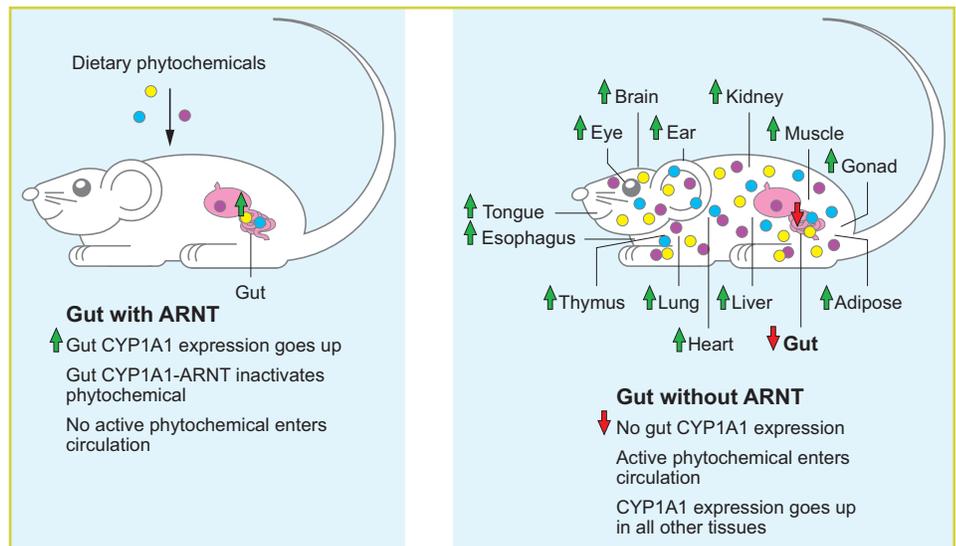


## Modulating Cancer Risk: The Gut Takes Control

Cancer risk is influenced by a number of factors, including exposure to chemicals in food and drugs and other molecules in the environment. Some of these chemicals may increase risk of developing cancer, while others, including many chemicals in vegetables, may confer protection.

The body has a sophisticated system for processing the chemicals with which it comes into contact. The workhorses of this system are metabolic enzymes called cytochromes P450, or CYPs. CYPs comprise a large family of enzymes; each CYP targets certain types of chemicals and may be more or less active in different parts of the body. Interestingly, the relationship between CYPs and cancer risk is not cut and dry. Some studies have suggested that CYPs elevate cancer risk by activating potentially carcinogenic chemicals that enter the body, but other studies have shown that CYPs have a protective effect. The truth likely falls somewhere in between—the interaction between this complex system and environmental chemicals is probably a delicate balance that can tip in favor of increased risk or prevention depending on a number of factors. Gaining a better understanding of the intricacies of this system could contribute to development of chemopreventive interventions.



When mouse gut has the *ARNT* (a nuclear transporter) gene expressed, the *CYP1A1* gene expression goes up, and phytochemicals in the diet are inactivated and removed from circulation. When *ARNT* expression is missing from the gut, phytochemicals circulate and *CYP1A1* expression rises in all other mouse tissues.

The intestines are one of the first lines of defense against chemicals ingested orally. In addition to absorbing nutrients, this lengthy organ expresses many CYPs that modify chemicals before they enter the circulation. A recent study published in *The Journal of Clinical Investigation* by Frank Gonzalez, Ph.D., Chief of CCR's Laboratory of Metabolism, and colleagues used a new mouse model to reveal an important role for the chemical processing system of the gut in regulating the activities of chemical processing systems virtually everywhere else in the body.

The study focuses on CYP1A1, a well-characterized CYP family protein that

has been observed both to confer protection from potentially carcinogenic agents and to increase cancer risk by converting procarcinogens into a form that can lead to DNA mutations. Expression of the *CYP1A1* gene is induced by a transcription factor called AhR. AhR interacts with foreign chemicals in the body and then forms a complex with another protein, AhR nuclear translocator (ARNT); together, these two proteins affect the expression of many CYPs, including CYP1A1.

The Gonzalez lab created a mouse that does not express the *ARNT* gene in the gut but has normal expression of the protein in all other tissues of

the body. As expected, loss of ARNT led to lower expression of the CYP1A1 protein in the cells of the gut. However, much to the surprise of Gonzalez and his colleagues, expression of CYP1A1 dramatically increased in virtually every other part of the mouse, despite the fact that both ARNT and AhR were expressed normally in these tissues. They found that the increase in CYP1A1 in peripheral tissues was dependent on a phytochemical—or chemical of plant origin—in the mice's diet. They concluded that CYP1A1 in the gut would normally metabolize this phytochemical,

preventing it from entering the body in its active form. However, when CYP1A1 is not present—in this case due to lack of ARNT—the phytochemical is free to move into circulation and induces expression of the *CYP1A1* gene in other tissues.

This study provides the first evidence that an intestinal regulatory system mediated by a dietary phytochemical can control the activity of chemical processing systems in the whole body. It is not known whether the shift in *CYP1A1* gene expression and activity from the gut to other tissues will be

protective or detrimental with respect to cancer, but the knowledge that the regulation of intricately intertwined chemical processing systems is involved should help researchers move one step closer to understanding how these systems can be manipulated to prevent cancer.

## Reference

Ito S, Chen C, Satoh J, Yim S, Gonzalez FJ. Dietary phytochemicals regulate whole-body CYP1A1 expression through an arylhydrocarbon receptor nuclear translocator–dependent system in gut. *J Clin Invest* 117: 1940–50, 2007.