QnAs with Rafael Radi

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Rafael Radi has received numerous awards for his work on free radicals, oxidants, and reduction/oxidation pathways in biomedicine. During a long and fruitful career, he has characterized the formation and chemistry of peroxynitrite, including its role in mitochondrial dysfunction, pathology, and in immune responses to intracellular pathogens, such as *Trypanosoma cruzi*. He has also helped develop redox-based drugs for various diseases, including neurodegenerative, cardiovascular, and inflammatory conditions. A professor of biochemistry at the Universidad de la República in Montevideo, Uruguay, Radi was elected as a foreign associate to the National Academy of Sciences in 2015. In his Inaugural Article (1), Radi reviews major advances in the scientific understanding of redox pathways in medicine. He recently spoke to PNAS about his many contributions to this field.

Rafael Radi. Image courtesy of Leo Barizzoni (photographer).

PNAS: How did you become interested in studying oxygen radicals, particularly, nitric oxide-derived oxidants?

Radi: There was a long tradition in my department of working on oxygen radicals, starting from the days of John R. Totter, a [visiting] American scientist. That work was continued in the 1960s and early 1970s by Eugenio Prodanov, who was trained by John Trotter. Unfortunately, in 1972–1973 a military government got into power and the university's research was shut down. In 1984 we again had democratic elections, and in 1985 many of the scientists who were in exile returned to the University, including Prodanov. I was then a young medical student and biochemistry instructor trying to find ways to do original research. I was introduced to Prodanov, and together we started to rebuild the oxygen radical research group.

The first 5 years were extremely hard, as we were starting from scratch. We didn't have instruments, we didn't have reagents, we didn't have publications, so we were really outsiders. The next 10 years were years of creating new hypotheses, and I was lucky to interact with Bruce Freeman and Joe Beckman at the University of Alabama–Birmingham at a time when they were introducing the role of nitric oxide (•NO) into the oxygen radical field. We found that in many cases, the good actions of •NO were shifted to toxic actions after interacting with oxygen radicals. In the beginning, the physiologists were very skeptical, but over time we started to convince them that if the cell/tissue redox status changes towards more prooxidative conditions, then •NO can turn into •NO-derived oxidants, including peroxynitrite. This subtle change depends on very fast reactions that are very hard to measure biologically. There was no doubt that the test tube biochemistry we were doing was good, but the main question was: How much of this can be translated to medicine and disease?

PNAS: How did you show that your findings were biologically relevant?

Radi: Oxygen radicals and oxidants are very short-lived and transient molecules. So it was much easier to demonstrate these reactions in test tubes, and harder to demonstrate these reactions in cells, tissues, and animals. It took a huge effort to show that in addition to being chemically feasible, these reactions were also biologically feasible and biochemically relevant. We had to develop several analytical and immunochemical methods, incorporating methods from physics and chemistry. By the mid-2000s I think it was totally accepted that these intermediates are being formed biologically and

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they are related to many disease conditions. That opened the possibility of pharmacological and therapeutic interventions to either inhibit the formation of these toxic oxidants, or after they are formed, to decompose them to minimize undesirable oxidation reactions. It's been a long process, and it's been a great feeling of satisfaction seeing all of the pieces come together.

PNAS: What have you discovered about the role of redox reactions in American Trypanosomiasis?

Radi: American Trypanosomiasis (Chagas disease) is now a global problem and a very debilitating disease, and one for which we basically are very limited in drug options. Over the last two decades I've researched the molecular basis of *Trypanosoma cruzi* infection in mammalian cells. We specialized in recognizing the redox cross-talk between *Trypanosoma cruzi* and the mammalian cell, because this is an intracellular parasite. *T. cruzi* are equipped with a strong antioxidant system that can neutralize the mediators being released by the mammalian cells to kill the parasite. We have identified the mediators going from the host to the parasite, and we have identified enzymatic antioxidant defenses of the parasite. We are trying to generate molecules that we can utilize to tackle the antioxidant defenses of the trypanosomes to kill them more efficiently, and these ideas can be extrapolated to other intracellular organisms, such as *Mycobacterium* and others that also utilize antioxidant defenses to escape the redox mediators of the host.

PNAS: What are some of the medical applications of your work on redox pathways?

Radi: I am in the school of medicine, so my commitment was to show, using animal models and human studies, that this chemistry was also happening in vivo in disease conditions. The oxidants that arise from $^{\bullet}$NO can become pathogenic mediators in diseases such as neurodegeneration, inflammation, atherosclerosis, hypertension, and even in the process of aging. In all these types of diseases, we were able to show that the redox processes were shared. In a way, we were defining some very common molecular mechanisms of disease.

In collaboration with investigators at different centers we are developing strategies to cope with excess formation of peroxynitrite. As a proof-of-concept, we have treated animals that are generating peroxynitrite and other oxidants in the motor neurons that lead to neuronal death, and which become paralyzed because of motor neuron collapse. We treat these animals with mitochondria-targeted antioxidants, and we find that they live longer, and also the muscles in their upper and lower limbs are much stronger. We are also planning to do human studies to test how nutrients and bioactive compounds from foods can modulate redox function in the nervous system. We're looking at two sides of the story: on [the] one hand, how to use good nutritional strategies to slow down the progression of neuronal deterioration and mild cognitive impairment, and on the other hand show how the rate of progression of Alzheimer's can be greatly enhanced just by having an unhealthy diet.

I believe that understanding how to slow down brain aging and how to protect and improve oxygen metabolism in neurons to improve brain health [are] big medical challenge[s].

1 Radi R (2018) Oxygen radicals, nitric oxide, and peroxynitrite: Redox pathways in molecular medicine. *Proc Natl Acad Sci USA* 115:5839–5848.

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