On the Invasiveness of Cancer Cells

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I have gone on about dissemination and metastasis formation as the scourge of cancer in previous editorials; if only all cancers were contained or containable, cancer would no longer be a major killer. My early days in research were devoted to studying cell movement when new techniques of imaging were becoming available, (interference, phase-contrast, and electron microscopy). Interestingly some of the work reported in those days did not come directly from what these techniques had to offer, but from the finding that the invasiveness of tumour cells often correlated with the onset of an immune reaction, which can quickly change their behaviour. The severity of a host-tumour reaction depends on the degree of immunogenicity has been provoked during malignant transformation. In *Oncology News*, Richmond Prehn [1] continues to emphasize how the immune response elicited by a tumour can significantly affect its subsequent behavior. A subtle response can promote tumour growth rather than restrain it. Exacerbation the response can make matters worse, which can be shown in animal models when heterologous or xenografted tumours are implanted. At one time, experimental tumours were being injected with BCG to stimulate a massive local immune and inflammatory reaction in the hope that the reaction would be strong enough to wipe out simultaneously the tumours. The outcome was usually pretty messy, not one worth pursuing as a therapeutic approach. Strong response to a tumour can lead to hemorraghic breakdown, massive ulceration, followed by widespread systemic disturbances, often septicemia, and early death. Immunological approaches to treating cancers in this way were soon abandoned; modern approaches by comparison are based on subtle targeting of modified antibodies to relatively tumour-specific markers.

Lymphocyte infiltration occurs in an immune response against a tumour. Lengthy investigations were undertaken with tumour infiltration lymphocytes (TILs) "instructed" to react to autochthonous tumour cells by growing them out in culture before returning them to the patient in massive amounts by Rosenberg and his colleagues [2], a book that only admits to the calamitous failure of yet another therapeutic approach.

An immune response, however small, will change the nature of the affected tissues, in this case the cancer and its stroma, and this leads to many other changes, one being neovascularization. Endothelial cells will inwards grow towards the more hypoxic regions of the tumour, thereby providing fragile blood vessels across its actively growing regions. New lymphatics will drain the area, which lays itself open to tumour cell migration into the systemic circulatory systems. Noteworthy are the changes involving many cytokines and other factors acting in the area that result in the diapedesis of lymphocytes. They take advantage of various matrix metalloproteinases (MMPs) being released that loosen up connective tissue and basement membranes. Their infiltration is a natural process of directional cell movement; these small cells can pass through minute gaps in local endothelial cells. In my early studies, I found tumour cells were capable of migrating through extraordinarily small gaps in a similar manner, a process that could be mimicked using coated filters of very small pore size. As tumour cells are commonly characterized by much looser adhesion to one another, the conditions are just right to promote a "reverse diapedesis." But some tumour types seldom metastasize while others (melanoma cells) seem to have high potential to disseminate. Experimental tumour cell lines can have weak and high metastasizing sub-strains. In general, we might expect that as a human tumour grows, heterogeneity will increase along with the probability of subsets of cells having a higher potential for metastasis. Differences in gene expression of metastatic versus non-metastatic clones from the same tumour need much more investigation in this regard.

The next problem relates to the seeding of disseminated tumour cells at distant sites. In this regard, more work needs to be done on why different types of tumour cells chose quite disparate tissues for resettlement. Two papers in this issue include revolve around these consideration, those by Piccirillo and Watts [3] and Aboukhatwa [4], the former arguing that there may be at least two different origins of GBMS cells and these stem-like cells can spawn not only more progenitor cells but more differentiated sisters cells possessing the potential to disseminate; to quote "Glioblastomas are highly invasive lesions and by the time of diagnosis, glioblastoma cells have already migrated great distances from the primary tumour." It has also been proposed that these highly migratory cells are, in fact, GBSCs, which will be just the type of cell that will get a reseeded tumour cell or nidus growing fast in the new site [3]. The question as to whether they are then accessible to immune cells remains open. If they are, then genetic, mutational, and proteomic profiling of these GBSCs will hopefully provide therapeutic targets unique to this small subpopulation. We all pin our hopes in such strategies being practical and effective. Much the same case for breast cancer dissemination is argued in the second paper [4], with the author acknowledging the fact that "millions of pounds and hours of investment into pre-clinical research and the development of a broad range of MMP inhibitors" have not done much to address the problem of restraining metastatic spread. She also draws attention to the fact that "the cancer cell needs to travel undetected by immune cells, through the blood-stream until it arrests at a site of metastasis". Is their initial escape mechanism now working in reverse [4] or are the processes involved quite dissimilar? While it may be too early to give an answer to this question, it clear that a cocktail of protease inhibitors has not proved effective in reducing metastasis in breast cancer. MMP9 alone or with other MMPs per se may not be the main culprits in metastasis formation. But the author draws attention to the possibility that protease action has not been adequately considered in relation to glycosylated forms of proteins. By using β-nacetylglycosaminidase (β-NAG) inhibitors [5] along with protease inhibitors, it is possible that some ground can be gained in reducing the reseeding of metastasizing tumour cells. One can only wait to see if some of the encouraging in vitro data can be translated into an effective anti-metastatic strategy in vivo.

References

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