It's shaped like a bow tie, and it sits right where such a tie would be worn—at the front of the throat. But the thyroid gland is anything but decoration. In fact, it's one of the master glands of the body, sending out signaling hormones that help control everything from heart rate and blood pressure to our body temperature, metabolism, and weight. But as with many organs in the body, things can go wrong. In fact, the thyroid gland is the single most common organ to be attacked by autoimmune disease. That's part of the reason that the thyroid is so interesting to doctors and scientists in the division of Metabolism, Endocrinology & Diabetes (MEND), like Ronald Koenig MD, PhD. Of all the physician-scientists in the MEND division, Dr. Koenig uniquely specializes in two widespread and terribly serious thyroid problems: abnormal thyroid hormone levels in critically ill patients, and thyroid cancer, which kills more than 1,500 Americans yearly.

“Doc, I can’t understand it, if the problem is not in my thyroid, then why are my thyroid hormone levels so low?”

Through research, Dr. Koenig and others have found that abnormal thyroid gland function is linked to many other illnesses that seemingly have nothing to do with it. It’s often associated with a profound downward spiral in a patient’s health status—particularly in critically ill patients in the intensive care unit. Amazingly, virtually every patient with any serious disease or injury develops thyroid dysfunction during the course of their illness. Once upon a time, this might have been a good evolutionary strategy, allowing our ancestors to conserve energy when they were seriously sick or injured.
But in the modern era of intensive-care unit medicine, physicians are beginning to suspect that the mechanism works against us.

In fact, low thyroid hormone levels in critically ill patients have been shown to correlate directly with risk of death. Whether it's patients with chronic heart or liver disease, or intensive-care patients trying to fight off an infection, levels of the thyroid hormone called T3 often drop far below normal. And the lower their T3, the more likely the patient is to die from their illness.

Dr. Koenig’s team is working to explain the roots of “non-thyroidal illness syndrome”—the formal name for this phenomenon. To find out why T3 levels drop, Dr. Koenig and his associate Jingcheng Yu, MS, have led an effort to study specific molecules in the body that underlie the syndrome.

Unfortunately, critically ill patients are not an easy group with which to perform molecular research studies. Instead, using sick mice as a model for sick humans, Dr. Koenig’s team is drilling down to the level of specific proteins and cell signals in a way that would not otherwise be possible.

They’re focusing on the interaction between three key molecules: T3 thyroid hormone; a liver protein known as SRC1 that helps T3 exert its control over the body; and inflammation which causes cell signal molecules called cytokines.

Normally, the liver plays a key role in the body’s production of active T3 by converting a precursor molecule called T4 after it is released into the bloodstream by the thyroid. But certain cytokines inhibit the liver’s ability to make this conversion—especially when a person suffers serious infection or other illness or injury, which causes cytokine release.

To outsmart these effects, Koenig’s research team has developed a way to increase expression of the SRC1 gene, which enhances the action of the remaining T3.

Thus far, this experimental gene-therapy approach has proved effective in preventing non-thyroidal illness syndrome in mice that were given a toxin that ordinarily would have made them very ill, with an associated low T3 level. Next, the team is testing the gene therapy approach against infections, to see if the protective effect can be replicated.

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Although human clinical trials are several years away, this remarkable research is revealing clues as to why non-thyroidal illness syndrome occurs, and it may have important implications for survival from otherwise lethal illness.

“I was referred to see you because my doctor says I have a thyroid nodule that could be cancer…”

Fortunately, the vast majority of thyroid nodules diagnosed each year are not cancers. However, like many other glands, the thyroid is prone to developing cancerous cells that multiply, alter their function, and in some cases spread to other areas of the body, becoming lethal.

Even so, the news is generally good for the 33,000 people diagnosed with thyroid cancer every year. Modern treatments have paved the way for outstanding long-term survival in most patients—with a more favorable outcome than for any other metastasizing solid tissue cancer.

For years, U-M has offered a specialized thyroid cancer clinic at its Comprehensive Cancer Center, where MEND endocrinologists work closely with radiation oncologists, surgeons, nuclear medicine specialists, and others to optimize each patient’s care.

At the same time, Dr. Koenig and his team are developing new tests that may someday allow doctors to better distinguish different forms of thyroid cancer from one another, to identify those thyroid tumors that are likely to be the most aggressive, and to identify in advance those patients most likely to develop certain inherited forms of the disease.

Michigan offers an ideal place to tackle these problems, due to a partnership between the research team and numerous U-M thyroid cancer patients who have allowed the team’s researchers to look in detail at their DNA, and search for genetic “fingerprints” that describe their particular form of thyroid cancer. This effort, which has engaged the advanced capabilities of the U-M gene expression facility, was made possible in part by the Marilyn Collins Thyroid Cancer Fund, created in memory of a patient who died from the disease.

Dr. Koenig and his colleagues—including Thomas Giordano, MD, PhD, of the Department of Pathology, Rork Kuick, MA, of the Cancer Center, and their collaborator Yuri Nikiforov, MD, PhD, of the University of Pittsburgh—have been actively pursuing one particular kind of “genetic shuffling” that can be detected in half of all cases of follicular thyroid cancer, the second most common form.

This shuffling involves transfer of genetic material between chromosomes 2 and 3, creating an abnormal hybrid gene called PPFP, and resulting in production of a two-headed protein that combines the properties derived from the two different parent genes.

The two-headed PPFP was thought to cause cancer by blocking the activity of the normal protein counterparts. But Koenig’s team’s gene expression analysis revealed just the opposite—that biological activity was actually abnormally enhanced by the two-headed protein.

The U-M team published its first findings in 2006, and is now actively pursuing promising leads. In one curious twist, one of the proteins whose activity is boosted by PPFP may be attacked by a class of drugs currently used to treat diabetes. The possibility of leveraging drugs that were developed for unrelated endocrine disorders in the treatment of thyroid cancer is a decidedly positive development.

Dr. Koenig’s research team, including Yu and Ericka Diallo, MS, has been developing a strain of mice that express PPFP in the thyroid, and might be used as a model for human follicular thyroid cancer. This will allow further study of PPFP in the living thyroid, and will accelerate the development of drug therapies to be used against it. Additionally, in collaboration with Cancer Center director Max Wicha, MD, and graduate student Dang Linh Vu Phan, the team is searching for stem cells that may underlie thyroid cancer development.

At the same time, the team is vigorously pursuing other genetic phenomena that might cause an additional type of thyroid cancer. Their goal is to develop precision “biomarkers”—simple blood tests that can catch thyroid cancers early and identify the type so that treatment can be tailored to the individual patient. This effort is aided by sophisticated DNA technology that looks for genetic mutations and patterns across a large number of cancer patients. In fact, this year Drs. Nikiforov, Giordano, and Koenig discovered a rare genetic feature in one U-M patient with papillary thyroid cancer—the most common type. This unusual finding may illuminate the search for a common pathway in all papillary thyroid cancer.

Dr. Koenig’s status and stature have been growing at U-M for the better part of two decades. As the director of the U-M Medical Scientist Training Program, Dr. Koenig is also deeply involved in the growth and development of our next generation of physician scientists. Perhaps one of them will be the one to cure thyroid cancer, for good.