Disrupting Cell Mitoses to Provoke Cancer Self-Destruction

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Abstract

The histories and approaches to eradicating cancer and malaria are amazingly parallel to each other and one would hope that a similar strategy to that used in malaria would be more successful at eradicating cancer. In the case of malaria, better understanding of the disease transmission has led to the current development of a transmission-block vaccine, a much more preferable approach than the current targeting of the mosquito vector and treating the infection.

In the case of cancer, taking advantage of the deep understanding of the events of cell division, particularly the anaphase in mitosis, an "inherent death mechanism" can self-eradicate duplicating cancer cells without impairing healthy cells in both normally and rapidly proliferating human cancer cells. The faster cancer cells proliferate, the faster and more efficiently they will be eradicated. The mechanism may be suitable for treating aggressive cancers that are not responsive to traditional chemotherapy, heralding a novel specific cancer target mechanism.

Introduction - The Experience with Malaria

Malaria, a tropical disease, is caused by four species of Plasmodium commonly known as the malaria parasites that live inside many species of Anopheles mosquitoes ("malaria vectors"). The disease spreads to people through bites by infected mosquitoes, mainly between dusk and dawn. Approximately half of the world or ~3.2 billion people are at risk of contracting malaria. If diagnosed and treated promptly, full recovery can ensue. The death toll from malaria (~ 584,000 people in 2013 and ~ 438,000 in 2015) has prompted intensive research around the world with the aim to hopefully attain malaria-free endemic regions and, ultimately, a malaria-free world. Unfortunately, the approach followed to curb the incidence of malaria, viz. targeting the mosquito vector and treating the infection, has so far not been very successful. Further, barriers to developing a vaccine against malaria are poor understanding of the underlying cell biology, of the host’s immune response to malaria’s infection, and technical complexities.

The problem with the above strategy is that mosquitoes continue to evolve resistance to insecticides, and parasites themselves are able to evolve resistance mechanisms to antimalarial drugs. A far more effective strategy would consist in devising a means of preventing malaria transmission in the first place. To achieve this goal, it is important to understand precisely how malaria is transmitted. During infection, parasites invade red blood cells, multiply and manifest clinical symptoms that may ultimately lead to death. However, to transmit the disease successfully, these previously asexual parasites must transform into male and female sexual stages (gametocytes), which continue the transmission cycle when ingested by blood-sucking female anopheline mosquitoes. Furthermore, additional extensive development of gametocytes in the mosquitoes leads to a rapid proliferation of the parasites thereby significantly increasing the chances of successful disease transmission. With this knowledge, the approach would naturally be to target gametocytes (both at formation and during survival) within the infected human host and to develop parasites inside the mosquitoes. The overriding objective is then not to treat but to eradicate at the source the malaria-causing agents (Plasmodium falciparum and Plasmodium vivax), an approach that is evidently much more preferable [1,2].

The situation is reminiscent of cancer cell proliferation and the various strategies that have been developed over the decades for treating cancer. One is therefore left to wonder whether a paradigm change similar to that in malaria would not provide the definitive treatment for cancer therapy.
Events of Cell Division

In all cells (except bacteria and some cells of the reproductive system), cell division consists of two sequential events:

A. Mitosis or division of the cell nucleus and, when mitosis is nearly completed,

B. Cytokinesis or division of the cytoplasm.

These two events are preceded by DNA replication so that, for a short time, the cell nucleus contains a “double dose” of genes.

Mitosis results in the formation of two daughter nuclei with exactly the same genetic information as the original mother cell and the original fertilized egg from which it came. The stages of mitosis include the following events:

A. Interphase (early; 1 cell),

B. Prophase (early, middle, late),

C. Metaphase,

D. Anaphase (early, late),

E. Telophase and

F. Interphase again (late; 2 cells).

Cytokinesis, or the division of the cytoplasm, usually begins during late anaphase and completes during telophase. Mitosis “gone wild” is the basis for tumors or cancers. Mitosis is basically the same in all animal and human cells. Depending on the type of tissue, it takes from 5 minutes to several hours to complete, but typically it lasts about 2 hours. Centriole replication is deferred until late interphase of the next cycle, when DNA replication begins before the onset of mitosis.

Prophase

As cell division begins, the chromatin threads coil and shorten so that visible bar-like bodies (the chromosomes) appear. Since DNA replication has already occurred prior to mitosis, each chromosome is actually made up of two strands (the chromatids) held together by a small button-like body (the centromere). The centrioles, which were so far floating in the cytoplasm outside the nucleus, separate from each other and begin to move toward opposite sides of the cell directing the assembly of the mitotic spindle (composed of thin microtubules) between them as they move. The spindle will provide the scaffolding for the attachment and movement of the chromosomes during the later mitotic stages. By the end of prophase, the nuclear membrane and the nucleoli have broken down and disappeared, and the chromosomes have become attached randomly to the spindle fibers by their centromeres.

Metaphase

In this short stage, the chromosomes cluster and become aligned at the center of the spindle, midway between the centrioles, so that a straight line of chromosome is seen.

Anaphase

During anaphase, the centromeres that have held the chromatids together split, and the chromatids (now called chromosomes) again begin to move slowly apart, toward opposite ends of the cell. The chromosomes seem to be pulled by their half-centromeres with their “arms” dangling behind. Anaphase is over when chromosome movement ends.

Telophase

Telophase is essentially prophase in reverse. The chromosomes at opposite ends of the cell uncoil to become threadlike chromatin again. The spindle breaks down and disappears, a nuclear membrane forms around each chromatin mass, and nucleoli appear in each of the daughter nuclei.

Cytokinesis

As stated earlier, cytokinesis begins during late anaphase and completes during telophase. Due to the activity of a contractile ring made of microfilaments, a cleavage furrow appears over the midline of the spindle and it eventually squeezes or pinches the original cytoplasmic mass into two parts. Thus, at the end of cell division, two daughter cells exist. Each daughter cell is smaller and has less cytoplasm that the mother cell, but it is genetically identical to it. The daughter cells grow and carry out normal cell activities until it is their turn to divide. Also mitosis and cytokinesis division go hand in hand, in some cases, the cytoplasm is not divided, forming a binucleate (two nuclei) or multinucleate cells (fairly common in the liver).

Unleashing A Natural Cancer Killing Mechanism

The various therapeutic approaches to cancer therapy have been described at length elsewhere, including surgery, chemotherapy, radiation therapy, electro chemotherapy, immunotherapy, synthetic chimeric antigen receptors, or a combination thereof, and their corresponding nano therapies [3-12].

In analogy with the malaria situation and the development of a malaria blocking-vaccine, one wonders whether cancer transmission, which is somewhat analogous to malaria transmission, could likewise be eradicated by going back to the basics of cell biology. This would be tantamount to a complete paradigm change in the approach to cancer therapy. Indeed, this seems to have been realized and accomplished by a team of Israeli researchers [13-16]. The research team led by Prof. Malka Cohen-Armon found that three proteins can be specifically modified during mitosis to unleash an “inherent death mechanism” that self-eradicates duplicating cancer cells without impairing healthy cells. The mechanism also works on normally and rapidly (or at least a variety) of proliferating human cancer cells. As he put it “the faster cancer cells proliferate, the faster and more efficiently they will be eradicated”. The mechanism may be suitable for treating aggressive cancers that are not responsive to traditional chemotherapy, heralding a novel specific cancer target mechanism.
The newly-discovered mechanism involves the modification of specific proteins that affect the construction and stability of the spindle (see the above-described mitosis event during anaphase). The Israeli team also found that certain compounds (the phenanthridine derivatives) were able to impair the activity of these proteins, distorting the spindle structure and preventing the segregation of chromosomes. Once the proteins were modified, the cells were prevented from dividing, inducing the cell’s rapid self-destruction and apoptosis. Further, a variety of additional drugs that also modify these specific proteins may now be developed.

Phenanthridine, discovered in 1891 by Ame Pictet and H. J. Ankersmit, is a nitrogen heterocyclic compound that is the basis of DNA-binding fluorescent dyes (ethidium bromide, propidium iodide) through intercalation. Its chemical properties in its standard state (at 250 C [770 F], 100 kPa) are provided in (Table 1).

Table 1: Chemical Properties of Phenanthridine.

<table>
<thead>
<tr>
<th>Properties</th>
<th>C13H9N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molar mass</td>
<td>179.217 g/mol</td>
</tr>
<tr>
<td>Melting point</td>
<td>107.4 °C (225.3°F; 380.5 K)</td>
</tr>
<tr>
<td>Boiling point</td>
<td>348.9 °C (660.0°F; 622.0 K)</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>slightly soluble</td>
</tr>
</tbody>
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Research was conducted using both cancer cell cultures and mice transplanted with human cancer cells. The scientists harnessed biochemical, molecular biology and imaging technologies to observe the mechanism in real-time. In addition, mice transplanted with triple negative breast cancer cells, currently resistant to available therapies, revealed the arrest of tumor growth. The researchers are currently investigating the potential of one of the phenanthridine derivatives to treat two aggressive cancers known to be unresponsive to current chemotherapy: pancreatic cancer and triple negative breast cancer.

Conclusion

Analogously with the development of malaria blocking-vaccine that resorted to the basic understanding of that disease transmission, a paradigm shift in cancer therapy has been accomplished. Modifying specific proteins that affect the construction and stability of the spindle, a newly discovered mechanism is able to arrest cancer cells from dividing and multiplying, thus stopping cancer progression in its track. The process is one of self-destruction by a natural mechanism and the faster the proliferation of the cancers the faster and the more efficient the mechanism of self-eradication. While only a phenanthridine derivative has been so far investigated, a variety of additional drugs can likewise be employed. This newly discovered mechanism may counter aggressive cancers that have so far proven unresponsive to chemotherapy such as pancreatic cancer and triple negative breast cancer. This is a hopeful new vista in cancer therapy.

Reference

2. Kumar N (2016) Report from Tulane University, School of Public Health and Tropical Medicine, Louisiana University.