chemically reacting in fixed and statistically predictable ways, like the contents of familiar test-tube solutions. Rather, they have intricate tasks to carry out — tasks requiring elaborate sequences of well-timed interactions. Even when these processes have been characterized in some detail, countless bright but befuddled students have twisted their imaginations into knots while trying to picture the actual textbook sequence of events in a coherent manner. This in itself testifies to the depth of directed wisdom at work in those molecular dramas.



Transmission electron micrograph of *Deinococcus radiodurans*. The bacteria typically join together in tetrads.

Photo from the laboratory of Michael Daly, Uniformed Services University, Bethesda, MD.

The work on *D. radiodurans* can remind us that the activity of the organism always reflects something like what we can only refer to metaphorically as a "sense of the whole." The coordinated elements coming to bear upon any particular part seem to "know" how that part is to be related to its larger context. And this work also makes obvious the falsehood in all references to DNA as if it embodied a computer-like program. Arbitrarily break a large program into a handful of separate pieces (let alone a thousand of them), and you face the certainty of its total collapse. Yet every organism deals routinely with a certain number of such disruptions to its genome.

The information we conceive as "encoded" in DNA is a bland reduction of the living intelligence at work in cellular *processes*. It is (to employ a rough analogy) as if we elevated a book of words, phrases, definitions, and grammatical guidelines to a pinnacle high above *Moby Dick* or *Faust* or *War and Peace,* worshipping the former as "information" while ignoring the kind of informed and meaningful activity through which mere words and phrases can be woven into soul-stirring tales.

A phrase-book or dictionary can be an essential resource, but it is the organism (*Deinococcus radiodurans* in the case we have been considering) that uses the dictionary to weave its own story — and even reconstructs the dictionary when the pages fall into a disorganized heap on the floor.

## REFERENCES

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