Scientists discover how cancer may take hold

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A team, led by researchers at the Carnegie Institution, has found a key biochemical cycle that suppresses the immune response, thereby allowing cancer cells to multiply unabated. The research shows how the biomolecules responsible for healthy T-cells, the body's first defenders against hostile invaders, are quashed, permitting the invading cancer to spread. The same cycle could also be involved in autoimmune diseases such as multiple sclerosis. The work is published in the September 25, 2007, issue of *PLoS Biology*.

The scientists used special molecular "nanosensors" for the work. "We used a technique called fluorescence resonance energy transfer, or FRET, to monitor the levels of, tryptophan, one of the essential amino acids human cells need for viability," explained lead author Thijs Kaper. "Humans get tryptophan from foods such as grains, legumes, fruits, and meat. Tryptophan is essential for normal growth and development in children and nitrogen balance in adults. T-cells also depend on it for their immune response after invading cells have been recognized. If they don't get enough tryptophan, the T-cells die and the invaders remain undetected."

The scientists looked at the chemical transformations that tryptophan undergoes as it is processed in live human cancer cells. When tryptophan is broken down in the cancer cells, an enzyme (dubbed IDO) forms molecules called kynurenines. This reduces the concentration of tryptophan in the local tissues and starves T-cells for tryptophan. A key finding of the research was that a transporter protein (LAT1), present in certain types of cancer cells, exchanges tryptophan from the outside of

the cell with kynurenine inside the cell, resulting in an excess of kynurenine in the body fluids, which is toxic to T-cells.

“It’s double trouble for T-cells,” remarked Wolf Frommer. “Not only do they starve from lack of tryptophan in their surroundings, but it is replaced by the toxic kynurenines, which wipes T-cells out.”

The scientists think that this cycle may be also be involved in cells involved in certain autoimmune diseases. In these cases the cells may not be able to take up or convert enough tryptophan. Without enough of the amino acid or the IDO enzyme to convert tryptophan, the cells cannot produce enough kynurenine. Lacking kynurenine, the body’s own T-cells cannot be kept in check, so they rebel and attack the body.

The FRET system detects metabolites such as sugars and amino acids using a biosensor tag. A protein is genetically fused to tags at opposite ends of a molecule. The tags are made from different colors of the jellyfish green fluorescent protein (GFP). When a metabolite binds to the biosensor, it changes the shape of the sensor’s backbone, altering the position of the fluorescent tags. When a specific wavelength of light activates one tag, it fluoresces. When the metabolite causes the tags to move close together, the other tag will also fluoresce—resonating like a tuning fork. This system allows the scientists to visually track the location and concentration of certain biochemicals.

“Our FRET technology with the novel tryptophan nanosensor has an added bonus,” said Thijs. “It can be used to identify new drugs that could reduce the ability of cancer cells to uptake tryptophan or their ability to degrade it. We believe that this technology could be a huge boost to cancer treatment.”

Source: Carnegie Institution