Jeff's view

The tragic matter

Living matter is the most complex matter we know in the entire universe and we admire it as the ultimate paradigm of hierarchy and order. No other matter embodies so much information. It is so unusual because it is so smart.

Yet living matter is not only order and information. Apollo may have crafted its fabric, but Dionysos rules its soul. Living matter has a dark side. It fights a lost battle against its own fragility and winds up scorched. It is a tragic matter.

Hold somebody's hand and feel its warmth. Gram per gram, it converts 10 000 times more energy per second than the sun. You find this hard to believe? Here are the numbers: An average human weighs 70 kg and consumes about 12 600 kJ per day; that makes about 2 mJ/g s, or 2 mW/g. For the sun, it's a miserable 0.2 μJ/g s. Some bacteria, such as *Azotobacter*, can convert as much as 10 J/g s, outperforming the sun by a factor of 50 million.

We are warm because inside each of our body cells there are dozens, hundreds or even thousands of mitochondria that burn the food we eat. They use part of the combustion energy to make ATP from ADP and inorganic phosphate, and release the rest as heat. Billions of tiny fires are burning in us. Yet we are tame compared to an *Azotobacter* cell, which has no mitochondria at all, but whose surrounding membrane burns food several thousand times faster than we do. A single gram of this passionate bacterium can make as much as 7 kg of ATP per day.

Before evolution hit upon respiration, life's inventive genius was crippled by a power shortage. There is no consensus on what happened during life's early stages, because witnesses are hard to come by. But most of us believe that life started when our atmosphere had little, if any oxygen gas and that cells gained energy through fermentation. We do not know what form of fermentation, but the fermentations in today's cells suggest that this ancient process must have been quite inefficient. As long as life had to rely on this primitive power source, it could not devise more sophisticated organisms because there was no way to give them enough sustainable power. Also, the fermentation fuels, whatever they were, were bound to run out quickly. But then came a cell that could capture the energy of sunlight. This feat was, and most likely always will be, the greatest event in the evolution of life on earth. Suddenly life had tapped into a nearly inexhaustible energy source – the nuclear fusions in a nearby star. Life's energy crisis had ended and sunlight-harvesting cells exploded over the entire planet. They used light to make ATP from ADP and inorganic phosphate, and to build organic molecules from inorganic ones. But these cells were big-time polluters: when gorging on light, they split water and released a poisonous by-product – oxygen gas. This gas was bad news, because life had not selected its building blocks for oxygen resistance. Unsaturated lipids, nucleic acids, proteins – now they were all sitting ducks for oxygen gas. Oxygen would destroy them all; it was just a question of time. A much-needed reprieve came from the immense amount of divalent iron that was dissolved in the oceans and that scavenged oxygen gas as insoluble iron(III) oxides. Life's refuse made the oceans rust, leading to gigantic 'banded iron formations' of Fe_3O_4 on the sea floors, and 'red beds' of Fe_2O_3 all over our planet's surface. But once this oxygen sink was exhausted, oxygen gas accumulated in the oceans and then escaped into the atmosphere until it reached its present level.

Rarely, if ever, has the success of one species been such a catastrophe for life on earth. The cloud of toxic oxygen gas must have caused mass extinction, and yet life learned to protect itself against oxidation. It began its epic battle with oxygen gas. It thought up enzymes that converted oxygen-induced disulfide bridges in proteins back to the original sulfhydryl groups; and it found ways to deal with the particularly vicious 'reactive oxygen species' superoxide radicals, hydroxyl radicals, singlet oxygen, and peroxides that form as by-products when oxygen gas reacts with electron donors. Cells started to buffer themselves with antioxidants such as α-tocopherol, ascorbic acid and carotenoids, and invented a battery of sophisticated enzymes, such as catalases, peroxidases, and superoxide dismutases, which could destroy 'reactive oxygen species'. And once these defenses held, life mounted a counterattack and used the oxidizing enemy as an electron sink for burning organic matter. To do so, it only had to fiddle a little with something it already had – its clever machinery for capturing sunlight. Now life had respiration. Now it could make ATP by lighting a fire.

For life, as for humankind, harnessing the fire marked a turning point, because it yielded an energy source of unprecedented intensity. Fermentation was too inefficient to make ends meet for anything but the most primitive forms of life. Photosynthesis was sophisticated and efficient, but could never provide intense bursts of power to a small organism – the number of photons hitting earth's surface was just too low. But with respiration, life had a high-performance engine unlike anything before. This engine could be revved up day and night, rain or shine, as long as there was oxygen gas around. In seconds, respiring cells could release energy that sunlight eaters had patiently collected over hours or even days. With this new power source, life could shift into high gear and devise ever more dynamic and complex organisms.

How well would I do with these three power sources during a 150-meter sprint? If I only fermented my body glycogen to lactic acid, I could reach the finish line fast and perhaps without taking a single breath, but by then the accumulated lactic acid would immobilize my muscles and I would probably fall flat on my face. Solar power? On a sunny day, my body surface receives at best 500 W of solar energy. Even if I could convert all of it into ATP (something no plant has yet managed to do), I would have only about a third of the power needed for a decent sprint. And with my surface of 2 m^2, I am still a lot better off than a humming bird or a tiny insect. It is respiration that keeps me going. There is no better example of its power than the flight muscles of insects. They are the Ferraris of muscles and packed with mitochondria. Thanks to them, a dragonfly can lift twice its own weight, beating

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our best helicopters by a factor of seven. But as with any high-performance engine, heat is a problem. To avoid overheating, large organisms respire less intensely and have lower levels of respiratory cytochromes than smaller ones. Also, our cells keep a tight rein over their respiration. When they rest and don't need much energy, they slow down respiration. When this respiratory control fails, hell breaks loose. We know of two – and only two – unfortunate humans to whom this happened. One was a 27-year-old Swedish woman who, in spite of her normal thyroid status, had the highest metabolic rate ever recorded for a human being. She ate prodigiously, yet remained thin and sweated even in winter. Mitochondria isolated from small biopsies of her skeletal muscles burned out of control – they respired full blast no matter whether or not ATP was needed. That was in 1959, long before we had the molecular tools to identify defective genes. The doctors could not help her, and she tragically committed suicide ten years later. The second case was a Lebanese woman who vainly sought help at a US hospital. She liked to sit in a hospital cold room, having fans blow chilled air at her – a desperate attempt to get rid of the heat from the fires raging in her. She has disappeared and nobody knows what happened to her.

But even a healthy respiration system is not perfect, because it emits sparks. Some of the electrons that should reduce oxygen gas to harmless water leak out from the respiratory system and reduce oxygen gas to the dangerous 'reactive oxygen species' I mentioned before. These nasty fellows react with almost anything. They oxidize sulfhydryl groups, peroxidize lipids, cross-link proteins and lipids, modify and displace bases from nucleic acids, and break the strands of DNA. They put any soccer vandal to shame. They hit the DNA in each of our cells between 10 000 and 100 000 times per day – up to once every second. What saves us is a host of enzymes that repair damaged DNA as well as possible. Oxidative pummeling is particularly violent with our mitochondrial DNA, because it sits right in hell's kitchen where respiration goes on and most of the sparks fly. To make things worse, mitochondria are not very good at repairing DNA. No wonder that mitochondrial DNA suffers ten times more oxidative damage, and has a 17-fold higher evolutionary mutation rate than nuclear DNA. This damage also shows in the short run. As I age, some of my mitochondrial genes for making the respiration system get damaged beyond repair. This sets off a vicious spiral because the defective genes now make defective respiratory chains that spark even more and cause still greater DNA damage. Finally, mitochondria can no longer make enough ATP and tell the cell to commit suicide. Much of this happens in my brain, which respires more intensely than most other parts of my body. And if my brain cells keep dying, it's tragedy down the road.

It seems that the ravages of oxygen also make many other things go wrong with me. Should I ever reach the ripe old age of 90, many of the mitochondrial DNA molecules in my brain will have lost big chunks; up to 1% of their deoxyguanosine bases will be oxidized and no longer do a proper coding job; my mitochondria will have ten times less cytochrome oxidase than I had as a boy; and the membranes in my cells will work less efficiently because they are encumbered by oxidized lipids that are cross-linked to proteins. It seems that I have a bright future.

If you are healthy (and not a chemist), oxidative damage is probably the most serious damage you suffer from the environment. What can you do to protect yourself? Rigorous experiments on this topic are difficult to do, hard facts rare, and consensus is still a long way off. Still, it is probably a good idea to eat lots of vegetables rich in antioxidants and to stay out of intensive sunlight. You might also do a good thing for yourself (and for some pharma companies) by adding pills of antioxidant vitamins to your breakfast menu. But the best-documented and cheapest way to fight oxygen damage is to eat less. Less food means less respiration, which in turn cuts down on reactive oxygen species. Here we go again – less food. But this time I am not talking waistline – I am talking oxygen. Animals that frequently go into extended low-metabolic torpor, such as the pocket mouse, tend to live much longer than close relatives that are always active. Now you know why we university professors have such a long life expectancy.

But sooner or later, oxygen gets us all. It helps us do great things and stay ahead of entropy, but exacts a steep price. When cells negotiated their covenant with oxygen, they forgot that they are not flameproof enough. That's life's molecular tragedy. Perhaps our descendants a billion years down the line will negotiate a better deal. But for now, oxygen always wins. Was this the message Ikarus tried to tell?

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