An alternative model of cancer cell growth and metastasis

Abstract  I propose an alternative model of cancer in which metastasis need not all arise out of spread from the "original" tumour. The model assumes that cancer cells arise from stem cells that best grow in the organ of their differentiation. When the internal milieu allows it they also grow at other sites as well, thus complementing the conventional (spreading) metastatic process. Several phenomena in the natural history of cancer, especially breast cancer, that challenge the conventional model, fit well after inclusion of the new model. These are (a) a very modest benefit of screening (b) frequent sparing of lungs from haematogenous metastasis (c) presence of occult cancers in autopsy studies (d) only a modest effect of local treatment (e) relative ineffectiveness of high-dose chemotherapy (f) constant time between surgery and peak of hazard of relapse irrespective of stage of the tumour. All these phenomena are much easier to explain when one rejects the dogma that all metastasis arise only from the primary tumour. This paper is aimed only to suggest an alternative perspective of natural history of solid tumours to stimulate research on the complex internal milieu that allows cancer cells to develop in new light.

The conventional model of cancer cell growth and metastasis is the following: cancer arises from a fault in a cell. This single faulty cell then multiplies to form a cluster of cells—a tumour. Tumour cells then spread to the whole body and these metastases can eventually kill the person.

I propose an alternative model. When the internal milieu of a person is disturbed, stem cells from all parts of the body can grow into tumours. This disturbance in the milieu may be mild or severe. The complex change in the milieu favours development of one type of differentiation of these tumours, for example, breast epithelial cells. The best tissue environment for a breast epithelial cell is the breast. So, the breast cancer stem cell in the breast grows the fastest and therefore is clinically apparent first, or when the internal milieu is only mildly disturbed. Severe disturbance of the internal milieu results in growth of breast cancer stem cells all over the body—clinically presenting as metastasis.

In reality, metastasis could be explained by both models each contributing to the whole picture, such that a proportion of systemic cancer foci could be arising from migration of cells from the larger tumour in the organ of its preference and a proportion "home-grown" at that site. This proportion could be different for different types of tumours.

Predictions from the alternative model would be the following:

Risk of a cancer would depend on number and sensitivity of stem cells in the body. Removal of the "primary" tumour should not affect the ultimate outcome, unless the act of surgical excision itself disturbs the internal milieu (favourably or unfavourably).
Multiple metastases could arise in the body many years after removal of the "primary".
Metastasis could arise in any part of the body, unrelated to the path which the cancer cell may take from the primary tumour to the site of metastasis; and this could also explain metastasis with "unknown primary".

Several phenomena that appear to be paradoxes in the conventional model are not paradoxical in the alternative model. Each of these could also be considered as natural experiments/phenomenon that failed to falsify the new hypothesis.

(1) If the "primary" breast cancer were the sole source of metastasis then earlier removal of the "primary" — by screening — should have resulted in a huge reduction in appearance of metastatic disease and mortality. Unfortunately screening mammography which manages to allow treatment of smaller and earlier cancers in the breast reduces mortality by only modest level. In the alternative model, when a small tumour is found in the breast — it is only incidental and could be the result of only a mildly disturbed milieu that would never allow the stem cells from rest of the body to grow so its removal may not have the expected impact. The impact will depend on how disturbed the milieu is and how much contribution the conventional spreading is making to the ultimate outcome. Thus the new strategy could also explain the difference in benefit from screening between different tumour types (for example, none in lung or prostate but modest in colon) or between age groups (for example, much higher benefit from screening mammography in those >50 vs. <50)? Taking the latter example, we should first remember that overall far fewer younger women die of breast cancer. Of course, those that are diagnosed do much worse — for in order to be diagnosed with cancer they had to have had much higher disturbance in their internal milieu than older women. The benefit from earlier diagnosis likewise will be less perhaps because the milieu plays much more important part in their disease than in older women. The latter argument would explain the differential benefits of screening for different tumours.

(2) One third of women of age 50–55 years harbour occult cancers in their breasts — this is never the incidence of clinical tumours. Being above the size that require vascularity to survive, these should have all given rise to metastasis and be fatal. However, without severe disturbance of the internal milieu none of these, or those in rest of the body would grow. On the other hand one could argue the reverse that these occult tumours themselves are biologically inert. It is like arguing whether this is written in blank in over white paper or with white ink covering almost all of black paper. It should be noted, however, that we have not been able to yet identify a single biological or morphological factor that can identify such "inert" cancers that would have not progressed and become clinically dangerous. The benefit from diagnosing these "cancers" early is perhaps overshadowed by the possible harm from disturbing the milieu of these women by intervention such as surgical excision stimulating angiogenesis.

(3) Following the venous drainage tumour cells need to move from the breast or almost any other organ, to the lungs first and thence to rest of the body. Thus lung metastasis should be the most common metastasis — but that is not often the case — bone or brain metastasis can arise in the absence of lung metastasis. This can be easily explained by the alternative model which does not require the "travel" from the "primary" to the metastatic site. The stem cells from the metastatic site grow into "breast" tumours in the internal milieu and favours differentiation into mammary adenocarcinoma. It is plausible that certain environments are more abundant in or more conducive to growth of stem cells such as bone marrow as opposed to muscle tissue.

(4) Some cancers such as basal cell carcinomas never "give rise" to systemic metastases — except in presence of immunosuppresion with AIDS. Some others rarely do such as squamous carcinomas of head and neck. The milieu in rest of the body is probably not conducive to growth of squamous carcinoma that may require exposure to atmosphere (including lung and gastrointestinal tract).

(5) Longer exposure to a faulty milieu should give rise to more cancer — this fits with the increasing incidence and mortality from cancer with age.

(6) The effect of local treatment of breast cancer on ultimate outcome is not 100%. The rate of reduction in mortality is only a fifth of the reduction in reduction of local recurrence such that if local recurrence rate is reduced by 20% from 30% to 10% then breast cancer mortality is reduced by only 4%. This suggests that metastasis by the conventional model may account for only about a fifth of the metastatic process and the alternative model may explain the remaining fourth-fifth.

(7) The hazards of relapse peak at a fixed time after excision of the "primary" tumour. In the conventional model if tumour starts in the breast and spreads to form metastasis, then the longer it has been in the body (and larger it is), longer would the metastasis have had to start growing. So a larger tumour should have metastasis developing sooner and smaller ones later. Thus the hazard of relapse should have peaked earlier in a larger tumour and later for an "early" cancer. But in reality it is not the case, in both cases, metastasis appear at the same time whatever the size of the tumour — they just have a higher risk of occurring in larger tumours — because again, the more disturbed is the milieu, the larger is the tumour and higher is the risk of appearance of relapse elsewhere. Perhaps the act of surgery disturbs the internal milieu even more and allows the cancer stem cells from rest of the body to grow, thus the duration between surgery and hazard-peak is constant irrespective of the size of the "primary" tumour in the breast.

(8) Systemic chemotherapy that is shown to work very well in "killing" cancer cells has only a modest effect on mortality and offers almost no survival benefit in metastatic disease. This is because it is designed to kill the already malignant cells and not to restore the internal milieu. It works well for haematological
malignancies perhaps because it depletes the sensitive haematopoietic stem cells themselves. High-dose chemotherapy with stem cell harvest does not work despite achieving "complete response" perhaps because of the stem cells that rescue the patient as well as the cancer. There is growing interest in the cancer stem cell. This is supposed to be less sensitive to current chemotherapy and its characterisation today has the obvious aim of better targeting this cell to cure cancer. Although therapies that are targeted to kill tumour cells or even cancer stem cells will work, the effect is still only modest. In addition the solid organ stem cells may have many other functions that are vital to its function and killing them may be more disastrous than killing haematopoietic stem cells. And even then, many patients would "recur" because the fundamental problem of faulty milieu is not solved.

"Disturbance of internal milieu" is a very broad concept and I have not attempted a description of its complexity here. Disturbances of this milieu could be simple factor either genetically driven or environmental — from BRCA gene mutations to tobacco smoking, or, hormonal such as increasing exposure to continuous cycling of female hormones or early abortion of the full pituitary—mammary axis by not breast feeding, or direct effect on immunity such as AIDS, treatment of childhood leukaemia or cyclosporine given for transplantation. It could also be more complex and need not always be extracellular. The PTEN (phosphate and tensin homologue) protein is a tumour suppressor and intracellular modulator of several major cell signalling pathways. It appears that11,12 PTEN via the PI3K/PTEN/AKT pathway, is critical component of a molecular switch that modulates the behaviour of stem cells — whether they remain quiescent, self renew, and create differentiating cells, or produce cancer stem cells that ultimately give rise to a tumour. With a conventional perspective, as has been followed by these authors11,12 we have now found a new way to kill cancer stem cells while preserving normal stem cells. With the novel perspective on the other hand, one would think "why does the PTEN not work properly in the patient with the tumour". Why did the Pten gene get mutated? We need to aim to repair that fundamental mechanism and not just try to repair the Pten gene or its products so that homeostasis can be restored. The mechanistic solution of the conventional model could be by substitution, albeit partially with rapamycin, that inhibits the AKT effector mTOR and restores normal stem cells and depletes cancer stem cells. This approach may well work — but at certain point will hit a ceiling. Ideally we need to find ways of keeping this PI3K/PTEN/AKT machinery (and other ones) intact on a continuous basis. Rather than only killing of the rogue cells or patching up the rogue pathways, we need to find and repair or restore that which makes them rogue.

The transfection theory10 suggests that mutated genetic material from the primary tumour cells could be transferred to normal differentiated host cells by the process of transfection via the cells of the reticuloendothelial (RE) system. This could be an example of a mechanism of disturbance of internal milieu, in this case the RE system. Looking at a wrecked car in isolation, without the knowledge of the road conditions and the recently attended party cannot tell us how it wrecked although alcohol level in the blood of the driver and the snow on the bonnet may give us a clue, but only if we think about it. This paper is aimed only to suggest an alternative perspective of natural history of solid tumours — to stimulate research on the complex internal milieu that allows the cancer cell to develop in new light. In the history of science, it is the change in perspective that has usually been the most important.

References


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