The Birth and Ironing Out of Ferroptosis

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Interviewee:

Brent Stockwell

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It’s easy to view science like researching technologies in the videogame Civilization or advancing to the next age in Age of Empires, where spending a certain amount of resources guarantees you a predictable level of progress, a linear function, if you will, where input equals output. But Dr. Brent Stockwell, Chair of the Department of Biological Sciences and a Professor of Biological Sciences and of Chemistry at Columbia University, knows all too well that this perception can’t be further from the truth.

Dr. Stockwell was named one of the 50 most influential life science individuals in New York; after all, it isn’t everyday you find a whole new phenomenon in cell physiology to add to the textbooks. As a chemical biologist, he is most widely known for discovering and coining the term “ferroptosis,” a form of cell death separate from the major types known to scientists so far: apoptosis, necrosis, and autophagy. What distinguishes ferroptosis is that it is driven by iron-dependent lipid peroxidation, where the cell's usual antioxidant defenses can’t sufficiently counter the iron-catalyzed peroxidation of polyunsaturated fatty acids (PUFAs) incorporated into membrane phospholipids, and the rapid propagation of lipid radicals throughout the membrane compromises its integrity.[1,2] This mechanism looks morphologically, biochemically, and genetically different from the other forms of cell death, and the beginnings of this concept are summarized neatly in Dr. Stockwell’s landmark paper in *Cell*, “Ferroptosis - An Iron-Dependent Form of Nonapoptotic Cell Death.”

Upon reading this paper, one will find a very logical sequence of experiments that led to the astonishing conclusion that what they were observing couldn’t be explained by preexisting science. Two structurally unrelated small molecules, erastin and RSL3, were found to be selectively lethal to RAS mutant tumor cells without any of the classical features of apoptosis, necrosis, and autophagy.[3,4] They did, however, cause an intracellular accumulation of reactive oxygen species (ROS), and this process was inhibited by iron chelation and potentiated by supplementation with exogenous iron but not other divalent metal ions. Further exploration of erastin’s mechanism showed that its inhibition of cystine uptake and consequently the production of the antioxidant glutathione was triggering ferroptosis, with later studies showing RSL3 inhibited the enzyme that used glutathione to detoxify ROS. And finally, a potent inhibitor of ferroptosis, ferrostatin-1, was discovered and used to show that ferroptosis also occurs in the glutamate-induced cell death in rat brains, suggesting this process may be implicated not only in cancers, but also in neurodegeneration.[1,2] One can only step back in awe at the elegance of the series of experiments that birthed this new phenomenon and wonder, “What genius of a mind does it take to pull off such a feat and how was it done with such logic that it almost seems, dare I say, easy?” But this highly condensed, packaged report of the methodology and results of ferroptosis’s discovery fails to capture the toil, complexity, and uncertainty of the whole process. The less obvious nature of the behind-the-scenes was the focus of my interview with Dr. Stockwell.

The first detail to point out is that the findings captured in this one paper was the culmination of 10 years' worth of work. In 2002, Dr. Stockwell's lab ran a synthetic lethal screen of over 20,000 compounds for tumor cells with a common proto-oncogene mutation, the RAS family of small GTPases, as RAS mutant tumors such as pancreatic, lung, and colorectal cancers were notoriously difficult to treat and no drugs targeted RAS directly at the time.[5] What they discovered were two small molecules, the aforementioned erastin and RSL3, that exhibited this highly desirable quality but through what appeared to be a novel type of cell death, and the investigation that followed was motivated by "pure curiosity," not by the question, "Can we get a paper?" but "Can we figure it out?"[3,4] Dr. Stockwell recalls immediately noticing the peculiarity of the observations, but also being aware of the need "to really test it carefully" before jumping to conclusions. He also knew that this could very much be another "black hole," a term he used for such projects as the one he worked on for 5-6 years that just "didn't pan out." One way he described it that struck me particularly poignantly was, "Everyday you have to decide, do I continue this project or do I give it up?" Without a single clue of the timescale this project would take, all Dr. Stockwell could do was tackle one research question at a time, in pursuit of the solution to this puzzle before him, and it took a decade to finally convince himself that this phenomenon he noticed back in 2002 was indeed real and novel.

The publication of the paper in *Cell* in 2012, by no means, meant all doubts were put to rest. The main apprehension on Dr. Stockwell's mind was now, "It could be just some obscure thing that no one would ever find interesting or see in any other case." In fact, he clearly remembered another scientist publishing that exact opinion in the same issue of *Cell*. But alas, over the following years, other labs and scientists started publishing data that corroborated Dr. Stockwell's findings in other models, tissues, and diseases. A particularly meaningful moment was when, encouraged by his colleague, Dr. Stockwell organized a workshop on ferroptosis in 2017, hosted and funded by the Banbury Center at Cold Spring Harbor Laboratory, one of the most renowned science think tanks in the world. This workshop brought together 20-25 scientists working on ferroptosis, and after witnessing for the first time up close this collective validation, Dr. Stockwell remembers finally thinking, "Okay, now I feel good about it." Of course, with the exciting realization that "this [was] becoming a big thing" came much pressure as well, with the possibility of mistakes being revealed in this "big spotlight," but thankfully, Dr. Stockwell's thoroughness in his decade-long, potential "black hole" investigation proved fruitful, and the concern never materialized.

The greater challenge was actually translating the results into therapeutics for clinical use. Despite the large advances in the mechanistic understanding of ferroptosis since the original 2012 paper, effective drugs that purely target ferroptosis have yet to be made 14 years later, although some existing

drugs have been found to partially work through this mechanism. Dr. Stockwell attributes this elusive progress to, in part, the ongoing efforts to identify the right biological target and mechanism of drugging this process, but also, perhaps more largely due to difficulties securing investment. There was a burst in ferroptosis-focused companies, including one founded by Dr. Stockwell and a collaborator, starting around five years ago, but most shut down after running out of funding and due to a lack of a direct path forward. He also pointed out that in the current financing climate, pharma "likes better versions of known drugs…as opposed to a brand new mechanism," as it takes more effort to convince investors on the returns for drugs made from scratch based on biology with less data and precedent for successful translation.

However, Dr. Stockwell remains optimistic, citing the numerous regular conferences around the globe and the substantial growth in the field that he writes about in his 10th anniversary review paper on ferroptosis.[2] His own lab is currently advancing full throttle on all aspects of translation, including finding better targets, improving the selectivity and therapeutic index of drugs, examining patient biomarkers for drug response, and also optimizing the diet as they are discovering the importance of food interactions in mice models. He also reminds me that it typically takes 20-30 years to "to go from basic discovery to the first drug," as demonstrated by "any important discovery from apoptosis to immune checkpoint blockade to CAR-T cells." This was the most transformative insight for me from our entire conversation, as someone who thinks on the scale of a year usually and, at max, four years. Science and furthermore, impact, require time on the scale of lifespans, and to be able to push through all the uncertainty that necessarily follows, one must adopt a grander perspective, a humble patience, and a love for curiosity itself, as Dr. Brent Stockwell has and continues to model.

References:

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