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Cancer for Dummies, Part 3 The Stem Cell Theory of Cancer

When I put together Part 1 of “Cancer for Dummies,” I blithely promised that if some part of what I’d written should become outdated, I would promptly issue an update. Little did I suspect that within a week – a week! - of publishing that newsletter, an essay in the Wall Street Journal by science writer Sharon Begley would catch my eye and make such an update necessary. Did I tell you things move rapidly in this field?

The new theory of cancer is getting to be known as the “stem cell theory of cancer.” It’s not actually that new; its first inklings emerged decades ago. And it doesn’t radically alter the portrait of cancer that I started with in the first issue of “Cancer for Dummies.” But it does resituate that portrait in an interesting way, a way that has important implications for treatment.



In the weeks I’ve spent researching the new angle, I discovered that Dr. Tannishtha Reya, the co-author of one key review article on the subject is right here in the Duke Medical School, an assistant professor in the Department of Pharmacology and Cancer Biology (depicted at left). I am very indebted to her for assistance on the current issue. Thanks too to Dr. Michael Colvin for putting me on the right track.

Dr. Reya and her colleagues entitled their review article, “Stem Cells, Cancer, and Cancer Stem Cells.” That’s a good order in which to take up the subject.

Back to Cell School, Folks

In Part 1 of “Cancer for Dummies,” I characterized a tumor as a collection of “wild-haired” descendants of an original cancerous cell, each genetically unstable descendant madly bent on growing and dividing and producing new, mutant offspring. With each new mutation holding the possibility that a new line of cells could spring up more resistant to treatment than the previous lines, the tumor becomes in effect an “infernal evolution machine.” Even with multiple treatment approaches, there’s still a chance that one cell of the infernal machine will survive and set loose a new growth of tumor. This is why, in theory, treatment must eradicate every cancer cell in the patient’s body.

OK, hold it right there.

What if that characterization is true, but only for a tiny *minority* of cells in the tumor? What if the majority of tumor cells, even the rapidly dividing ones, are not really able to keep the tumor going in the absence of that tiny minority? This is the new portrait of tumor growth that is beginning to take hold in the cancer research world. It is an almost exact parallel to the portrait of how normal tissues are produced in our bodies. To get a grasp of this new portrait, let’s go back to cell school for a moment and learn how our normal tissues are maintained and replaced.

The fully mature cell: I didn’t know it at the time I wrote, you probably didn’t know it at the time, but there is a *hierarchy of cells* behind every

tissue and organ in your body. The lowest levels of the hierarchy behave differently from the highest levels, especially when it comes to growing and dividing. Look at your skin. Everything you see on the surface, with the naked eye or even under a microscope, consists of fully mature, differentiated, skin cells. They are spoken of as “post-mitotic” because fully mature cells are destined never to divide and propagate future cells. Their fate is to sooner or later become detritus and slough off. Millions of them do so every day. They will be replaced by newly minted, sparkling fresh versions of their kind that are the outcome of propagations going on higher up the hierarchy. When your beautician applies scrubs and packs to your face, she is essentially hastening the process of sloughing and bringing the newly minted to the surface.

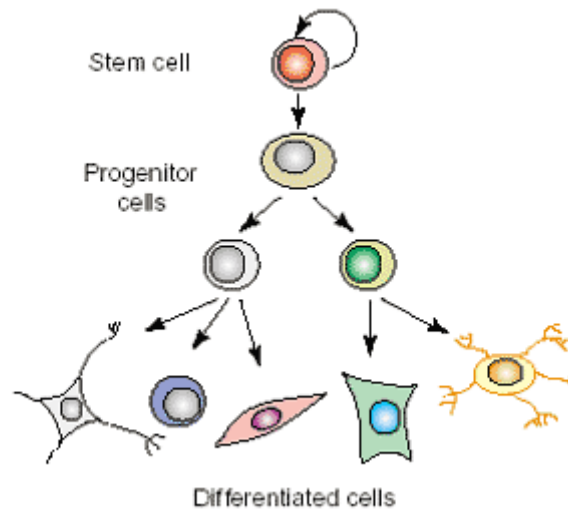
Not just skin, but muscle and brain, heart, blood and artery; prostate gland and breast duct, kidney, bladder, intestine, etc. are thought to work on the same principles. I picked skin here as just an easy example.

The progenitor cell: Higher up the hierarchy, and below the surface of the skin, in the basal layer, we run into the progenitors of these post-mitotic cells. These will look more immature under the microscope and they will be rapidly dividing. The fate of any given *progenitor cell*, as it is called, is to divide into two cells that are more mature and differentiated than itself, until in the final generation, a terminal point is reached, and a genetic program shuts division down for keeps. Another word for progenitor cells is *transit amplifying cell* or sometimes, *transiently amplifying cells*. It is important to note that a progenitor, or transit amplifying cell is not able to make a perfect clone of itself. When it divides, its progeny are always going to be one step further along the hierarchy that leads to full maturity. This is like a moving escalator; you can’t go backward and at a predefined point, you step off.

How many steps are there in the hierarchy? This is debated, but if you do the math, you can already predict that the bulk of our organs and tissues are composed of terminal and nearly terminal cells. Just start with one progenitor, (the 0 below), and start dividing:

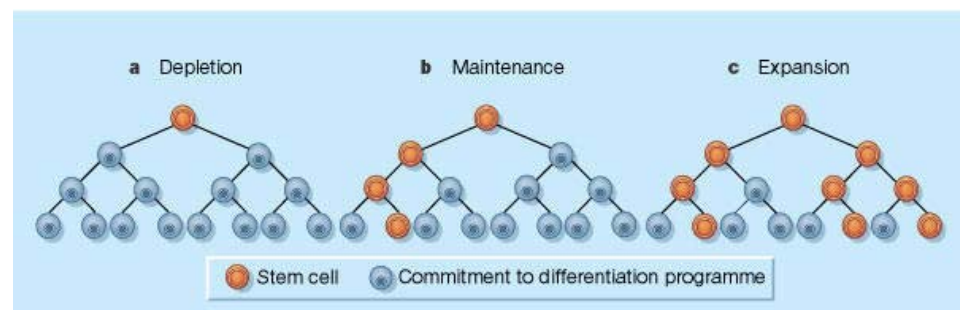
Progenitor cell divisions
?
0
00 [once]
0000 [twice]
00000000 [3 times]
0000000000000000 [4 times]
00000000000000000000000000000000 [5 times]
XX
etc

In a mere six generations, one is not able to get all the fully mature “X” cells on one line. This is the magic of exponential growth, and exponential growth is the reason it takes very few first-step progenitors to propagate a big mass of tissue.



The stem cell: At the top of the hierarchy – where I put the question mark – is the mother cell that started it all, one of the *stem cells* for that tissue or organ. Stem cells are responsible for maintaining our tissues and organs and for regenerating them when injury occurs. As it takes very few first-step progenitors to propagate a big gob of tissue, it takes even fewer stem cells to produce these progenitors. There will, of course, be more than one stem cell for any given tissue or organ; there may be millions. But scientists estimate the stem cell population in our bodies is probably less than 1% of the total cell population, which numbers in the trillions. The number of stem cells is kept under strict regulation by the genetic program of the body. Only under special circumstances, such as serious organ and tissue damage, or the stimulation by certain drugs and hormones, will a stem cell population briefly expand.

Stem cells have one special feature that their progenitors do not. Like a queen bee in the hive, the stem cell is the only cell capable of making a perfect clone of itself as well as unleashing the progenitors of the organ or tissue. For this reason, it is spoken of as self-renewing. Each time the stem divides, one of the two new cells will be a “xerox” of the mother cell. The other will be a first-step progenitor. No other cell type in the hierarchy has the ability to self-renew. (When in the expansion mode, instead of making a clone of itself and a progenitor, a stem cell will make two clones of itself.)



In the normal mode, the stem cell acts as in "b" above; cloning itself and putting out a progenitor with each division. Under appropriate circumstances, it acts as in "c" above, putting out two clones before starting with progenitors. Finally, there is a depletion mode, seen in "a" above, when the stem itself is no longer active. (Graphic from Nature, May 2003, used with permission of author.)

Stem cells hang out in weird places. Deep in the hair follicles there is a pattern called the “bulge” that seems to house multipotent stem cells that can regenerate the follicle or the epidermis. The linings of the intestine and colon contain microscopic pockets called “crypts” where the stem cells for these linings lurk. The bone marrow is rich in stem cell “niches” and a certain number of stems circulate in the blood. The hiding places, even the existence, of many tissue stems are not known. Scientists are still looking for the heart stem cells and the pancreatic islet stem cells, for instance.

Adult tissue stem cells vs. embryonic stem cells. One thing that must be made clear is that the stem cells found in adult tissues are not the embryonic, or fetal, stem cells that are the subject of so much political controversy. Embryonic stem cells can, indeed, generate any part of the body, but in order to harvest and study them, you must make, and destroy, the earliest stages of an embryo. Hence the political controversy. The *adult stem cells* are what I am discussing here. They appear to be less plastic and versatile, but the full range of their abilities is only now beginning to be explored. At least there is no ban on studying them, and no ban on using them for therapeutic procedures. It is adult stem cells that get harvested from blood, from bone marrow, and sometimes from placental cord blood (“adult” may be the wrong adjective here, but hey, it’s not a fetus), and used to regenerate a patient’s immune system after high dose chemotherapy. In burn repair, adult skin stem cells are harvested and grafted to regenerate the damaged epidermis. Exciting new clinical trials, featured in a recent PBS special, indicate that stem cells taken from bone marrow can regenerate damaged heart muscle; while neural stem cells harvested from the olfactory nerve can initiate the regeneration of a damaged spinal cord.

Getting to Cancer

Everything I have described so far is part of the normal and vital process of tissue and organ maintenance and regeneration. What has it got to do with cancer? I will preface the answer with a fascinating little research achievement that illustrates as well as any how stem cells work and how scientists figure it out. In the late 90’s Edith C. Kordon and Gilbert H. Smith, of the National Cancer Institutes, took cells derived from a mouse mammary gland, and, using carefully controlled experimental sites, performed eight transplants. Five did not take. Two showed some proliferation of the transplanted cells before regeneration stopped. *One generated an entire lactating ductal mammary gland.* Conclusion: the five duds contained only mature ductal cells, the two partials contained progenitor ductal cells. The one complete reproduction contained a true mammary ductal stem cell.

Now let’s turn to cancer.

The cancer stem cell: Researchers who work with leukemia, such as John E. Dick, have held a stem cell view of the disease for a while now,

but the idea that solid tumors too might have stem cells didn't hit big until very recently, when Dr. Michael F. Clarke and associates at the University of Michigan, were able to show that breast cancer tumors contain the same sort of cell hierarchy as I have described for normal organs and tissues. Peter Dirks and associates, at The Hospital for Sick Children in Toronto, Ontario, came up with similar findings for brain tumors.

Not unlike Kordon and Smith, the breast cancer researchers used a succession of transplants to show that the bulk of tumor cells, cancerous and abnormal-looking though they may be, were duds when transplanted. Apparently these tumor cells have arrived at some sort of terminal point and are not able to divide and multiply. Since they are doing nothing, it doesn't matter if they are shed into the patient's blood stream or lymph system. No metastasis will occur. By contrast, a very tiny subset of breast tumor cells were able to generate tumor tissue. Amazingly, when they did so, they recapitulated the original tumor in all its diversity. They produced clones of themselves but also caused the reappearance of the same genetically diverse 'dud' cells that existed in the original tumor – as if following a blueprint. This strongly implies that they are putting out *transit amplifying cells* that proceed down the same predictable pathways toward maturity, defective maturity to be sure, but still a terminal end point. (Clarke and his associates have not, to my knowledge, published regarding the differences between the true breast stems and the progenitors).

Clarke and associates estimate that breast tumor stem cells vary in their ratio, from being perhaps 1 in 100 of the cells in a tumor, to being 1 in one million. Obviously the higher their ratio, the more dangerous the cancer. Obviously too, these are the cells that if shed into the blood or lymph system can establish metastases at distant sites.



The little cell that couldn't, quite. There is something rather poignant about this new perspective on the tumor. Instead of being a massed assortment of competing little fiends, each dividing like crazy, each capable of starting its own fresh tumor elsewhere the minute it struggles

free of the mass, the tumor, in the words of Dr. Reya and associates, takes on the appearance of an "aberrant organ." Inside it are a few energetic little stem cells, trying with all their might to regenerate a kidney, or a breast duct, or a colon lining, etc. But all they are capable of putting out is more and more tumor. They're doing what comes naturally, but somehow it isn't working. Very sad for all concerned.

How does this come about?

Good guys gone bad. Are cancer stem cells normal stem cells gone wrong, or are they just any old cell that, hit with enough mutations, has

regained the ability to self-renew and send out progenitors, i.e. act like a stem cell? Further research has established that cancer stem cells share, with normal stem cells, certain proteins, molecular markers, and signaling pathways. (Later stage cell types lack these features). But is this because they've never had to lose these, or because they've re-acquired these features through mutation?

The most reasonable answer to these questions is that cancer stem cells are, most commonly, normal stem cells gone wrong. Normal stem cells would require fewer mutations to arrive at a cancer stem cell outcome than would a later stage cell.

Instead of having to regain, through mutation, the turned-off ability to self-renew, the so-called "immortality" of the cancer cell, they simply retain this ability unchanged. Instead of regaining certain molecular markers etc., they simply carry on, cancerously, with the ones they already have. One of the most inelegant parts of the old theory – that cancerous cells have to develop their amazing powers exclusively through mutation – drops by the wayside.



This does not mean that cancer stem cells are genetically stable. All indications, so far, are that cancer stem cells have the instability that all cancer cells were reputed to have in the old theory, an instability that allows further mutations to arise and thus allows the cancer to "adapt" to changes in its environment, like the presence of chemotherapy drugs. We haven't gotten rid of the fiendish evolution machine entirely, but we've reduced its numerical starting point.

Another feature of normal stem cells that is significant for cancer, is that, if we count self-renewal as persistence, they are the longest-lived cells in our bodies. True, our supply of stems dwindles as we age. They are not truly immortal and in fact their dwindling is the primary cause of our aging. This being said, at any point in time, our existing stem cells are the same age as we are, and they've had however many years that is to accumulate mutations. Later stage cell types cannot make this claim.

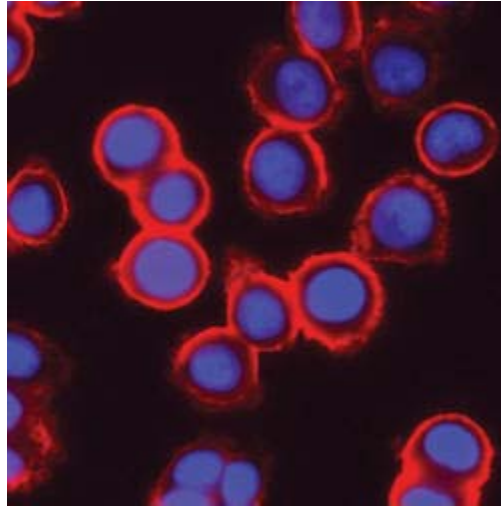
Dr. Reya urges that we also consider early progenitor cells as at relatively greater risk of mutating to cancer, because they are closest to the lost self-renewal ability. In one possible scenario, a progenitor might inherit some of its cancer-leaning mutations from the mother stem cell, but pick up the last and crucial mutation, self-renewal, while in the progenitor state. If this happens, then what was an almost normal *progenitor cell* is now a fully functioning *cancer stem cell*.

All agree that the fully mature normal cell is the least likely candidate for a cancerous transformation. Not totally ruled out, but highly unlikely.

Accumulating enough mutations to become a cancer would seem to require a longer life span than mature cells possess. This is nice. The

great mass of our bodily tissue is not going to hurt us!

Some mysteries cleared up. One sign that a new theory has more power than the old is that weird facts no one's been able to make sense of suddenly fit somewhere, a loose end gets tied up. This has been the case with all those earlier transplantation experiments that frustrated the researchers' efforts to grow a tumor from extracted tumor cells. Earlier researchers found it took about a million cells to get anything to grow. One can just imagine those researchers muttering to themselves about the undependable nature of the culture medium or animal tissue into which they were transplanting. It wasn't until later researchers began to fractionate *the clump that did grow* into sub-sets and to re-transplant these that it became clear that some sub-sets held the magic key to growth while others did not. Fractionate further and further, each time eliminating the duds, and eventually you have a subset that is rich in the magic cells. Compare this clump to a dud clump and, hmmm, differences become apparent. The magic cells turn out to be highly immature looking creatures with the capacity to self-renew and with many of the molecular markers of a normal stem cell. These are the cells that drive the tumor.



Immature cells show a higher ratio of nucleus (blue) to cytoplasm (red).

Another loose end that could be tied up is what I will call the mystery of the peritoneveous shunt procedure. I refer to a commonly used medical procedure in which the rapidly accumulating fluids in the bodies of certain cancer patients are shunted into their veins so that they can be eliminated as normal waste. Since the fluids from a locally advanced abdominal or thoracic cancer would contain millions of cancer cells, it is to be expected – under the old theory – that the flooded veins would carry millions of metastases out into the body. This does not happen. In a study, autopsies of some of these patients revealed that half of them had acquired no metastases whatever; the other half, only a few. One explanation given is that the migrating cancer cell must find a hospitable niche in which to settle down before a metastatic tumor will develop. This is undoubtedly true, since it is well known that metastases have “favorite locations,” viz. the liver, lungs, bone and brain. But an additional explanation could well be that the migrating cell must be a cancer stem cell and not just any old tumor cell. Since these are in the

minority in any tumor, the chance of metastases from the shunt procedure are accordingly reduced.

The new theory would also predict that sometimes clumps of *non-growing* tumor cells, genetically kin to the original tumor, would occur in the bodies of patients. These would be the results, in theory, of a migrating cancer *progenitor* cell which had a few generations of division left in it, but no capacity to self-renew. The few generations used up, the expansion of the clump grinds to a halt. In fact, the study of the shunt procedure, cited above, did reveal such clumps lodged in the shunt patients' vasculature. Not infrequently, scans of surviving cancer patients will turn up non-expanding bits of tumor that are classified as "stable disease." True, some of these are active tumors being held in check by treatment. But others linger on, unmovingly, once treatment is finished. They've become duds. The queen bee has left the hive, or never was in it.



What if we could eliminate all the cancer queen bees and turn all the patients' tumors into duds? A method that accomplished this would have profound implications for the treatment of cancer. It would even conceivably cure metastatic cancer.

Cancer Treatment in a New Light

Where's the pipeline? The first thing that needs to be said is that I am unaware of any treatment now in the pipeline that is deliberately based on the stem cell theory. The theory is only now gaining ground and is a long way from widespread acceptance. We don't even know where to find many of the stem cells that our organs and tissues are presumed to have. This is just the most blatant of the many particulars that need to be spelled out before clinicians will begin to jump on the bandwagon. In fact, I'm willing to bet that if you run to your oncologist today and say, "Give me a treatment that kills off those cancer stem cells," he or she is going to say, "Hunh?" (But try it, anyway).

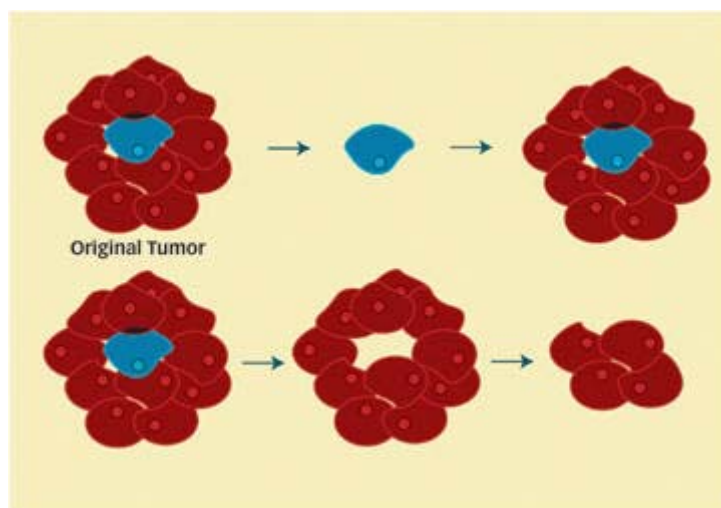
Are we targeting correctly? The second thing that needs to be said is that the treatments that target only rapidly dividing cells, such as most chemotherapies, are probably not having much of an impact on the real source of the problem, which is the cancer stem cells. The rapidly dividing cells in tumors, just like the rapidly dividing cells in normal tissue, are the *progenitor* or *transit amplifying cells*, not the stems. The stems are cycling at a much slower rate and able to fly beneath the radar of most treatments. Even in the face of radiation, they appear to be hardier than other cells, and indeed, why wouldn't they be? In their normal state, stem cells are the most necessary cells in our body and evolution has always protected them from easy damage. Cancer's

hardiness in the face of treatment makes even more sense when we consider that at its core is an already very hardy type of cell.

It would seem that when treatment is so toxic as to require a *stem cell transplant* or *bone marrow transplant* to restore the patient's blood system and immune system afterwards, only then is the treatment toxic enough to crash certain stem cell populations. But even then, it is the blood and bone marrow populations, the haematopoietic stem cells, that are most impacted. And it is the blood and immune system cancers – the leukemias and lymphomas – that are the cancers most responsive to these highly toxic treatments. The same treatments have been tried for breast cancer, but with no improvement in prognosis. Apparently the stems for a breast cancer are not sufficiently impacted, even with highly toxic doses of existing chemotherapies. Tumors may shrink to the point of undetectability, but re-emerge at a later date. It appears that for breast cancer and many other solid tumors, we spend a lot of treatment time just cutting the weeds without getting to the roots. We need the equivalent of "Roundup" for cancer.

But now, as things get better and better understood, there is ever more reason for cancer patients to hang in there, keeping the weeds well cut, while waiting for the silver bullet that will take out the roots. Is this realistic? I think so.

Targeting cancer stem cells: With the dominant trend in cancer treatment being toward ever more precise targeting of cancer cells, the step to painting the bulls-eye on those cancerous stem cells should not, in theory, be that great. It is likely that some of the targeted treatments discussed under the heading of monoclonal antibodies in our earlier March issue, are already – though unintentionally – addressing features found on the cancer's stem cells and not just hitting “rapidly dividing cells,” or “any cell in the path of the radiation beam.” But obviously intentional targeting must take over. To quote from Dr. Reya and associates, “The next frontier will be to purify the cancer stem cells from the whole tumor...and perform gene-expression profiling on those cells.” With a genetic profile, precise targeting becomes possible.



The blue cell represents a cancer stem cell embedded in the non self-renewing cells of the tumor. When the other cells are killed by treatment, the stem simply renews them (top line). Only when the stem is knocked out does the tumor cease growing (bottom line). (Graphic by E. Roell from Science News, March 20, 2004 used with permission.)

As we develop our profiling capabilities and learn to single out how the cancerous versions of a stem cell can be safely distinguished from the normal versions (one wouldn't want to kill off the normal ones), we can begin to hope for side-effect free and, finally, permanent cancer arrest. No weed, no root, no problem!

We will keep you posted.

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