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BIM gene variation in East Asians found to explain resistance to cancer drugs

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A multi-national research team led by scientists at Duke-NUS Graduate Medical School has identified the reason why some patients fail to respond to some of the most successful cancer drugs.

Tyrosine kinase inhibitor drugs (TKIs) work effectively in most patients to fight certain blood cell cancers, such as chronic myelogenous leukemia (CML), and non-small-cell lung cancers (NSCLC) with mutations in the EGFR gene.

These precisely targeted drugs shut down molecular pathways that keep these cancers flourishing and include TKIs for treating CML, and the form of NSCLC with EGFR genetic mutations.

Now the team at Duke-NUS Graduate Medical School in Singapore, working with the Genome Institute of Singapore (GIS), Singapore General Hospital and the National Cancer Centre Singapore, has discovered that there is a common variation in the BIM gene in people of East Asian descent that contributes to some patients' failure to benefit from these tyrosine kinase inhibitor drugs.

"Because we could determine in cells how the BIM gene variant caused TKI resistance, we were able to devise a strategy to overcome it," said S. Tiong Ong, M.B.B. Ch., senior author of the study and associate professor in the Cancer and Stem Cell Biology Signature Research Programme at Duke-NUS and Division of Medical Oncology, Department of Medicine, at Duke University Medical Center.

"A novel class of drugs called the BH3-mimetics provided the answer," Ong said. "When the BH3 drugs were added to the TKI therapy in experiments conducted on cancer cells with the BIM gene variant, we were able to overcome the resistance conferred by the gene. Our next step will be to bring this to clinical trials with patients."

Said Yijun Ruan, Ph.D., a co-senior author of this study and associate director for Genome Technology and Biology at GIS: "We used a genome-wide sequencing approach to specifically look for structural changes in the DNA of patient samples. This helped in the discovery of the East Asian BIM gene variant. What's more gratifying is that this collaboration validates the use of basic genomic technology to make clinically important discoveries."

The study was published online in *Nature Medicine* on March 18.

If the drug combination does override TKI resistance in people, this will be good news for those with the BIM gene variant, which occurs in about 15 percent of the typical East Asian population. By contrast, no people of European or African ancestry were found to have this gene variant.

"While it's interesting to learn about this ethnic difference for the mutation, the greater significance of the finding is that the same principle may apply for other populations," said Patrick Casey, Ph.D., senior vice dean for research at Duke-NUS and James B. Duke Professor of Pharmacology and Cancer Biology. "There may well be other, yet to be discovered gene variations that account for drug resistance in different world populations. These findings underscore the importance of learning all we can about cancer pathways, mutations, and treatments that work for different types of individuals. This is how we can personalize cancer treatment and, ultimately, control cancer."

"We estimate that about 14,000 newly diagnosed East Asian CML and

EGFR non-small-cell lung cancer patients per year will carry the gene variant," Ong said. "Notably, EGFR NSCLC is much more common in East Asia, and accounts for about 50 percent of all non-small-cell lung cancers in East Asia, compared to only 10 percent in the West."

The researchers found that drug resistance occurred because of impaired production of BH3-containing forms of the BIM protein. They confirmed that restoring BIM gene function with the BH3 drugs worked to overcome TKI resistance in both types of cancer.

"BH3-mimetic drugs are already being studied in clinical trials in combination with chemotherapy, and we are hopeful that BH3 drugs in combination with TKIs can actually overcome this form of TKI resistance in patients with CML and EGFR non-small-cell lung cancer," Ong said. "We are working closely with GIS and the commercialization arm of the Agency for Science, Technology & Research (A*STAR), to develop a clinical test for the BIM gene variant, so that we can take our discovery quickly to the patient."

Provided by Duke University

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