MedicalXpress

New research uncovers diverse metabolic roles for PML tumor suppressor gene

August 30 2012

Two papers led by scientific teams from the Cancer Genetics Program at Beth Israel Deaconess Medical Center (BIDMC) shed new light on the genetic mechanisms underlying cellular energy and metabolism and, at the same time, highlight both the challenges and opportunities of genetic approaches to cancer treatment.

Appearing in the September 2012 issues of The Journal of Clinical Investigation (JCI) and *Nature Medicine*, the new findings reveal surprising insights into how PML regulates metabolism via the fatty acid oxidation (FAO) pathway and, in the process, uncover paradoxical roles for this tumor suppressor gene.

"The real story lies in the juxtaposition of these two papers, the way they jointly illuminate the braided function of PML in the FAO pathway," says the papers' senior author Pier Paolo Pandolfi, MD, PhD, Director of Cancer Genetics at BIDMC and George C. Reisman Professor of Medicine at Harvard Medical School. The Pandolfi laboratory has been studying the PML (promyelocytic leukemia protein) tumor suppressor gene, for more than 20 years.

Fatty-acid oxidation is the fat-burning metabolic process that is of importance to the energy of all cells. The two studies examined the impact of the FAO process in different biomedical situations including obesity, breast cancer and hematopoetic stem cell maintenance. Importantly, both publications determined that the FAO pathway could be a target for pharmacologic treatments.

The *JCI* paper defines the mechanism by which PML regulates FAO (involving the regulation of peroxisome proliferator-activated receptors or PPARs). According to first author Arkaitz Carracedo, PhD, a former postdoctoral fellow in the Pandolfi laboratory and currently Ikerbasque Research Professor at the research institute CIC bioGUNE, Bizkaia, Spain, the findings demonstrate that alterations in this pathway result in excessive fat accumulation and obesity in genetically engineered mouse models. In other words, when PML is highly expressed, cellular metabolism is enhanced and the mice were able to briskly burn fat and avoid gaining weight. Conversely, when PML was lost, the animals grew obese.

But, the team also made the paradoxical discovery that PML's enhanced cellular metabolism appeared to provide breast cancer cells with the energy needed to survive. These findings are further supported by data showing PML is highly expressed in a subset of breast cancers with poor prognosis, notes Carracedo. Instead of maintaining its function as a tumor suppressor and keeping breast cancer cells under control, PML is providing breast cancer with a survival advantage. These findings aligned with work by other labs that have found a relationship between high PML expression and breast cancers with poor prognosis.

In the second paper, in the September 2012 issue of *Nature Medicine*, Keisuke Ito, MD PhD, together with co-lead author Arkaitz Carracedo, looked at PML's role in regulating hematopoetic stem cells (HSCs), again through the FAO pathway, and defined for the first time the contribution of lipid metabolism to maintaining the function of HSCs.

HSCs replenish blood cells throughout the lifespan of an organism, and so they are critical to the aging process, explains Ito, also a former postdoctoral fellow in the Pandolfi laboratory and currently a member of the faculty at the Albert Einstein College of Medicine. The authors discovered that inhibition of fatty acid oxidation could represent an

effective therapy for leukemia, as well as other forms of cancer – but that it simultaneously posed a risk to the replenishment of HSCs. "Our results uncover a crucial metabolic requirement involving PPAR-delta signaling and FAO for preservation of the delicate equilibrium between HSC maintenance and function," the authors write. The findings have straightforward therapeutic implications for the improvement of both the efficacy of bone marrow transplantation (BMT) and the treatment of hematological malignancies.

"These two studies highlight both the opportunities and complexities of genetic approaches to human disease," notes Pandolfi. "Our next logical step will be to identify a potential path for therapeutic intervention through the opposing Scylla and Charybdis-like threats and benefits of this pathway," he says, referring to the two sea monsters that sailors of mythology had to navigate. "Through pharmacological dosage and scheduling, we will come up with a way to reap the benefits of PML and FAO regulation, while reducing or even eliminating its risks. The opportunity is there since we have drugs that can modulate both PML levels and FAO, and we have begun testing these concepts right away in our 'mouse hospital.'"

Provided by Beth Israel Deaconess Medical Center