A Lesson From the Thalidomide Tragedy
— The Past Is Never Dead. It’s Not Even Past. William Faulkner,
From “Requiem for a Nun” —

Kenta Yashiro, MD, PhD; Shigeru Miyagawa, MD, PhD; Yoshiki Sawa, MD, PhD

Thalidomide is well known to cause syndromic congenital defects, so-called thalidomide embryopathy (TE).1 In 1957, this drug was released into the market as an over-the-counter drug of a non-addictive/ non-barbiturate sedative as well as an antiemetic. Thalidomide ameliorated “morning sickness” in pregnant women and was tragically believed to be harmless. As a result, at least over 10,000 babies were confirmed to suffer from severe congenital defects in many organs, including limb, face, eyes, ears, external genitalia, vertebrae, heart, kidney, and gut. Unfortunately, it remains unclear how many women took this drug during their pregnancy until it was withdrawn from most parts of the world in 1962. Given the potential miscarriage and stillbirths caused by thalidomide,1,2 the number of affected babies and the range of TE-associated phenotype might have been considerably underestimated.

Although TE is the biggest man-made disaster in modern medicine, thalidomide is still prescribed. In addition to its sedative and antiemetic actions, it is known to be antiangiogenic, immunomodulatory, and antineoplastic (Figure 1). These pharmacological actions are beneficial for treating erythema nodosum leprosum and multiple myeloma,3 and it is now used to treat them. In industrialized countries, its use is carefully monitored under strict guidelines such as “THALOMID Risk Evaluation and Mitigation Strategy” in USA (http://www.thalomidrems.com/about.html) and “Thalidomide Education and Risk Management System” in Japan (http://www.fujimoto-pharm.co.jp/priyakuhin/thalido/pdf/TERMS-5.pdf). However, we already know that TE is not a past problem.1,3 In 1996, it was reported that TE had still been occurring in South America since the early 1960s. That report revealed that a total of 34 patients with TE were confirmed to be born between 1969 and the 1990s. All of them, 33 cases in Brazil and 1 in Argentina, were related to leprosy treatment.

In developing countries, where leprosy is at endemic
YASHIRO K et al.

also suggesting that kidney development in the fetus is susceptible to thalidomide. Despite the anatomical anomalies, kidney function of all the patients was not problematic. Thus, functional impairment of the kidney is not generally a concern in many cases of long-term TE survivors, albeit morphologically anomalous. Of note, the authors indicate that severe cases were probably filtered from the study population in their report, because all of the subjects were long-term survivors. We should understand that this result does not necessarily certify that kidney function is not impaired in TE patients with anatomically anomalous renal systems. The authors highlight the importance of careful examination of the internal organs of TE patients before they may have to undergo a surgical procedure.

This report reminds us again of the critical problems to be solved in TE. We do not yet know the whole picture of potent anatomical anomalies of the internal organs. The old information in the 1960s has been fragmented and/or limited mainly to severe cases. The details that can be identified with currently available methods are missing. Given the possibility that the spectrum of organ malformation caused by thalidomide is wider than we ever thought, we should carefully follow up both old and new cases, as well as performing further basic scientific study on teratogenicity. Importantly, we do not yet know the detailed molecular mechanism of thalidomide affecting organ development as well as providing a beneficial pharmacological effect. In 2010, CRBN (Cereblon) was found to be a direct molecular target of thalidomide (Figures 1, 2).

Figure 2. CRBN theory. Cereblon (CRBN) plays a significant role in ubiquitin-mediated protein degradation. Normally, CRBN binds E3 ubiquitin ligase, specifying the ubiquitin ligase complex for its substrate. If thalidomide binds CRBN, the original specific substrate cannot interact with the ubiquitin ligase complex and it accumulates without degradation. Thalidomide likely affects the specificity of the ubiquitin ligase for its substrate, and alternative substrates are possibly degraded via the proteasome. Note that some phenotypes associated with thalidomide embryopathy might result from another function of CRBN that has nothing to do with ubiquitination.

proportions and the prescription is difficult to robustly control, new TE babies are still potentially born.4,5

It is widely believed that the antiangiogenic action of thalidomide is responsible for the majority of TE phenotypes, including phocelemia.1,6 This action might cause as-yet-unknown congenital vascular anomalies. Nevertheless, we do not know much about vascular defects in TE cases. Only one previous study has systematically elucidated this issue.7 In that report, persistent left superior vena cava, duplicated middle cerebral artery, aberrant right subclavian artery, and anomalous azygous vein connection to superior vena cava were identified among 22 Japanese TE patients who had survived up to around 50 years old, with a higher prevalence rate (13.6%) than in a healthy control population (0.6%). Unfortunately, in addition to a relatively small population size for statistical analysis, CT scan was used, although magnetic resonance imaging/angiography (MRI/A) is superior for such purposes. Thus, some anomalies might have been missed in that report.

In this issue of the Journal, Weinrich et al.8 report their systematic elucidation of the anomalies of both vasculature and internal organs of TE patients. They recruited 78 patients who were surviving thalidomide babies born in the late 1950s and early 1960s, and examined them using MRA. Although the population size was limited, they found that (1) 69% of patients had arterial anomalies, (2) 31% had venous anomalies and (3) 19% had kidney and/or gallbladder anomalies. All these anatomical defects showed a higher prevalence than normal. The evidence of vascular phenotypes other than those identified in the previous study7 suggests that thalidomide affects a wider range of vascular developmental stages. No anomalies of other organs apart from the kidney and gallbladder were identified, and renal arterial anomaly was the most frequent, also suggesting that kidney development in the fetus is susceptible to thalidomide. Despite the anatomical anomalies, kidney function of all the patients was not problematic. Thus, functional impairment of the kidney is not generally a concern in many cases of long-term TE survivors, albeit morphologically anomalous. Of note, the authors indicate that severe cases were probably filtered from the study population in their report, because all of the subjects were long-term survivors. We should understand that this result does not necessarily certify that kidney function is not impaired in TE patients with anatomically anomalous renal systems. The authors highlight the importance of careful examination of the internal organs of TE patients before they may have to undergo a surgical procedure.

This report reminds us again of the critical problems to be solved in TE. We do not yet know the whole picture of potent anatomical anomalies of the internal organs. The old information in the 1960s has been fragmented and/or limited mainly to severe cases. The details that can be identified with currently available methods are missing. Given the possibility that the spectrum of organ malformation caused by thalidomide is wider than we ever thought, we should carefully follow up both old and new cases, as well as performing further basic scientific study on teratogenicity. Importantly, we do not yet know the detailed molecular mechanism of thalidomide affecting organ development as well as providing a beneficial pharmacological effect. In 2010, CRBN (Cereblon) was found to be a direct molecular target of thalidomide (Figures 1, 2). CRBN was initially thought to regulate the development of the brain and cognition through ATP-dependent protein degradation affecting calcium signaling as a Lon protease family protein.9–12 Now, CRBN is known to significantly play a role in ubiquitin-mediated protein degradation as
well (Figure 2). Direct binding of thalidomide to CRBN interferes with this process, consequently resulting in downregulation of the FGF signal and immune system modulation. The antiangiogenic effect, immunomodulation, and pathological process of phocomelia can be explained by the CRBN theory to some extent; however, the existence of another possible molecular target is not excluded. Thus, further study is vital to better understand the molecular action of thalidomide.

Conflict of Interest Statement

K.Y. is affiliated with the endowed department sponsored by Terumo and DNP, and S.M. by ROHTO Pharmaceutical.

References