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Oxidative stress as an iceberg in carcinogenesis and cancer biology

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ABSTRACT

After the conquest of numerous infectious diseases, the average life span for humans has been enormously prolonged, reaching more than 80 years in many developed countries. However, cancer is one of the top causes of death, and its incidence continues to increase in many countries, including Japan. I was deeply influenced during my career as a cancer researcher by the concept of oxidative stress, which was established by Helmut Sies in 1985. I have no doubt that oxidative stress is a major cause of carcinogenesis in humans but that other factors and chemicals modify it. Notably, established cancer cells are more oxidatively stressed than their non-tumorous counterparts are, and this stress may be associated with selection under oxidative stress and, thus, faster proliferation compared with non-tumorous cells. For cancer prevention, both avoidance of specific risks that are associated with genetic susceptibility and decreasing oxidative stress in general should delay carcinogenesis. For cancer therapy, individualization and precision medicine require further research in the future. In addition to the currently burgeoning array of humanized antibodies and protein kinase inhibitors, novel methods to increase oxidative stress only in cancer cells would be helpful.

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1. Introduction

The concept of oxidative stress was established by Helmut Sies in 1985 [1], which is when I graduated from the medical school of Kyoto University. When I reflect on all of my present publications, I recognize how deeply I have been influenced by the concept of oxidative stress, and I am satisfied that what we have been heading is still true (Fig. 1).

When I was a medical student, I belonged to the Department of Pathology, under the guidance of Shigeru Okada (assistant professor) and Osamu Midorikawa (professor) as my mentors. At that time, they were very excited to find that an iron chelate, ferric nitrilotriacetate (Fe-NTA), could induce renal carcinogenesis in rats [2,3] and mice [4]. Basically, iron is insoluble in water at neutral pH. However, Fe-NTA as a chelated iron is soluble at neutral pH [5,6] and is present in this form at least for a few hours *in vivo* [7]. Fe-NTA has been used to load iron to transferrin [8]. Michiyasu Awai of Okayama University noticed that intraperitoneal injections of Fe-NTA into rats loaded iron in various parenchymal cells, which was not possible by other means. He proposed this as a model of hemochromatosis and revealed the iron deposition in hepatocytes and β-cells in pancreatic islets [7]. The point is that Shigeru Okada's finding of renal cell carcinoma after repeated Fe-NTA administration was serendipitous because he did not euthanize the rats after the subchrionic repeated treatment of Fe-NTA for a few months. Then, Okada and Midorikawa found a high incidence of renal cell carcinoma, and this model was first reported in Japan in 1982 [2]. At that time, the exact molecular mechanisms of renal cell carcinogenesis were not known.

2. Role of iron in oxidative stress

Helmut Sies edited and published a book on the concept of oxidative stress in 1985, which was fortunately translated into the Japanese language by Masayasu Inoue [1]. Then, after reading the book and the many subsequent discussions, Prof. Okada's research team members and I became interested in oxidative stress associated with the Fe-NTA model.

Iron is a catalyst for the famous Fenton reaction: $Fe(II) + H_2O_2 \rightarrow Fe(III) + OH\cdot + OH^-$ [9]. However, this is a chemical reaction in the tubes. Few people at that time believed that this reaction could occur *in vivo*. Indeed, hydroxyl radical is the most reactive chemical species in the biological system [10,11]. In 1979, Prof. Kunio Yagi established a method to measure lipid peroxidation using thiobartiburic acid [12]. Shuji Hamazaki

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Fig. 1. Helmut Sies, Yuji Naito (left) and myself (right) at the 17th Biennial Meeting of the Society for Free Radical Research International held in Kyoto on March 24–27, 2014. Yuji Naito and I were co-chairmen of the meeting, and Helmut Sies gave a Trevor Slater award lecture.

in Okada's laboratory used this method and showed a renal increase in lipid peroxidation in an acute phase of Fe-NTA treatment [13].

In 1987, I officially entered the project as a graduate student under Shigeru Okada. Thereafter, morphological methods became available through the use of frozen sections [14], and we could show the localization of lipid peroxidation catalyzed by iron in the renal proximal tubules [15], which are the target cells for carcinogenesis in this model. Then, we developed monoclonal antibodies to detect oxidative stress using 8-hydroxy-2′-deoxyguanosine (8-OHdG) [16]- and 4-hydroxy-2-nonenal (HNE) [17]-modified keyhole limpet hemocyanin as antigens. This was based on the fact that hydroxyl radicals could produce such products with a most prominent increase [18,19] and that the levels of 8-OHdG and HNE-modified proteins are the sum of production and the repair [20]. Using these monoclonal antibodies, it became possible for the first time to localize oxidative stress in paraffin-embedded sections; this is a routine method for pathologic diagnosis in medicine, and the paraffin blocks for sections can be stored at room temperature for decades. Currently, these antibodies are commercially available and popular among researchers [11].

3. Role of iron in carcinogenesis and cancer as evolution

Then, we realized that the iron-induced oxidative stress of chronic nature is indeed able to cause cancer in mammals. In 1996, I summarized the strong association between iron overload and carcinogenesis with a great deal of evidence [10]. The rodent renal carcinogenesis model by Fe-NTA was the first to demonstrate iron carcinogenicity, with an anatomical location other than the iron injection site as the target. Thereafter, the evidence based on human epidemiology and animal experiments greatly increased to support the role of iron-induced oxidative stress [21,22]. The paper that appealed most strongly to me was one demonstrating that phlebotomy twice a year for 5 years (500 ml each) significantly reduced both cancer risk and cancer occurrence in the US [23]. It is known that there is no active pathway to excrete iron to outside the body once it is absorbed into the blood. Only hemorrhage/phlebotomy or iron chelation therapy can decrease the total body iron stores.

With the development of next-generation sequencing, it is now established that the genomic alterations in cancer cells are similar to the evolution from apes to Homo Sapiens, as suggested by Charles Darwin [24]. Specifically, advanced or metastasized cancer cells have obtained new mutations in addition to the original genomic alterations found in the primary tumor [25]. I have been long interested in the issue of whether there are any target genes in oxidative stress-induced carcinogenesis. In the 1990s, we used F1 rats from two genetically distant inbred strains and microsatellite analysis in Fe-NTA-induced renal carcinogenesis to determine that *p16/p15* tumor suppressor genes are the major targets for deletion [26]. In 2012, we used a more sophisticated method (array-based comparative genomic hybridization) to confirm the *p16/p15* results and, further, to find *c-Met* amplification in a large proportion of tumors [27]. Thus, there are definitely target genes in iron-mediated oxidative stress-induced carcinogenesis. Of note, these genomic alterations at the chromosomal level were similar in pattern to those of human cancers, which have not been observed in other rodent models. Therefore, we hypothesized that iron-induced oxidative stress is a major cause, i.e., an iceberg, of human cancer (Fig. 2). A recent finding that cell-of-origin chromatin organization shapes the mutational landscape of cancer [28] strongly supports our hypothesis by suggesting the presence of a common endogenous mechanism to induce mutation in all types of cells.

Asbestos is a natural fibrous mineral that has been commonly used over the last century worldwide because of its resistance to heat, acid and friction with economical merits. However, it now presents a burden to society because of the unexpected occurrence of malignant mesothelioma (MM), which has an extremely long incubation period of 30–40 years after exposure. The expected peak year for asbestos-induced MM is 2025 in Japan [29,30]. Given this situation, my laboratory is focused on elucidating the molecular carcinogenic mechanisms of asbestos-induced mesothelial carcinogenesis using rodents. During this process, we found that iron overload in the nearby mesothelium is an important pathology in a rat model. Notably, asbestos-induced rat MM showed similar genetic alterations to Fe-NTA-induced rat renal carcinogenesis, including the homozygous deletion of *p16/p15* tumor suppressor genes, which is also a frequent observation in human MM [31,32]. Based on these observations, we tested iron chelation therapy with deferasirox as a preventive strategy after asbestos exposure in the rat model. We observed a fractional change in histology from highly aggressive sarcomatoid subtype to epithelioid subtype that shows a more favorable prognosis [33].

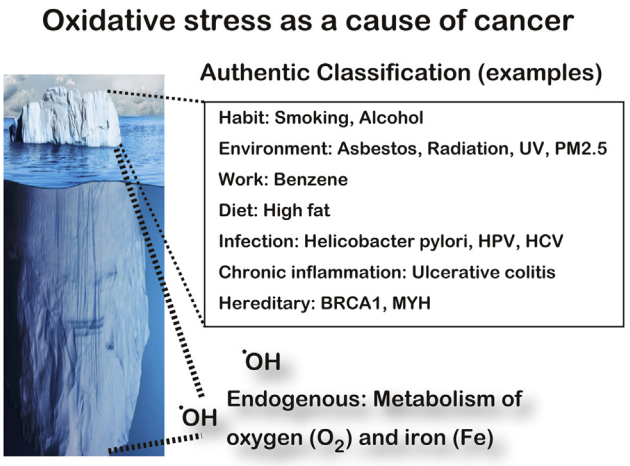

Fig. 2. Oxidative stress as an iceberg in carcinogenesis.

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