

Craig Thompson: The method to cancer's madness

Thompson studies the metabolic requirements of dividing immune and cancer cells.

Cancer cells proliferate with abandon and in defiance of the restrictions usually placed on dividing cells. How do cancer cells—or normal dividing cells, for that matter—fuel rampant growth? That's a question Craig Thompson is bent on answering.

Thompson trained in research while serving as an MD in the US Navy (1). Though he never went to sea, he has made waves throughout his career—first as an immunologist with his work on the T cell-specific signaling receptor CD28 (2, 3), then with his lab's efforts to characterize the mechanisms by which Bcl-2 family members regulate apoptosis (3, 4), and now in the field of cancer biology investigating the metabolic requirements of dividing cells (5, 6). Along the way, Thompson has taken the helm of research institutes at the University of Chicago and the University of Pennsylvania, and is now transitioning to president and CEO at Memorial Sloan-Kettering Cancer Center in New York. We caught him fresh off the train from a visit to his lab's future site to talk about the currents he's followed in his career.

ON THE BASE

What did you want to be when you were a kid?

I never really thought about it. My father was a career Coast Guard officer, which meant I grew up all over the country. One thing you do when you're a military brat is that every time you move, you have to make new friends and integrate yourself into the community. My way to do that was to play sports.

What sports did you play?

I played soccer and basketball in high school. I was able to go to college because I was recruited to play sports. Some schools recruited me to play soccer, but I went to Dartmouth to join their whitewater kayaking team. I got my varsity letter in whitewater kayaking,

and I tried out for both the national and Olympic teams, but I didn't make either.

What did you study in college?

During school I took science courses. They were the easiest things to get good grades in, because I liked them. In fact, I had a huge falling out with the soccer coach at Dartmouth because I wouldn't give up my lab courses, which he thought were hurting my soccer career. So I quit the soccer team, took the lab courses and realized that I might like to become a scientist. The only person I had ever met who made a living using their science knowledge was the base doctor when I was growing up, so I decided to go to medical school.

Why did you enlist in the navy after medical school?

The navy paid my way through medical school; otherwise I wouldn't have been able to afford it. In exchange for that, when I finished my medical degree, I went into the navy for eight years—I completed the regular four-year enlistment, then re-

upped. My first assignment was at a very cool place, the Naval Blood Research Laboratory. It's the laboratory that figured out, starting in the late '40s, how to freeze and thaw blood cells and still have them function. I was assigned to work on a new blood particle that people were just starting to take seriously in the clinic: the platelet. I worked on meas-

uring platelets and figuring out whether we could cryopreserve them.

My next job in the navy was to work as a general medical officer at the National Naval Medical Center and as a researcher at the Naval Medical Research Institute, which is directly across the street from the NIH. I worked for a guy named Irwin Scher who ran a very good immunology lab, and I learned all my immunology there.

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Craig Thompson

CAREER CRUISE

What brought you to studying cancer biology and metabolism?

A central aim of my lab has been to understand how cells are licensed to divide in two, and how they are permitted to survive long term. Lymphocytes (T and B cells) are a great setting in which to study this question because they proliferate throughout their lives, but their proliferation and survival is tightly controlled. T cells, for example, require two specific signals to expand their populations. One signal comes from the T cell receptor, and the other signal comes from a class of proteins called costimulatory receptors, the most famous of which is CD28. In collaboration with Carl June, I've studied CD28 since I started my first lab at the University of Michigan. Recently, we found that CD28, through the PIP3 kinase/AKT pathway, instructs cells to take up and metabolize glucose, in direct proportion to the magnitude of CD28 signal transduction.

We found that CD28-stimulated T cells switch from using primarily oxidative metabolism to using glycolytic metabolism as they enter exponential growth. Glycolysis is thought of as a wasteful form of energy utilization, because the

vast majority of the glucose taken up is secreted as lactate instead of being fully catabolized into CO_2 and ATP. So we asked, why is it that cells, when engaged in maximal proliferation, prefer to use glycolytic metabolism?

Why is that?

Glycolytic metabolism breaks down glucose into the building blocks for growth: the precursors for the nucleotides, non-essential amino acids and, critically, lipids that cells need to replicate their genome, synthesize proteins, and build membrane to surround themselves with as they grow. As long as you have an abundant supply of all the intermediates in the glycolytic pathway and you don't catabolize those to CO_2 , you can use them to grow.

Cells can also use another fuel source: glutamine. Glutamine plays an essential role, first, in the ability to produce enough NADPH to fuel macromolecular synthesis. Secondly, it allows glucose-derived carbon to be diverted into serine, glycine, and ribose biosynthesis. And third—and we were not the first to discover this—glutamine is essential for the uptake of non-essential amino acids. Except for ribose biosynthesis, glutamine can do everything that glucose can. It only has one consequence to the cell, which we're starting to

think of exploiting for cancer therapy, which is that it produces ammonia as a byproduct.

TARGET IN SIGHT

How does a cancer cell behave differently than a normal cell with regard to metabolism?

We think that metazoan cells, in coming together in large collections as multicellular organisms, have given up the cell-autonomous ability to continuously take up nutrients from their environment. Even though they may be surrounded by nutrients all the time, their ability to take up and capture nutrients is regulated by signal transduction. The corollary to that is if your signal transduction is stuck "on" all the time, you'll pick up more nutrients than you know what to do with. We believe that is what oncogenic transformation primarily does in most human cancers. It fixes "on" the ability to scavenge glucose, glutamine, or both from the environment. For example, we have shown that Myc transformation makes cells glutamine addicted.

Most transforming events are pro-apoptotic because when you turn on a pathway that instructs the building of macromolecules without the resources to do it, you create a bioenergetic crisis for a cell. The only way the cell can deal with that is either to eat itself by autophagy, or to recognize the problem and initiate apoptosis. Therefore, we think a productive cancer cell has to acquire a mutation in what we call the fuel-sensing pathways. In addition, we have proposed that mutations in pathways that render nutrient uptake cell autonomous arise first in almost every successful cancer. After that, other mutations may accumulate because the extra electrons produced during the catabolism of excess nutrients generate reactive oxygen species that damage DNA.

What will be your focus once you're set up at Memorial Sloan-Kettering?

We're looking at whether acquiring mutations that render nutrient uptake cell autonomous is a part of what transformation and



Thompson is taking the long view on cell metabolism.

cancer are really about, and whether mutations in, or altered regulation of, metabolic enzymes might represent new clinical targets. For example, we're working on a protein called isocitrate dehydrogenase, which is one of the three human enzymes that produce NADPH. It was shown about two years ago to be mutated in a small set of patients with glioblastoma, and we started

looking at why it was mutated. We found that the mutation does not cause a loss of enzyme function, as was previously thought, but in fact creates a new enzyme activity that produces a new metabolic product that's not normally part of our metabolism, called 2-hydroxyglutarate. We think that's the first neomorphic enzyme that has ever been described in human disease.

"We think a productive cancer cell has to acquire a mutation in what we call the fuel-sensing pathways."

How is it used by cancer cells?

For that answer you'll have to read the paper we're writing right now!

1. Thompson, C.B., et al. 1983. *Blood*. 62:487–494.
2. June, C.H., et al. 1987. *Mol. Cell. Biol.* 7:4472–4481.
3. Boise, L.H., et al. 1995. *Immunity*. 3:87–98.
4. Chang, B.S., et al. 1997. *EMBO J.* 16:968–977.
5. Vander Heiden, M.G., et al. 2001. *Mol. Cell. Biol.* 21:5899–5912.
6. Ward, P.S., et al. 2010. *Cancer Cell*. 17:225–234.



Thompson, discussing what heading to take in the lab.