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THE MISUNDERSTOOD KNIGHT?

Relevant for: Science & Technology | Topic: Biotechnology, Genetics & Health related developments

Arsenic is an acknowledged villain because of the way it has contaminated groundwater reserves. Its reputation as a poison has a long history and stretches back to fourth century treatises on medicine. This has often led inventive physicians to use the metal's poisonous nature to treat infections.

Its elusive nature has also complicated an understanding of the relationship between arsenic and cancer. Beyond certain thresholds in drinking water, arsenic is strongly linked to various cancers; however, at other doses, it has been linked to unusually low rates of breast cancer.

Arsenic trioxide (ATO) is an oxide of arsenic that was approved by the U.S. Food and Drug Administration in 1995, and when used in combination with another drug called all-trans retinoic acid (ATRA), it was effective against a kind of leukaemia called acute promyelocytic leukaemia (APL). However, it wasn't fully clear what cellular target(s) these drugs act on, how they interact with each other, or whether they might be effective against other types of cancer.

Last week, U.S. researchers reported in *Nature Communications* that they had unearthed a vital clue: Arsenic in combination with an existing leukaemia drug worked to destroy Pin1, a unique enzyme that the same group of researchers had discovered more than 20 years ago. When given in clinically safe doses, the drugs effectively inhibited numerous cancer-driving pathways and eliminated cancer stem cells in cell and animal models as well as patient-derived tumour models of triple-negative breast cancer, which has the worst prognosis of all breast cancer subtypes.

Pin1 is known as a master regulator of cancer signalling networks that activates more than 40 cancer-driving proteins and inactivates more than 20 tumour suppressing proteins. The enzyme was found to be over-activated in most human cancers and is especially active in cancer stem cells — a subpopulation of cancer cells believed to drive tumour initiation, progression, and metastasis, but not effectively targeted by current therapies.

The researchers found that mice that lack expression of Pin1 were highly resistant to developing cancer even when their cells over-expressed oncogenes (cancer causing genes) or lacked expression of tumour suppressors. Notably, these animals displayed no obvious defects for over half of lifespan, suggesting that targeting this master switch of an enzyme may be safe.

Although the anti-cancer effects of ATO are potently amplified by ATRA co-treatment, ATRA has a very short time span of effectiveness. This insight could help hitch ATO to existing therapies particularly triple-negative breast cancer.

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