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The Winding Roads of Sterile-20s

The Need for Personalized Treatment in Untangling the Inextricable Web of Cancer

Written by Aaron Perles
Illustrated by Steven Mentzer

Imagine, for a moment, the entirety of the human body. Picture it: every limb, every bone, every muscle, every blood vessel, every electrified nerve running through it. Now zoom in. At a depth invisible to the naked eye, that sack of flesh is packed to the brim with proteins: large molecules that, quite literally, make up the meat of our bodies. They are like brick and wood to a building, the raw materials determining how we look — everything from our height and facial structure to the color of our hair or the length of our fingernails. They make us move, digest food, pump blood, circulate oxygen, see and hear and smell; our proteins determine what we are and nearly everything we do, and scientists estimate that we could have anywhere between 10,000 and several billion different types of proteins in our body.

Now zoom in more. Of those several thousand or several billion proteins, about five hundred belong to a special class of protein called kinases. The job of a kinase is to stick a phosphorus atom on another protein to help the protein do its job, like putting gas into a car to make it go. Zoom in again. Of the 500 kinases, only 28 belong to a family called the Sterile-20 family (or STE20s). A conservative estimate of 10,000 human proteins makes the STE20s less than three-tenths of a percent of all proteins. The liberal estimate of several billion proteins puts STE20s in a niche so minuscule that it escapes imagination. And yet, this tiny handful of kinases deep within the human body is responsible for handling a vast array of activities so vital that without them, that entire body — every limb, bone, muscle, blood vessel, and nerve — would shut down, ravaged by a harrowing disease we call cancer.

How could so much power be held in the hands of so few molecules? As with many things in molecular biology, the key to understanding function lies in understanding structure. The STE20s are unique among other kinase families in their structure: despite being members of the same family, the only structural similarity STE20s share with each other is a stretch of 34 identical amino acids (the chemical building blocks of proteins). Beyond this stretch, the proteins are wildly diverse in their composition, more so than other kinase families. Some have domains (that is, specialized regions of the protein) that accept phosphorus atoms from other kinases, while others have domains that can take up free-floating phosphorus themselves. Some activate other proteins using their catalytic domain (the phosphorus-carrying domain), while others can do the same with their non-catalytic domains. Some STE20s even have rare domains called CRIB domains that other STE20s lack entirely. It's not hard to see, then, that structural diversity begets functional diversity, giving STE20s the power to perform so many crucial functions throughout the cell.

Although other proteins have a role in these functions, STE20s are key players. They diverge to many locations throughout the cell and assist long series of molecular reactions, called pathways, to work towards a specific cellular activity. One such activity is breaking down the cellular skeleton, allowing cells to die when they're under stress. STE20s also help healthy cells to make a new copies of themselves: when a cell replicates, its chromosomes need to be anchored in the center of the cell, and STE20s take care of that. They also keep a protein called YAP suppressed so that tissues don't start growing out of control, and so that cells don't start migrating to other parts of the body where they're not supposed to be. We need all of these pathways to keep our bodies running smoothly, and as regulators of pathways so numerous, it's no wonder that STE20s are such important proteins.

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But here's where it gets complicated. STE20s perform functions so varied that they might appear to be going down far-flung but straightforward roads far removed from one another. The truth, however, is that these roads are far more winding, and these pathways far more interconnected, than they appear. STE20s break down the cell's protein skeleton when it needs to die, but they also break down the skeleton when the cell replicates, making the cell fluid enough that it can split itself in two. The cell's skeleton is made of a protein called actin, the same protein that anchors the chromosomes to the center of the cell. STE20s break

down actin by activating a protein called JNK, meaning that failure to do so could possibly compromise all three functions.

Furthermore, STE20s suppress YAP through a protein called MST1, but MST1 also suppresses a protein called Aurora B, which, coincidentally, helps anchor the chromosomes when the cell divides. And now consider that JNK, the same molecule thatw breaks down actin, is also a suppressor of MST1. In addition, certain STE20s stimulate a protein called CDH2, which is frequently involved in cell migration, and

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some evidence shows that CDH2 might suppress — wait for it — YAP. Perhaps all of these relationships seem incredibly difficult to keep track of. In fact, they are. These pathways are highly intricate. The criss-crossing of all these molecules into each other's pathways suggests that they all might depend on each other if they are to carry out their functions properly. One misstep in a single molecule might have untold consequences in any number of seemingly unrelated pathways. The winding roads of STE20s form a web that looks impossible to untangle.

The terror of this web truly sets in once we consider what could happen to the body if any one of these functions goes awry. Unregulated cell division and tissue growth is the textbook definition of cancer; the rapidly-dividing cells pile up, causing organ function to shut down. The same cell migration stimulated by YAP and CDH2 is the first step of metastasis, the spread of cancer to other parts of the body. If the cells can't die, then they stay there forever. And even if malfunctioning STE20s aren't directly responsible for these problems in a cancer patient, they can still cause other aberrant genetic activity. If the cell has misaligned chromosomes, then the cell could have the wrong amount of genetic information when it divides. Too much could mean an overabundance of cancer-causing oncogenes, and too little could mean an absence of cancer-preventing tumor-suppressor genes. The consequences of aberrant STE20 activity compound upon each other, and these consequences may be impossible to isolate when it comes to treating disease.

This is why STE20s serve as a case study that demonstrates why cancer is so difficult to treat. As we've seen in the case of this tiny protein family, cancer-causing mutations can act alone or in tandem, discretely or synergistically. Mutations can trigger other mutations, and their effects can fuel each other, a byproduct of the overlapping pathways of STE20s. And the sheer number of possible genetic quirks and combinations, not just among the 28 STE20s, but among the 200 known cancer-causing mutations, makes nearly every case of cancer different. When we talk about cancer, we often envisage it as "cancer," writ large: a single disease characterized by an overabundance of cells in the body. However, the bodily conditions that give rise to cancer are numerous and interconnected. When we consider the activity of STE20s alone, we see that the web of kinase activity creates an equally inextricable web of cancer, one that cannot be cured by the ever-elusive and oft-sought-after "silver bullet."

This is why many cancer researchers have turned to personalized treatment as the focus of their work. Scientists are still trying to untangle the web of STE20s and understand their role in cancer more precisely, which has proven difficult because STE20s, by dint of the wide variety of things that can go wrong with them, operate differently in each case of cancer. Compounded on top of this is the fact that STE20 mutations are common in a wide variety of cancers, such as prostate, breast, lung, and colorectal cancer. A one-size-fits-all treatment for STE20-related cancer may never make itself clear, which is why studying patient tumors one at a time is likely the best approach. Figuring out what's gone wrong in one particular tumor — whether it be impeded cell death, or unanchored chromosomes, or unrestrained tissue growth — allows researchers to target those mechanisms specifically for treatment. If we get better at determining these mechanisms, and producing more efficient therapeutics for them, then personalized treatment in a vast network of hospitals, universities, and medical centers may be the way forward towards a cure, and untangling the inextricable web of cancer. Zoom far out from the STE20s, from all the kinases and other proteins, from the limbs and bones and muscles, and we see that the solution may require global participation, one patient at a time. ●

If you would like to read more about the role of STE20s in cancer research, check out the following articles:

Dan, I., Watanabe, N. M., & Kusumi, A. (2001). The Ste20 group kinases as regulators of MAP kinase cascades. Trends in Cell Biology, 11(5), 220-230.

Mcneill, H., & Badouel, C. (2011). Faculty of 1000 evaluation for The sterile 20-like kinase Tao-1 controls tissue growth by regulating the Salvador-Warts-Hippo pathway. F1000 - Post-publication Peer Review of the Biomedical Literature.

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Shrestha, R. L., Tamura, N., Fries, A., Levin, N., Clark, J., & Draviam, V. M. (2014). TAO1 kinase maintains chromosomal stability by facilitating proper congression of chromosomes. Open Biology, 4(6), 130108-130108.