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Retinoic acid's reproducible future

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Abstract

Science is facing a reproducibility crisis. In the biomedical sciences, the inability to validate and reproduce findings is slowing progress in understanding basic biological principles. Among the fields hindered by irreproducibility is retinoic acid (RA) research. Fortunately, new techniques provide a way forward.

Vitamin A (retinol) has been known for more than 100 years to be a nutrient essential for growth and development, and 30 years ago its metabolite RA was discovered to function as a ligand for nuclear RA receptors that control gene expression (1, 2). Since then, conclusions based on treatment of cell lines or animals with RA or antagonists of RA receptors have often not been supported by animal studies in which genes encoding RA biosynthesis enzymes or RA receptors are deleted (3). In addition, many conclusions based on treatment of cell lines or animals may be questionable because nonphysiological amounts of RA or RA receptor antagonists were used or because we don't know whether a function identified in a cell line occurs in vivo (4). After three decades, it is clear that understanding the widespread endogenous function of RA—including in the development of the limbs, vertebrae, heart, spinal cord and brain, reproductive system, and other internal organs—requires the rigor of gene “knockout” studies to validate what is reported in treated cultured cells or animals.

To improve credibility in the biomedical sciences, researchers should provide evidence that the gene, protein, molecule, or DNA control element they plan to examine is required for a specific biological process in vivo before they embark on detailed studies to explore the mechanism. With the advent of gene-editing tools, such as the CRISPR/Cas9 system, the generation of gene knockout animals is much easier and knockouts of gene families are possible (5, 6). A clear distinction between studies that report physiological functions versus pharmacological functions will clear the path toward a true understanding of biology, while ensuring that pharmacological insights relevant to combatting disease are put into the correct perspective. In this way, those who study RA signaling can most effectively further the great efforts that resulted in the discovery of the RA receptors 30 years ago. With the constant improvement of gene editing tools, biomedical scientists can begin to move beyond the obstacles that have led to the field's reproducibility problems.

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