Unlocking a mystery of thalidomide

May 1 2014

In the 1950s and 1960s, pregnant women with morning sickness were often prescribed the new drug thalidomide. Shortly after the medicine was released on the market, a reported 10,000 infants were born with an extreme form of the rare congenital phocomelia syndrome, which caused death in 50 percent of cases and severe physical and mental disabilities in others. Although various factors are now known to cause phocomelia, the prominent roots of the disease can be found in the use of the drug thalidomide.

Now, half a century later, new research by Dr. Noam Shomron, Prof Arkady Torchinsky, and doctoral student Eyal Mor at Tel Aviv University's Sackler Faculty of Medicine, published in *Archives of*

Toxicology, identifies a regulator responsible for the malformation of limbs in phocomelia, pinpointing a specific target for possible future intervention.

"We were reading old textbooks from the 1950s and '60s, trying to understand the studies carried out then on this intriguing topic, and we saw that we could undertake an in-depth examination of the disorder's processes using careful planning and execution of experiments on mouse and rat models," said Dr. Shomron. "We hoped to gain a much better understanding of embryo malformation."

In the genes

Prof. Torchinsky worked together with Mor to carry out an experiment on animal models in the laboratory. They injected mice and rats with an embryo malformation factor or "teratogen" (called 5-aza-2'-deoxycytidin) with effects similar to thalidomide. The chemical is also used in chemotherapeutics. With the factor, the researchers induced phocomelia in either the forelimbs or hind limbs of the animals.

Afterward, by analyzing the entire gene and tiny regulatory RNA molecules called microRNAs in all the mouse limbs (both healthy and afflicted), the researchers were able to pinpoint the genetic regulator—the precise "switch" turned on or off during genetic processes—responsible for the malformation, p53, and its downstream target gene, MicroRNA34.

"We have added another perspective to the overall picture by investigating the genetic mechanisms involved—in other words, the gene expression rather than the genetic code affected during pathology," said Dr. Shomron. "I expect that further understanding of the mechanisms involved in teratogens and how they induce phocomelia will help reveal the dangers associated with toxins and will also reveal the underlying

functional role of genes and microRNAs modulating genetic expression in the process."

Dr. Shomron said the work carried out by the team addresses a long-standing paradigm of limb malformation in mammals and reflects the role that epigenetic regulation, as opposed to genetic regulation, plays in the development of disease. In other words, embryonic development can be caused by a genetic mutation (a "mis-print" in the book of life) or, in this case, by turning the genes on or off without any change in the genetic code itself. Dr. Shomron and his team are currently studying the effects of other toxins on the mal-development of mammalian embryos.

Provided by Tel Aviv University