Table 1. Kinetic parameters of ParM and actin. All values are for the Mg^{2+}-bound form unless otherwise indicated. K_d, dissociation constant.

Parameter	Actin	ParM	Method
Steady-state ATP critical concentration (Mg^{2+})	100 nM	2.3 μM	Pelleting, FRET assay, microscopy
Steady-state ATP critical concentration (Ca^{2+})	440 nM (in 100 mM KCl)	6.8 μM	Pelleting
ATP critical concentration	Barbed end: 100 nM Pointed end: 600 nM	550 to 680 nM	FRET assay (BeF-ATP-ParM and ATP-E148A)
ADP critical concentration	1 μM	~100 μM	Pelleting
ATP-monomer on-rate	Barbed end: 10 μM^{-1} s^{-1} Pointed end: 1 μM^{-1} s^{-1}	4 to 5.3 μM^{-1} s^{-1}	Microscopy (wild-type and E148A)
ADP-monomer off-rate	Barbed end: 7.2 s^{-1} Pointed end: 0.2 s^{-1}	64 s^{-1}	Microscopy (catastrophe rate of ATP-ParM)
ATP K_d	1.2 nM	42 nM k_-: 0.008 s^{-1} k_+: 2.32 × 10^5 M^{-1} s^{-1}	ε-ATP fluorimetry
ADP K_d	0.3 nM	2.4 μM k_-: 0.56 s^{-1} k_+: 1.85 × 10^5 M^{-1} s^{-1}	ε-ADP fluorimetry
Hydrolysis rate (estimated)	0.3 s^{-1}	0.1 to 0.2 s^{-1}	Modeling
Nucleation rate	1×	300×	Concentration dependence of maximal velocity

high cellular concentrations of ParM (12 to 14 μM) (*7*), nucleation is unlikely to be the point at which ParM assembly is regulated. It appears that the property of ParM kinetics most amenable to regulation is filament stability. We propose that, at cellular concentrations of ParM, spontaneous nucleation and filament elongation occur throughout the cell, and that these filaments will spontaneously disassemble unless they are stabilized by interaction with ParR-*parC* (*8*). In this model, only filaments with plasmid bound to both ends are stabilized against catastrophic disassembly (*7*, *8*), and bidirectional elongation of ParM filaments at the interface with the ParR-*parC* complex drives plasmid segregation (Fig. 4B). Such insertional polymerization mechanisms have been proposed for elongating microtubule ends attached to kinetochores and actin filaments bound to formin-family proteins.

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Supporting Online Material
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Accumulation of Mn(II) in *Deinococcus radiodurans* Facilitates Gamma-Radiation Resistance

M. J. Daly,[1]* E. K. Gaidamakova,[1] V. Y. Matrosova,[1] A. Vasilenko,[1] M. Zhai,[1] A. Venkateswaran,[1] M. Hess,[1] M. V. Omelchenko,[1,2] H. M. Kostandarithes,[3] K. S. Makarova,[2] L. P. Wackett,[4] J. K. Fredrickson,[3] D. Ghosal[1]

Deinococcus radiodurans **is extremely resistant to ionizing radiation. How this bacterium can grow under chronic γ radiation [50 grays (Gy) per hour] or recover from acute doses greater than 10 kGy is unknown. We show that *D. radiodurans* accumulates very high intracellular manganese and low iron levels compared with radiation-sensitive bacteria and that resistance exhibits a concentration-dependent response to manganous chloride [Mn(II)]. Among the most radiation-resistant bacterial groups reported, *Deinococcus*, *Enterococcus*, *Lactobacillus*, and cyanobacteria accumulate Mn(II). In contrast, *Shewanella oneidensis* and *Pseudomonas putida* have high iron but low intracellular manganese concentrations and are very sensitive. We propose that Mn(II) accumulation facilitates recovery from radiation injury.**

Deinococcus radiodurans is a nonpathogenic, nonsporulating, obligate aerobic bacterium that typically grows in undefined rich medium (TGY) as clusters of two cells (diplococci) in the early stages of growth and as four cells (tetracocci) in the late

stages (*1*) (Fig. 1A). *D. radiodurans* is extremely resistant to ionizing radiation (IR) and desiccation (*2*) and maintains four to eight genomic copies per cell (*3*). The repair of IR- and desiccation-induced DNA double-stranded breaks (DSBs) (*2*) is known to be mediated by homologous recombination (*4*), but no SOS response (*5*) (table S1) or nonhomologous end-joining of DSBs (*6*) is observed in this organism. Yet, the complexity of the genetic systems underlying DNA repair in *D. radiodurans* remains poorly defined (*4–8*), and three hypotheses have been proposed: (i) *D. radiodurans* uses conventional repair pathways with greater efficiency than other bacteria (*4–6*); (ii) there are repair functions encoded among its hypothetical genes (*8*); or (iii) repair is facilitated by its ringlike nucleoids (RNs) (*9*). These hypotheses emphasize repair of DNA damage caused by the direct effects of γ photons and the indirect effects of reactive oxygen species (ROS) induced during irradiation (*10*). When ROS exceed the capacity of endogenous scavengers to neutralize them, cells become vulnerable to damage, a condition referred to as oxidative stress (*11*).

One DSB repair model for *D. radiodurans* (*9*) attributes the resistance phenotype to the presence of RNs (Fig. 1, B and D). *D. radiodurans* grows predominantly as diplococci in defined minimal medium (DMM) (*12*), even in the late stages of growth (*13*). We examined cells grown in DMM or TGY by transmission electron microscopy (TEM) to determine the prevalence of RNs (Fig. 1) and also tested cells for their resistance to IR (Fig. 2). The resistance of *D. radiodurans* cultures grown in TGY (Fig. 2) that contained cells that lacked RNs (Fig. 1A) was greater than the resistance of cultures grown in DMM (Fig. 2 and SOM Text) that contained cells with RNs (Fig. 1, C and E). *Deinococcus grandis* grows as single cells (*14*), is similarly resistant to IR in either TGY or DMM (Fig. 2), and rarely displayed RNs (Fig. 1, F and G). So far, neither genomic (*5*, *7*) nor experimental (*3–9*) analyses unequivocally support any model that explains the radioresistance of *Deinococcaceae*.

We determined that growth of *D. radiodurans* in DMM is dependent on Mn(II) (Fig. 3A) but not on Fe, Co, or Mo (Fig. 3B). Moreover, growth and resistance of *D. radiodurans* was unaffected by Fe chelators

[1]Uniformed Services University of the Health Sciences, Bethesda, MD 20814, USA. [2]National Institutes of Health, Bethesda, MD 20894, USA. [3]Pacific Northwest National Laboratory, Richland, WA 99352, USA. [4]University of Minnesota, St. Paul, MN 55108, USA.

*To whom correspondence should be addressed. E-mail: mdaly@usuhs.mil

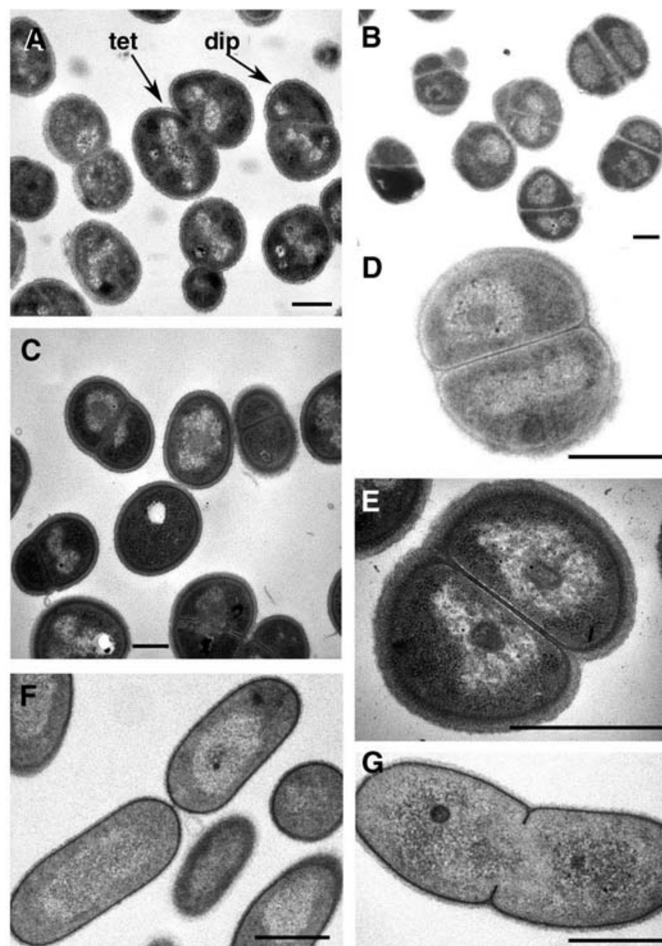

Fig. 1. TEM (*12*). (**A**) *D. radiodurans* grown in TGY, late-log phase (LLP). tet, tetracoccus; dip, diplococcus. (**B**) *D. radiodurans* grown in TGY, early-stationary phase (ESP). (**C**) *D. radiodurans* grown in DMM, ESP. (**D**) *D. radiodurans*, diplococcus, grown in TGY, ESP. (**E**) *D. radiodurans*, diplococcus, grown in DMM, ESP. (**F** and **G**) *D. grandis*, grown in TGY, ESP. Scale bars, 0.5 μm.

Table 1. D_{10} survival values and intracellular Mn and Fe levels (*12*).

Strains*	Radiation dose yielding 10% CFU survival	Desiccation dose yielding 10% CFU survival**	^{59}Fe accumulation, atoms/cell	^{54}Mn accumulation, atoms/cell	Total Fe: ICP-MS/nmol Fe/mg protein	Total Mn: ICP-MS/nmol Mn/mg protein	Intracellular Mn/Fe (ICP-MS) concentration ratio
D. radiodurans†	16 kGy	>30 days	2.7×10^3††	1.08×10^5††	1.49 (±0.39)	0.36 (±0.11)	0.24
Deinococcus geothermalis†	10 kGy#	>30 days	7.7×10^3 (±1.1×10^3)	2.17×10^5 (±3.7×10^3)	1.7 (±0.39)	0.78 (±0.15)	0.46
Enterococcus faecium‡	2.0 kGy#	>30 days	ND	ND	6.3 (±2.8)	1.1 (±0.21)	0.17
E. coli§	0.7 kGy	8 days	7×10^5 (*16*)	3.8×10^4 (*16*)	2.72 (±0.63)	0.0197 (±0.0027)	0.0072
Pseudomonas putida§	0.25 kGy#	1 day	ND	ND	6.8 (±0.70)	<0.001	<0.0001
S. oneidensis§	0.07 kGy	<1 day	2.7×10^4††	$<5 \times 10^2$††	4.98 (±0.40)	0.0023 (±0.00005)	0.0005
D. radiodurans‖ low-Mn DMM	10 kGy	ND	ND	ND	2.1	0.7	0.33
D. radiodurans¶ high-Mn DMM	ND	ND	ND	ND	1.6	3.9	2.5

*Unless stated otherwise, strains were grown to OD_{600} 0.9 in TGY medium, washed twice in 1 × PBS containing 1 mM EDTA, and subjected to ICP-MS (*16*). †*Deinococcus-Thermus* phylum (*5*). ‡Gram-positive. §Gram-negative. ‖Grown in/recovered on DMM + 25 nM Mn(II). ¶Grown in/recovered on DMM + 2.5 μM Mn(II). #See fig. S3. **See fig. S5. ††See Fig. 3D. For TGY, ICP-MS showed 204 (±78) nM Mn and 6085 (±1111) nM Fe. For DMM/DRM [without Mn(II) supplementation], ICP-AES (Atomic Emission Spectrometry) showed 5.6 (±2.1) nM Mn and 1799 (±2.8) nM Fe. CFU, colony-forming unit. ND, not determined.

(Fig. 2) (Fig. 3C). To further examine the dependence of *D. radiodurans* on Mn and Fe, we used ^{54}Mn and ^{59}Fe to assay accumulation relative to the bacterium *Shewanella oneidensis* (Fig. 3D) (*15*), and the total Mn and Fe contents of *D. radiodurans* and other bacteria were determined by using an inductively coupled plasma-mass spectrometry method (ICP-MS) (*16*). *D. radiodurans* accumulated substantially more Mn than *S. oneidensis* but less Fe (Table 1). Mn(II) is essential for the detoxification of ROS in most bacteria, principally as a cofactor for the Mn-dependent enzyme superoxide dismutase (Mn-SOD). However, *Lactobacillus plantarum* incorporates Mn(II) as a protectant in place of Mn-SOD (*17*); *L. plantarum* is an Fe-independent, radioresistant bacterium that exhibits energy-dependent Mn accumulation (*16–18*). Mn transport in *D. radiodurans* is also energy dependent, because carbonyl cyanide 3-chlorophenylhydrazone inhibited ^{54}Mn accumulation by >75% (Fig. 3D).

Because *D. radiodurans* does not grow as a monococcus (*1*, *3*), survival frequencies for a single-celled population cannot be determined experimentally (SOM Text). At 12 kGy, 17% of *D. radiodurans* cells are statistically calculated to survive (*12*). The IR doses that yield 17% survival of *Escherichia coli* and *S. oneidensis* cells are lower by factors of 20 and 200, respectively, than those for *D. radiodurans* (Fig. 2, inset). High levels of Mn(II) have been reported to be associated with *D. radiodurans* DNA (*19*) (fig. S1), but it is unlikely that Mn(II) protects DNA during irradiation itself, because the numbers of DSBs per Gy per genome for a given dose in *D. radiodurans*, *E. coli*, and *S. oneidensis* are very similar (fig. S2). However, the differences in resistance observed between these and other organisms reported here mirror the trend in their intracellular Mn/Fe concentration ratios (Table 1).

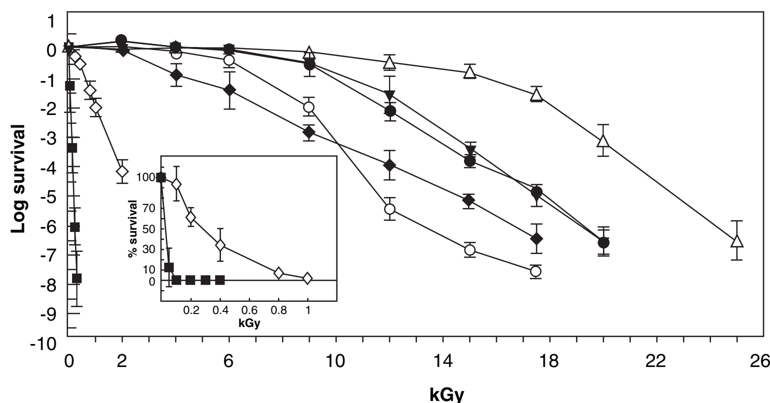

Fig. 2. Survival of strains exposed to acute IR (*12*). Open triangle, *D. radiodurans* (pregrown in TGY, plated on TGY) (LLP, Fig. 1A); solid circle, *D. radiodurans* (pregrown in DMM, plated on TGY) (ESP, Fig. 1, C and E); solid triangle, *D. radiodurans* [pregrown in DMM + 50 μM 2,2′-dipyridyl (Dp) and 50 μM deferoxamine mesylate (Ds) (Dp and Ds are Fe-chelators), plated on TGY] (ESP); open circle, *D. grandis* (pregrown in TGY, plated on TGY) (LLP); solid diamond, *D. grandis* (pregrown in DMM, plated on TGY) (ESP, Fig. 1, F and G); open diamond, *E. coli* (OD_{600} 0.9) (pregrown in TGY, plated on TGY); solid square, *S. oneidensis* (OD_{600} 0.9) (pregrown in TGY, plated on TGY).

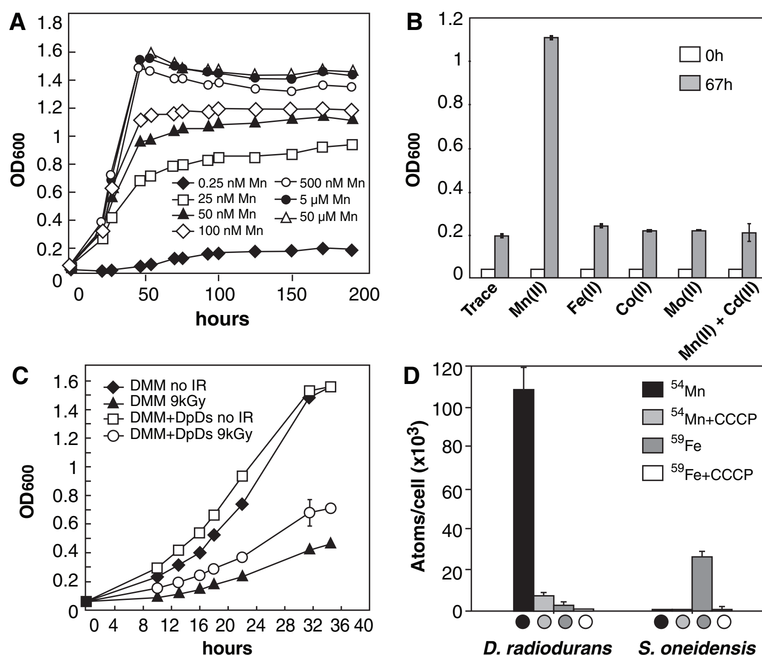

Fig. 3. Role of transition metals in wild-type *D. radiodurans* (*12*). (**A**) Growth dependence on Mn(II) in DMM. (**B**) Dependence on transition metals in DMM containing 2.5 μM Mn(II), Fe(II), Co(II), Mo(II), or [Cd(II) (2.5 μM) + Mn(II) (2.5 μM)]. Trace, 0.2 μM each of Mo, Cu, Cr, Bo, Zn, and I. (**C**) Effect of Fe chelators (50 μM Dp and 50 μM Ds) on recovery from IR. (**D**) *D. radiodurans* accumulated ^{54}Mn, but not ^{59}Fe, in an energy-dependent manner. Inset circle for designation.

ROS produced by IR or metabolism can kill cells (*10*, *11*, *13*). Hydroxyl radicals ($HO^{\cdot}$) are a primary product of the radiolysis of water, are extremely toxic (*10*), and in the presence of O_2 can generate other ROS, including superoxide ions ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2). Probably the most important source of ROS in aerobic cells is the respiratory chain, which can give rise to high levels of $O_2^{\cdot-}$ and H_2O_2 (*11*). Irrespective of source, H_2O_2 is relatively stable and diffusible, but in the presence of free Fe(II) the Fenton and Haber-Weiss reactions decompose H_2O_2 to $HO^{\cdot}$ (*11*). In contrast, Mn(II) is not known to participate in Fenton-type chemistry in vivo (*17*). The mechanism by which Mn(II) scavenges $O_2^{\cdot-}$ is not understood but requires considerably higher intracellular Mn(II) levels than those needed for Mn-SOD–mediated protection (*17*). ICP-MS analysis showed that the Mn content of *D. radiodurans* grown in high-Mn(II) conditions is 5.6 times as much as that in low-Mn(II) conditions (Table 1). In the presence or absence of 50 Gy/hour, *D. radiodurans* growth was similarly good on high-Mn DMM (Fig. 4A). However, growth was inhibited on low-Mn DMM under chronic radiation but not in the nonirradiated control (Fig. 4A). For cells unable to grow under 50 Gy/hour on low-Mn DMM, increasing the concentration of amino acids restored growth (Fig. 4A). Thus, oxidative stress produced by metabolism potentiates the lethal effects of radiation in *D. radiodurans*, where cells growing on DMM limited in amino acids and Mn(II) are overwhelmed by two sources of ROS, metabolism and irradiation.

The intracellular concentration ratios of Mn and Fe in *D. radiodurans* grown in TGY or low-Mn DMM are similar (0.2 to 0.3), and no significant differences in cell-survival (*12*) were observed on either medium for acutely irradiated cells (D_{10}, ~10 to 12 kGy) (Table 1). *D. radiodurans* can grow in defined rich medium (DRM) without Mn(II) supplementation (no-Mn DRM) (*12*), and the

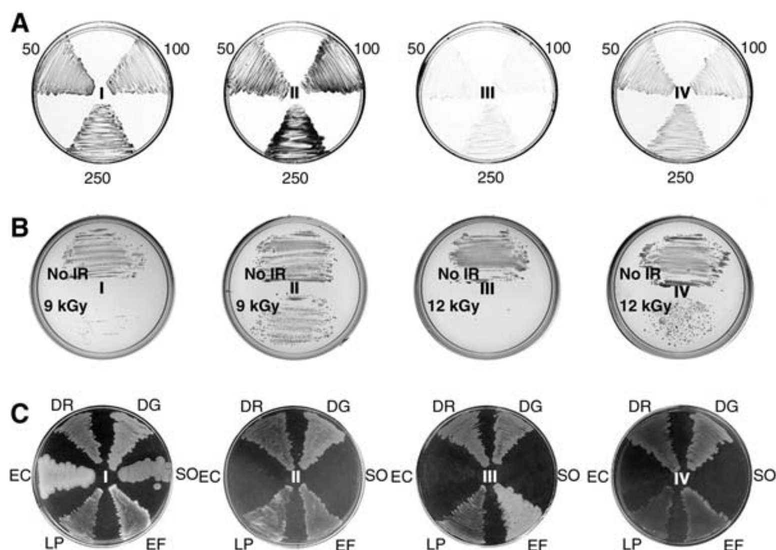

Fig. 4. Effect of γ radiation on Mn-accumulating bacteria (*12*). (**A**) Growth of *D. radiodurans* on DMM plates under 50 Gy/hour is dependent on Mn(II). Cells were pregrown in DMM with 50 nM Mn(II), 100 nM Mn(II), or 250 nM Mn(II). I, no irradiation control, [DMM + 25 nM Mn(II)]; II, [DMM + 2.5 μM Mn(II)] + 50 Gy/hour; III, [DMM + 25 nM Mn(II)] + 50 Gy/hour; IV, [DRM (*12*) + 25 nM Mn(II)] + 50 Gy/hour. (**B**) Recovery of *D. radiodurans* from acute IR exhibits a concentration-dependent response to Mn(II) (fig. S3). I and III, no-Mn DRM; II and IV, DRM + 2.5 nM Mn(II). (**C**) Growth in genotoxic environments. I, control, TGY; II, TGY + 50 Gy/hour; III, TGY + Dp + Ds (each, 125 μM); IV, TGY + 50 Gy/hour + Dp + Ds (each, 125 μM). DR, *D. radiodurans*; DG, *D. grandis*; SO, *S. oneidensis*; EF, *E. faecium*; LP, *L. plantarum*; EC, *E. coli*.

effect of Mn(II) depletion on recovery was tested (Fig. 4B). For *D. radiodurans* grown in no-Mn DRM, the intracellular Mn/Fe concentration ratio was 0.04, and the D_{10} cell-survival value on no-Mn DRM was ≤2.5 kGy (fig. S3), quantitatively similar to the IR resistance of several highly sensitive *D. radiodurans* DNA repair mutants (e.g., DNA polymerase I) (*20*). Mn-SOD is not critical to survival following acute irradiation (*21*), and we have shown that Mn-SOD is not needed for growth under 50 Gy/hour (fig. S4). In this context, we note that *D. radiodurans* has one of the highest catalase activities reported for any bacteria (*22*), and this would serve to remove H_2O_2 generated by nonenzymic Mn(II)-based dismutation of $O_2^{\cdot -}$ (*17*).

In general, most of the radiation-resistant microorganisms reported have been Gram positive and the most sensitive have been Gram negative (*23*). One exception is the Gram-negative cyanobacterium *Chroococcidiopsis*, which is extremely resistant (D_{10}, 5 kGy) (*24*). We believe it is noteworthy that the most resistant non–spore-forming bacteria reported belong to the deinococci (*5*), cyanobacteria (*25*), enterococci (*23*), and lactobacilli (*18*). These groups share traits including Mn accumulation (Table 1) (*17*, *25*), high intracellular Mn/Fe concentration ratios (Table 1) (*16*, *25*), resistance to desiccation (fig. S5) (*24*), and growth in the presence of Fe chelators and/or 50 Gy/hour (Fig. 4C) (*16*). An exception to this paradigm is *Neisseria gonorrhoeae*, which accumulates Mn(II) but is sensitive to IR (D_{10}, 0.125 kGy) (*26*). However, *N. gonorrhoeae* also has a high Fe requirement; the intracellular Mn/Fe concentration ratio of *N. gonorrhoeae* is 0.004 (*27*).

DNA repair systems identified in *D. radiodurans* appear less complex and diverse than those reported for *E. coli*, *S. oneidensis*, or *P. putida* (tables S1 and S2). Regarding the three hypotheses presented above, the high intracellular Mn/Fe concentration ratio of *D. radiodurans* might underlie the efficiency of its repair pathways by protecting cells from ROS generated during recovery. Our findings do not preclude the existence of novel DNA repair genes, but few have been identified to date (*5*, *8*), and they do not support a role of RNs in resistance (*9*). For Fe-rich, Mn-poor cells, death at low doses might not be caused by DNA damage inflicted during irradiation. For example, 90% of *S. oneidensis* cells do not survive 0.07 kGy, a dose that induces <1 DSB/genome (fig. S2) (Table 1). Instead, *S. oneidensis* might be primed for Fenton-type chemistry by the release of Fe(II) during irradiation (*28*) but unable to recalibrate enzymic defense systems (table S3) in time to counter sudden increases in $O_2^{\cdot -}$-related ROS during recovery (*11*). In contrast, accumulated Mn(II) would be unaffected by radiation and functionally poised to act against increases in $O_2^{\cdot -}$; similar arguments can be made to explain resistance to desiccation (*2*) (fig. S5) (Table 1).

We have demonstrated a critical role for the accumulation of Mn(II) in *D. radiodurans* in a mechanism toward surviving IR that is independent of Mn-SOD. The existence of high intracellular Mn/Fe concentration ratios in phylogenetically distant, radiation-resistant bacteria but not in sensitive cells supports the idea that Mn(II) accumulation (with low Fe) might be a widespread strategy that facilitates survival. Taken collectively, our results indicate that Mn(II) transport and regulation systems (figs. S6 and S7) are potential new targets to control recovery from radiation injury.

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