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The immune system as key to cancer treatment: Triggering its activity with microbial agents

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Abstract Traditional methods such as chemotherapy and radiation therapy offer only limited success in treating cancer. Part of the reason is related to our misunderstanding of what cancer is: it is not the cause but the consequence of a weakened living system. Localized cellular stress, caused by toxins, mutagens or radiation, coupled with a weakened systemic response or inability to support or defend the cells that are under attack, cause these cells to revert to an ancient, unicellular mode of survival, therefore cutting links with the overarching organism and defend themselves from the threat as if they were individual entities. We hypothesize that strengthening the organism, specifically the immune system, is a more promising approach toward a cure for cancer than attempting to exterminate cancer cells. The hypothesis can be tested by experiments that are designed to strengthen the immune system by both traditional means (e.g., ingestion of natural substances known to increase the activity of the immune system, such as fruits, vegetables, and nuts), diminish immune system inhibitors released by cancer cells (e.g., TGF-β), and by the injection of heat-killed or genetically altered pathogenic bacteria to trigger a massive response (fever response) of the immune system into the affected area and compare those results to traditionally used methods.

What is cancer?

Cancer is probably the most feared word in the industrialized world. The fear is easily justified by the verification that cancer became the leading cause of death in industrialized countries, being responsible for 1 out of 4 deaths in the United States [17]. After decades of astounding investments into finding the cure for this disease, we are still far from achieving it. Despite the lifetime dedication of thousands of cancer researchers, 1500 people still lose their battle with cancer every day in the United States alone [17].

We clearly have not made the headway in cancer treatment as we should. Given that our current attempts to defeat cancer continue to fail us, one cannot help but wonder whether we really know what cancer is. Do our failed attempts reflect a deep misunderstanding? Given the indescribable suffering that cancer patients undergo each day in search of recovery, stepping back and taking a second glance at the enemy with fresh eyes seems a reasonable endeavor.

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What we know thus far is that cancer appears to originate when regulation of the normal cell cycle is somehow disrupted. This happens frequently and is usually dealt quickly by a variety of different mechanisms internal and/or external to the affected cell that ultimately cause the cell to be destroyed. In cancer cells though, this is not accomplished. Cancer cells manage to survive natural and artificial attempts to provoke their destruction. They do so through an incredible variety of pathways that continues to deceive both our immune system and our thought strategies to fight cancer. But this is just the beginning of cancer. After evading its destruction, cancer cells start a replicating rampage, stepping on neighboring cells, re-building blood vessels to their own feeding purposes and eventually migrating to new locations. In the meantime, our keeper, the immune system that so fiercely defends us from all harm, internal or external, sits passively. Cancer often eventually causes vital organ failure due to the uncontrolled cellular growth that disrupts normal functioning and severely weakens its host due to the high energetic demands of tumor growth. But this is still not the most incredible fact about cancer. What makes cancer so difficult to defeat is that it does not strike in a straight line, neither through several of them, nor by any clearly defined path. The hallmark of cancer is chaos. Cancer accomplishes all of the above through the use of the most sophisticated weapon, evolution. A high mutational and replication rate guarantees that at least a few cells will make it to the next round and those that do can just bet on exactly the same strategy to keep going.

Current therapies can destroy cancer cells, but not without destroying surrounding tissues, severely weakening general well being, nearly ablating the immune system for the course of the treatment and leaving permanent damage behind. Even if the treatment is successful, resurgences are the norm, and in an even more aggressive form than before.

Somehow, this story seems incomplete. It answers the where, when, how, but not why. Can such an intricate evolutionary mechanism as cancer exist without a reason?

What cancer is not?

Duesberg and Li [10] brilliantly summarize current likely misconceptions regarding cancer. Among the most important are that carcinogens are mutagens. In fact, half of them are not. This simple fact is staggering. A raised mutation rate makes the evolution of tumorogenesis faster but is not necessary for it to occur [28]. A higher mutation rate is not the source of the problem, it is a consequence. Mutations are what allow cancers to evolve and prosper. It should be kept in mind that this does not mean cancer cells do not have a higher mutation rate. It simply means that carcinogens do not necessarily induce a higher rate of mutations (in fact gene mutation rates of many cancers are normal). If carcinogens are not causing a higher rate of mutations but do cause the onset of cancer, what is it that they are primarily doing?

Cancer is not pure randomness; it is not one mistake after another; it is not a foreign agent attempting to kill its host; nor is it a combination of any of these.

What cancer might be?

We realize that the more traditional hypothesis of cancer based on a set of mutations within an evolutionary context can explain many of cancer's features by requiring a sufficiently large and arbitrary set of mutations occur. We wish to propose a theory that can also explain the facts, but does so with fewer assumptions. What makes it more parsimonious is that one assumption explains many features, rather than many independent assumptions about the nature of the evolution of cancer cells. Although cancer may be the result of natural selection on a population of unregulated cells within the span of a lifetime (at most), this does not seem to us the most parsimonious explanation for the following reasons. If cancer was indeed the result of the above phenomenon, then its occurrence should be much more common [11]. Uncontrolled cell proliferation, the hallmark of cancer [25] is not rare and rarely results in cancer. Any multicellular organism is well-equipped to solve these occurrences, as they need to get rid of cells that are in excess, in the way, or potentially dangerous [15]. A whole lot more has to go wrong for cell proliferation to get out of control and lead to cancer.

If we separate chaos from the common features found in the great majority of cancer lines, we are left with a clear stepwise mechanism.

(1) TGF-beta has been consistently isolated from a variety of malignant tumor cell lines and detected in plasma of tumor-bearing hosts [32]. This is the most powerful immune suppressor described to date.
(2) Cancer cells lose functional homologous or heterologous gap junctional intercellular communication (GJIC) [26]. These gap junctions are the communication portal between cells.
(3) Cancer cells lose contact inhibition that prevents normal cells from moving over each other [23]. This allows for tissue invasion and disruption of surrounding normal functioning.
(4) Cancer cells undergo a transition from a localized to a metastatic phase [24]. This transition effectively results in the spread of cancer.
(5) Cancer recurrence and long periods of remission are frequent; latency periods can range from years to even decades [2]. This is why assays measuring apoptosis are likely to give misleading results [4].

This list is by no means exhaustive and foremost is devoid of the highly complex and intricate biochemical and genetic mechanisms that permit the completion of these steps to occur. From an evolutionary perspective, cancer cells are rather clearly an attempt of individual escape from the overarching organismal multicellular organization. The 1st step prevents a reaction of the organism to the escape attempt of the cancer cells, by in effect, depleting natural mechanisms that allow for the cancer's detection and elimination. The 2nd step cuts ties with all surrounding cells, blocking cell signaling — most importantly for apoptosis. The 3rd step allows for the beginning of the escape from the overarching organization, typically a slow progression, which is completed in step 4, a more

aggressive attempt of spread and progression. Step 5 consists of a defensive mechanism in response to a direct attack. In this phase cancer cells effectively hide and wait for the attack to stop and attempt escape again, just like certain bacterial organisms will undergo dormancy in the form of spores when conditions are unfavorable for their prosperity.

In order to understand cancer we need to be able to see beyond the chaos. It is rather unlikely that chaos can result invariably in identical outcomes within a short span of time. The evolution of complexity from chaos takes time. When looking at what cancer accomplishes in such a short span of time one cannot but associate this phenomenon to a developmental mechanism (like embryogenesis) rather than to a simple phenotypic change. Cancer has previously been proposed as an evolutionary and ecological process [21]. No doubt cancer evolves before our eyes through natural selection on a mutating population, the question is, how long ago did it evolve? How long did it take cancer to reach the current state? The fact that cancer development is stochastic does not mean it does not follow a plan. The development of stem cells is stochastic [30] and so is the development of natural killer cells [12]; and yet, the end result is clear, complex and identical. Stochasticity is perhaps the most powerful developmental motor, but it is not to be mistaken with randomness. Stochastic processes like cancer involve random variables and mutations, but follow a plan — not a deterministic plan, but nonetheless a plan. A survival plan, a plan to deceive those who can and will destroy them, a communication blockage, an exodus and a protective mechanism, in case things go wrong. Chaos is an integral part of the plan; what best to distract attention?

But what causes cancer in the first place? What are carcinogens doing? Our interpretation is that carcinogens are potent stress factors, localized ones that continuously threaten the survival of a specific group of cells. Afflicted cells will attempt recovery on their own first, and then request help from the overarching organismal organization. When both continuously fail to stop the threat, cancer development sets in motion. Cancer is excess self-survival of a part at the expense of the whole. As Maser and DePinho [20] pointed out, crisis plays a more prominent role than senescence in tumorigenesis. When multicellularity fails them, they set unicellularity in motion. This program works out just fine for nutrient-starved bacteria living in a biofilm [22], in an overcrowded environment or under attack. A cancer cell is simply trying to escape a certain death, except that in a multicellular organism, there is nowhere to go. The strength of life is in its resilience, and the survival instinct will always be the last plan in case all else fails. But it is a plan. Unfortunately, cancer's frantic attempt of escape causes chaos and destruction resulting in the deadly consequences for which it is mostly known.

Thus, cancer might be as ancient as multicellularity. In times of extreme localized stress cells can revert to a unicellular state. This reversion can be quite useful in a colonial environment, but it is detrimental in a multicellular organism. It is unlikely that specific genes have survived more than 500 My of natural selection or even drift. So, they must have been selected for some other function. Given that carcinogenesis utilizes the same network used for normal cellular growth [14], it is reasonable to postulate that cancer is a mode of operation that restructures the logic of the original cell without restructuring the physical components. The normal growth and the cancerous growth can be considered as different modes of a multi-modal system, rather than different systems. The expression of the gene set can create several different patterns of behavior without altering the genes. Thus, in principle, it should be possible to revert the cancer state of cells back to the 'normal' state of multicellularity within an organism, though there is no current evidence for this possibility.

A helping hand

Based on the previous discussion we postulate that cancer is an abnormal (though not accidental) response to extreme localized stress and that this response reverts the afflicted cells to a primordial state, close to a unicellular state, where survival becomes the only goal and all multicellular connections are actively disabled. In principal, there are two theoretical solutions to the problem: (i) blocking the cause of the localized stress. This should be helpful as a preventive treatment and as a means to avoid the aggravation and resurgences of cancer. Although, this is unlikely to be sufficient when the tumorigenesis process is already in place, as carcinogenesis is in itself a major cause of localized stress; (ii) boost the immune system, especially the immune alert state. This should necessarily include the induction of fever, as it signals response to a stressful condition threatening the whole organism.

If our hypothesis is correct that cancer is a reversal to the unicellular state as consequence of a stress response, then using aggressive methods such as chemotherapy and radiotherapy might only worsen the problem, because they increase the stressful conditions that the organism is exposed to. Although these clinical methods do indeed appear to be the only reasonable approach to provide any hope to cancer patients in an advanced condition, that is likely not the case in earlier stages. If cancer starts because of declining conditions, weakening the organism only reinforces and expands the problem. It is well known that every time cancer resurges it comes on even stronger. Every time history repeats itself, the cost is higher.

Responding to distress signals with destructive means can only worsen what is already a critical situation. The second procedure should be to search for the cause of the outbreak. Is the organism malnourished, is the target area under nutrient restrictions? Is it under attack, are its defenses depleted? Its cause should be thoroughly searched for. If found, attempts to address it should be the highest priority.

Only when the cause is taken care of, can its consequence be healed. Any attempt to treat the end result can only at its best, result in a delay of the collapse that is already taking place. There is plenty of support for this hypothesis already. The so called cause of cancer, the mutagenic agents, do not by themselves cause cancer [5]. Instead, they are poisonous, irritant substances that simply threaten the normal functioning of an organism.

Instead of a negative, destructive approach, may be we should try a constructive one. Instead of weakening the problem, we can strengthen ourselves. We have been in an arms race with cancer for way too long. And we are clearly losing the battle. Although most patients with cancer respond to therapy, few are cured. Moreover, objective clinical responses to treatment often do not even translate into substantial improvements in overall survival. Patients who achieved complete remission with conventional-dose therapies have not been shown to experience a survival advantage over similar patients treated with a ''watch and wait'' approach [16].

A new approach

Most reports of spontaneous cancer remissions occurred after an accidental acute infection in the vicinity of the cancer [7]. Cann et al. [8] have suggested that cancer outbreaks tend to occur in individuals whose medical background resulted in a reduced exposure to acute infections due to the use (and abuse) of antipyretics, anti-inflammatory and antibiotic medicines. The overuse of this medication negatively impairs immune response and severely limits its development if misused in early life stages. This immune underdevelopment negatively impacts the ability for the immune system to recognize and act upon future threats including tumor emergence and development.

Maybe we can provide further help to the immune system by highlighting and pointing to where the problem is. The strength and reaction time in the face of a clear foreign agent can under certain favorable circumstances provide the jump start for an aggressive defensive response, something not easily achieved when the organism's own cells are the threat.

Cancer is a manifestation of a deeply rooted life process that seeks for survival at all costs even if at the cost of escaping an overarching order. Current efforts attempt to 'fix mistakes' and 'redirect pathways'. And although it is possible that temporary and partial solutions may be found, it is fundamental that we understand cancer for what it is and not for its consequences. Cancer has a multitude of mechanisms that act to achieve its goal and even solving some of them will not stop its resurgence. Cancer will often utilize alternative routes and find less direct pathways to escape the overarching order. Instead of fixing what cancer breaks, we propose to circumvent it.

Our approach aims to:

(1) diminish or eliminate TGF-β abnormally high levels after cancer onset;
(2) request immune response in the cancerous area by injecting an infectious agent (e.g., heat-killed or genetically altered bacterial strain or consortia) in the tumor-affected area;
(3) strengthen the immune system, stimulating its state of alert.

Our strategy is based on the few reports of spontaneous cancer remissions. These have occurred after an accidental acute infection in the vicinity of the cancer [8]. After each fever episode the tumors shrank until finally disappearing completely [6]. Fever initiates a cascade of events of inflammatory factors which activate resting dendritic cells that lead to the activation of T-cells [19]. Fever episodes are therefore fundamental to the healthy build up of an efficient immune system.

Unfortunately, in modern medicine, fever is often understood as a harmful event and is quickly blocked. Indeed, fever is in most cases only harmful if life threatening, which is rarely the case. But fever has enjoyed a better reputation in the past. In fact, reports from the late nineteenth and early twentieth centuries describe tumor regression associated with systemic bacterial infections [29]. We know now that PAMPs (Pathogen-associated molecular patterns) — consistently found in pathogens — interact with Toll-like receptors, leading to the up-regulation of co-stimulatory molecules such as CD40 and proinflammatory cytokines such as IL-12 [1]. The interpretation then was that an immune reaction against the infectious material cross-reacted with and destroyed the tumor cells [33]. This approach circumvents direct confrontation with cancer cells and increases apoptotic signals, characteristic at the end of an immune response [3].

We believe this is a correct interpretation and we look forward to reviving it. The strength and reaction time in the face of a clear foreign agent, can under certain favorable circumstances, provide the jump start for an aggressive defensive response, something not easily achieved when the organism's own cells are the threat and actively deceive the immune system. The interaction of cancer cells with the innate and adaptive immune system has recently been classified as complex and unpredictable at best [18] and as ''partners in crime'' at worst [9].

Although, the immune system is as much a player as are stroma cells, recently pointed out as cancer accomplices [13], it is clear by now that cancer onset subverts its own cellular machinery and that of its surroundings. Destroying cancer's 'partners' as suggested by Condeelis and Pollard [9] will lead us through a very dark path. Our immune system has been our guardian long before we became humans. Attacking it is likely to compromise our only hope to overcome cancer.

The two main problems of chemotherapy are its toxicity to normal cells and failure to kill cancer cells [27]. This has led some authors to believe that most of the increased longevity that western societies enjoy today has come through better prevention rather than better treatment [31]. It is about time for us to do better than this.

Testing the hypothesis

The hypothesis states that cancer is a primordial (ancient, not simple) escape mechanism and that the immune system has the potential to handle the threat if given the appropriate circumstances can be tested.

The proof that the immune system can do it already exists in the form of spontaneous cancer recoveries after an inflammatory response to an accidental infection in or nearby the tumor. It is important to reinforce the notion that these cases were reported in terminally ill patients, not in patients in an initial tumorigenesis phase. This shows that the immune system can effectively cure cancer even if at an advanced stage.

The challenge is to understand what happened in these patients that allowed their recovery against all odds. We can simply attempt mimicking the process and increase the frequency of these situations, turning a fortunate accident into a controlled occurrence. We suggest that the first step should be to block the attempts of cancer cells to cripple the immune system. Maintaining the immune system active and in a state of surveillance is crucial. The next step would be to simulate an infection in the vicinity of the tumor to trigger immune response into the affected area. This simulation can be accomplished by the use of inert infectious agents, so that no risk of a real infection is present. The fact that the immune system will not attack the cancer cells directly might also be important in preventing an aggravation of the cancer state. The immune system will clean the vicinities of the infection as a standard procedure, potentially removing cancer cells with it. There is another potential benefit from this approach which is the fact that the immune system might act promptly on a second resurgence of cancer by association.

Conclusions

We postulate that cancer is as ancient as the rise of multicellularity and might in fact represent a strategy that remained from times when cells collaborated in a colonial environment such as biofilms. As an ancient mechanism we hypothesize that it should be handled by ancient solutions that have evolved side by side with it: the immune system. In particular, we suggest that the immune system can be lent a helping hand with the injection of microbial pathogenic cells in the vicinity of the tumor. These cells would be heat-killed or genetically altered to avoid posing a danger themselves, but would nonetheless be able to trigger the immune system.

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