FEBS 27576 FEBS Letters 551 (2003) 1–2

Jeff's View
Mighty manganese

When our children were still children, I often told them stories. I made these up, so that kind-hearted monsters or beautiful princesses could deliver my educational pitches. I am a professor – so what? When I discovered that my students, too, loved stories, I tried to give my lectures in the form of stories. Although kind-hearted monsters and beautiful princesses would no longer do, thrilling discoveries and whacky scientists easily filled the gap. And chemistry – with or without 'bio' – is made for story-telling. It is so sensual. Which other science enchants you with colors, crystals, smells, and explosions? If you are looking for a science that does not forget your limbic system, pick chemistry and Primo Levi as a guide. Each of the twenty-one tales of his *Il Sistema Periodico* pays tribute to a chemical element – and to the human spirit. There are gripping stories on argon, zinc, nickel, mercury, iron, and on sixteen other elements – but none on manganese. Indeed, when Levi's classic appeared in 1975, manganese was a metal in search of distinction. It meant longer-lasting batteries, better steel, or crush-resistant aluminum cans. Protecting a six-pack of Budweiser was not the topic to fan Primo Levi's imagination.

Since then we have learned how profoundly manganese has shaped evolution of life on earth and the face of our planet. Somebody just has to tell its story, so it might as well be I.

Manganese is a cosmic late-comer, a byproduct of the life and death of stars. As late as one thousand million years after the 'Big Bang', the universe was still only vast clouds of hydrogen gas hundreds of thousands of light years across. As these clouds collapsed into galaxies and then into individual stars, the immense heat of compression made hydrogen fuse into helium, turning stars into nuclear furnaces. When a star ran out of hydrogen, it switched to helium as a fuel, fusing it into successively heavier nuclei. The bigger the star, the heavier were the nuclei it could form. That's how the first manganese atoms were born. But once these primary nuclear fires had burned their way up to iron, they ground to a halt because converting iron into still heavier elements does not yield, but consumes energy. This Iron Curtain spelled the star's doom. Most small stars died peacefully by ballooning into Red Giants, giving off much of their mass (including the manganese they had made) into the interstellar space, and finishing their days as slowly cooling White Stars. Big stars (and special pairs of smaller stars) made a much more grandiose exit. Their outer layer collapsed into the exhausted inner core, releasing for a few seconds as much energy as all the hundreds of billions of stars in the entire galaxy. The colossal energy release of such a *supernova* could forge all the 'energy-expensive' elements up to uranium and beyond. It also created lighter elements, including most of the universe's manganese. The manganese-containing cinders of supernovae were blown deep into the galaxy and coalesced again into the next generation of stars. Finally, some of the manganese ended up on our planet.

With each stellar life-cycle, the universe became richer in manganese. But it's still only one atom of manganese in about five million others. In our body, manganese accounts for one atom in 50 million. When life picked its building blocks, it selected against manganese.

Yet without manganese, life would not have developed the way it did. Early on, life used RNA to store information and to catalyze metabolic reactions. Later it entrusted long-term information storage to DNA, which is more stable than RNA, and metabolic catalysis to proteins, which offer much greater chemical and structural flexibility. Lipids were fine for membranes, and polymeric carbohydrates for tough cell walls. To make all of this work in the long run, cells needed lots of energy, which they could only get through energy-releasing electron transfer reactions. But life's major building materials were not very good at electron transfer. Although some proteins could shuttle electrons by oxidizing and reducing sulfhydryl groups, these reactions were too limited and too slow to quench life's growing thirst for energy. Cells therefore devised a new generation of electron transfer catalysts by spiking proteins with iron, nickel, cobalt, vanadium, molybdenum and, occasionally, manganese. These metals quickly and reversibly take up and give off electrons in many different ways. None of them is as clever in this department as manganese. Manganese is the only element that can assume up to 11 different valence states, and the colors of its different compounds cover the entire visible spectrum. Molybdenum, nickel, iron, vanadium or copper are electronic whizzes in their own right, but manganese bests them all. When it comes to trading electrons, manganese is the champ.

Life seems to have taken a while to notice this electronic talent, because it used mostly iron, molybdenum, vanadium, or nickel to build its early generation of high-tech metal-containing enzymes. These could do amazing things. They reduced sulfur, carbon dioxide or nitrate with hydrogen gas, or converted nitrogen gas to ammonia. If manganese was used at all, it was mostly put into electronically dull enzymes that broke down sugars or polypeptide chains.

All this changed when some early photosynthetic bacteria built a manganese–protein complex that used sunlight to wrest electrons from water. The bacteria did not design this complex from scratch, but tacked it on to the photosynthetic machine they already had. It took biochemists a long time to identify this water-splitting complex and to work out its composition and three-dimensional structure. It contains four manganese atoms, some calcium, chloride and perhaps also bicarbonate, and four proteins. The protein that binds the manganese atoms also binds chlorophyll and is a key part of the photosynthetic machine that converts sunlight into an electrochemical potential. The other three proteins are in close vicinity to the four manganese atoms, but it is not yet clear what they do. The four manganese atoms successively collect the electrons extracted from water and plug them back, one at a time, into light-oxidized chlorophyll. This reduction resets the photosynthetic machine for another round. A protein-bound tyrosine helps the electrons to flow from manganese to chloro-

0014-5793/03/$22.00 © 2003 Published by Elsevier B.V. on behalf of the Federation of European Biochemical Societies.
doi:10.1016/S0014-5793(03)00885-8

phyll. It is a fantastic machine. If you can think of one that's more impressive, please let me know.

Because the extraction of electrons from water releases oxygen gas, this solar-powered manganese complex changed our planet's face. The face became bluish – and oxidizing. That spelled big trouble, because life had devised its enzymes for a reducing habitat, and now all bets were off. Many of the enzymes with built-in molybdenum, nickel or vanadium could not withstand the oxidative onslaught and cells that depended on them either perished, or had to take refuge in anaerobic biological niches. Some of them coped with the new oxygen-containing atmosphere by surrounding their oxygen-sensitive enzymes with oxygen traps, such as oxygen-binding heme proteins. These were exceptions, though. With the dawn of the Oxygen Age, many of the sophisticated enzymes containing nickel, molybdenum or vanadium became molecular dinosaurs.

But the metal that had caused all this turmoil also helped life to cope with it. Threatened by oxygen gas and its byproducts, the 'reactive oxygen species', cells built a manganese enzyme that could detoxify a particularly noxious oxygen byproduct, the superoxide radical. The manganese-containing *superoxide dismutase* converted superoxide radicals to less toxic hydrogen peroxide, which other enzymes (some of them having, once again, manganese in them) then broke down to water and oxygen gas. Cells had devised a superoxide dismutase already during the Anaerobic Age, but had equipped it with iron instead of manganese. The iron enzyme could apparently deal with the occasional oxidative stress that cropped up even during anaerobic life, but now, as things were getting tough, it could no longer rise to the challenge. Replacing iron by manganese yielded an industrial-strength enzyme, which became one of life's key defenses against oxygen. Most of today's cells cannot do without it, except those that only grow in the strict absence of oxygen. When some respiring bacteria penetrated into other cells and developed into today's mitochondria, they held on to their manganese superoxide dismutase. This enzyme still protects our mitochondria from oxidative damage and mice that lack it die as early embryos.

Prokaryotes are still trying to invade our body cells, and when they succeed, we are in trouble. Once inside our cells, these unwelcome guests are usually protected from antibacterial drugs, making intracellular bacterial infections a doctor's dread. *Mycobacterium tuberculosis*, which gives us tuberculosis, *Mycobacterium leprae*, which causes leprosy, and *Legionella pneumophila*, the culprit of legionnaire's disease, are three of these intracellular invaders. Our cells try to fight back, of course, and none more valiantly than our macrophages. They engulf the bacteria and hold them captive in their cellular stomach, the *phagosome*. The phagosome membrane has a battery of enzymes that generates reactive oxygen species and directs them at the entrapped bacteria. Luckily for us, this molecular flame thrower usually kills the bacteria. Unluckily for us, some of them have learned to hide behind a fire wall: they secrete large amounts of a manganese-containing superoxide dismutase into the phagosome and destroy the oxygen radicals that are coming at them. The enzyme is normally in the cytosol, and how the pathogenic bacteria export it is still a little mysterious. Without this fire wall, the invaders would have little chance: mutations that inactivate either the bacterial superoxide dismutase or its special export system diminish or abolish the bacterium's potential for intracellular infection.

Our macrophages seem to know all this, and try to monkey-wrench the building of this firewall. Although they cannot block the activity or the export of the bacterial superoxide dismutase, they can stop its synthesis by starving the bacteria of manganese. Manganese, like all metals, cannot simply diffuse across biological membranes, but must be ferried across them by specific transport proteins. We know some of these transporters, but many are still unidentified. One of them was discovered when scientists tried to understand why some Indian subpopulations were more resistant to tuberculosis than others. They traced the resistance to a slight sequence variation (a *polymorphism*) in a macrophage protein. Scientists being what they are, they christened the protein *natural resistance-associated macrophage protein 1*, or Nramp1. Others then went on to show that Nramp1 resides in the macrophage's phagosome membrane, and one of my Israeli friends found Nramp1-like proteins in yeast cells and showed that these proteins transport manganese from the outside into the cytoplasm. Now the pieces of the puzzle fell into place, revealing a mortal combat between macrophages and bacterial invaders: macrophages use their Nramp1 to pump out manganese from their phagosome so that the entrapped invaders cannot build their fire wall. But the bacterial invaders also have manganese transporters (some of them similar to Nramp) with which they try to suck up manganese from the phagosome. It is a tug-of-war between manganese transporters. In the course of human history, this cellular battle for manganese has probably cost more human lives than all the national battles for silver and gold.

My life as a biochemist has never dimmed my enthusiasm for the inorganic world. The intense and virtually indestructible colors of cadmium sulfide or mercury oxide, the knife-like odor of chlorine gas, or the lurid glow of a sulfur flame always make my heart beat faster. They are primeval, zero baselines that let me feel the privilege of my own existence. The emotional force of manganese struck me in full a few years ago when I was flying across Northern Canada in late spring. Most of the snow was already gone, and the vast sweeps of land far below seemed to be colored by a gigantic brush: blue-green run-offs of copper carbonates, mountain ranges brilliantly red from iron oxides – and voids of black manganese oxides. Even from my comfortable airline seat ten kilometers up, these black deserts had something ominous. They stood guard over immense amounts of manganese that lay imprisoned at concentrations at least 10 000 times those in my body. A chunk the size of my little house could easily supply all the manganese for our planet's annual production of biomass. If I ever saw a sleeping giant – there it was. Mighty manganese! After iron oxide, jet engines, and me – what are you up to next?

I thank Heimo Brunetti, Christoph Dehio, Sabeeha Merchant, Andreas Tammann and Charles Yocum for helpful comments.

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