Is spontaneous regression of cancer due to immunity or failed healing? A view from the "danger model" of immunity

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Abstract

The view of tumours as inflamed wounds that will not heal conflicts with the notion that they are parasite-like growths controlled by the immune system. The need to resolve this central paradox of onco-immunology is cast in stark relief by our limited understanding of human cases of spontaneous regression of metastatic cancer. It is argued that most regressions are not due to anti-tumour immunity *per se*, but to ultimate failure of an inflammatory healing process due to loss of support from monocyte-derived cells (MDCs). This may occur because tumours and/or inflamed tissues out-compete one another for MDCs, leading to failed healing and cataclysmic regression of all deposits. Alternatively, remote inflammation may out-compete myeloid-derived suppressor cells thought to block T cell mediated attack on tumours.

Introduction

Although cases of spontaneous regression of metastatic cancer are extremely rare, and many mechanisms for their occurrence have been postulated, the default explanation offered by most authors is immunological, i.e. that the immune system must have suddenly become activated against the metastatic tumours and eliminated them[1-3]. This viewpoint dates back to the late 19th and early 20th century work on unexpected regressions of sarcomas during severe local infections of erysipelas, and to treatments with Coley's mixed bacterial toxins, which still provides the foundation of modern immunotherapy against cancer[4,5].

Yet no one really knows how some infections can lead to regression of sarcomas; the only immunological explanation available until recently was that infections incite a general inflammatory response against the tumours that somehow eradicates them. But this viewpoint

becomes less and less tenable with increasing recognition that *cellular inflammation* is the primary driver of tumour growth[6-11]. In addition, tumour-antigen-specific immune responses have been ineffective against cancer[12,13], and only those immunotherapies that produce unintended autoimmune phenomena in previously normal tissues have increased survival[14-16].

Importantly from a conceptual standpoint, it is only with the advent of Matzinger's danger model of immunity that we have a possible explanation for how adaptive immune T and B lymphocytes might have been activated by erysipelas infections[17]. Furthermore, the danger model provides the first framework with some explanatory power necessary to more fully assess claims that anti-tumour immunity is the cause of spontaneous regression[18-20]. Indeed, as excitement about the so-called "abscopal" effect of radiotherapy has been growing, the danger model has become the main theoretical framework for explaining the probable mechanism of regressions of all metastatic deposits following irradiation of a single site[21-24]. It therefore makes sense to analyze all available data where cancer resistance seems to be occurring, to develop a hypothesis for explaining these data, and finally attempt to explain the mechanism of regression.

Abscopal effects and the Danger Model of Immunity

The more remarkable instances of unexpected regressions of metastatic deposits are known as "abscopal" effects: ("ab" – away (Latin), and "scopal" - target (Greek)). In current parlance, abscopal effects are those that occur when therapeutic irradiation of one tumour in a patient's body leads to disappearance of many or all of the other metastases[3], but the term describes virtually all remote effects of local cancer treatments. The main explanation for such effects currently derives from the "danger model of immunity". In contrast to the traditional the self/non-self model, the danger model holds that activation of the immune system is not incited, for instance, by bacteria or transplants because they are foreign, but because they damage extracellular matrices and kill cells by primary or secondary necrosis[18]. This leads to the release of molecular detritus that engage receptors on monocyte-derived dendritic cells (DCs), activating them to present antigen to T lymphocytes[25]. Using the danger framework, radiobiologists increasingly contend that, in certain poorly understood circumstances, irradiating one tumour creates enough tissue damage to provide an adjuvant or boosting effect to DCs so that they take up and present tumour antigens to T cells, activating them to kill other tumours elsewhere in the body[21,23,24].

As a new and expansive theoretical framework, the danger model accommodates this view as a possibility. However, it has at least 2 other implications which put that evolving viewpoint in a more complete perspective: 1) the immune system is as much involved with tissue healing as defense against invaders,[26-30] and 2) *any* sudden destruction of tumours by *any* mechanism will produce epiphenomena of an immunological reaction that might easily be misinterpreted as having been the result of immunity against those tumours[18,31]. In fact, most cases of cancer

resistance identified either clinically or epidemiologically have been so construed; a brief review follows.

Cancer resistance as a general phenomenon

Construed broadly, "cancer resistance" phenomena are those which are unintended by the investigator. In rough order of how well known those are to oncologists and others, they include: 1) resistance mediated by an already-growing tumour to growth of a second primary or its metastases[32-34], 2) increased survival of inherited cancers relative to sporadic tumours of the same type[35-39], 3) inverse association between cancer and other chronic diseases in terms of incidence in populations (mainly neurodegenerative, multiple sclerosis, and atopic disease),[40-48] 4) inverse association between cancer and other chronic diseases in mortality or severity/extensiveness within bodies of individual patients (mainly atherosclerosis and autoimmunity)[49,50] including unexpected increases in cancer mortality in cardiovascular risk intervention trials,[51-53] and 5) autoimmune enhancement of immunotherapy treatments[16,54].

Category 4 is little known, but is now becoming increasingly well documented. More than 55,000 autopsies had shown a reciprocal relation between cancer and atherosclerosis,[55-62] and this inverse relation has now been borne out in prospective studies[63-65]. An inverse association between cancer and atherosclerosis is now one of the best documented relationships in human pathology. Although the relationships among cancer and autoimmune diseases (AID) are not as clear-cut, as the incidence of several cancers increases in AID, most are blood-borne malignancies - usually leukemias and lymphomas - which are probably due to chronic antigenic stimulation; some solid tumours increase in incidence while others decrease in some AID[45,66].

But of interest is that, despite such variability, autoimmune phenomena remote from tumors within the bodies of individual patients almost universally decrease the severity or extensiveness of cancer (in other words, except for the autoimmune-targetted cells in non-HLA-linked AID).[66] This is so for paraneoplastic anti-neural and rheumatic autoimmunity and patients treated by "immunotherapy."[54,67-69] In the latter instance, it is still unexplained why highly antigen-specific vaccines have largely failed, whereas general pro-inflammatory interventions that lead to unanticipated autoimmune phenomena are most likely to reduce tumour burden and increase overall survival[15].

Except for enhancement of metastatic growth following removal of primary tumour, believed to be due mainly to abrupt decline in anti-angiogenic substances secreted by the primaries,[34] the above phenomena have usually been explained as due to either competition for nutrients/bioenergetics or anti-tumour immunity.[70,71]

Hypothesis: wounded tissues including tumours compete for sustaining monocyte-derived cells

In an attempt to integrate the notion of competition with that of immunity, I postulate that tumour growth is driven mainly by the presence of adequate numbers of inflammatory cells, particularly monocyte-derived cells (MDCs). Furthermore, when there are multiple tumours and/or damaged tissue sites in the body, they must compete for adequate numbers of MDCs including those designated as myeloid derived suppressor cells (MDSCs), tumour associated macrophages (TAMs) and Tie2-expressing monocytes (TEMs).

How might tumours and/or damaged tissues "compete" for MDCs? What might the mechanistic basis or bases be for such competition? At least 4 mechanisms are conceivable, including limitations on bone marrow production, neural mechanisms ("counter-irritation"), anti-inflammatory milieu created by acute phase responses[72] and/or superiority of chemoattractant effectiveness of one site over the other. So far, this general mechanism of competition between wounds and neoplastic foci has only been shown experimentally by Antonio in fish larvae[73], although there is mouse data demonstrating that reduction of inflammation in tumours through "counter-irritation" can lead to reduction in size of lesions[74,75].

We have begun to explore only the first possibility. Although bone marrow production of monocytes might seem unlimited in that almost a trillion are produced daily, another picture emerges if one examines monocyte production per unit time (7×10^6 cells/kg/hr)[76]. Biomathematician Bard Ermentrout (personal communication) has derived the following 3 differential equations in a preliminary attempt to explore this idea.

Simultaneous equations describing "monocyte competition" between 2 tumours or between tumour and second inflammatory site -

$$m' = s\text{-}m\text{-}a \times m \times (p \times t1+t2),$$

$$t1' = -\gamma \times t1+c \times p \times t1 \times m$$

$$t2' = -\gamma \times t2+c \times t2 \times m$$

Where *m* = monocyte numbers in blood; *t1* is one tumour; *t2* a second tumour or remote damaged/inflamed tissue site in same body; *γ* = the death rate of tumour lost naturally; *a* = parameter characterizing numbers of monocytes acquired by a growing tumour; *c* = parameter for production of new tumour aided by monocyte-derived cells (MDCs); *S* = number of monocytes coming from the bone marrow; and *p* sets the heterogeneity of the tumours - it weights them in terms of how much inflammation they would get. p>1 means that one tumour gets an advantage over the other, e.g. due to size etc., and p<1 indicates a disadvantage.

In the general case of 2 tumours, *t1* and *t2*, competing for monocytes, "*t2*" stands either for second tumour or inflammation in a site remote from first tumour. Setting *t1* as smaller than *t2*, when *t1* is multiplied by a weighting factor *p* as 1, *t1* is able to overtake *t2* in growth, and would tend to continue growing, whereas *t2* would lose the competition and die off. Any externally applied damaging agent, such as radiation, would tend to weight the smaller tumour

with additional cellular inflammation, and allow it to outcompete the large tumour under certain conditions. Although these equations constitute a very preliminary "toy" model, they suggest that the overall idea of monocyte competition is plausible.

Spontaneous regressions viewed through the lenses of danger and monocyte competition

For unknown biological reasons, metastatic regression is most likely to occur in some of the most deadly cancers, including melanoma and renal cell carcinoma (RCC)[24]. In many ways, RCC is the most difficult to explain because its behaviour is almost unique after removal of the primary tumour. Unlike many tumours - in particular melanomas, sarcomas and breast cancers[77] - no generalized enhancement of metastatic growth occurs following nephrectomy. It appears quite the opposite - in many cases the regression of lung metastases in RCC occurs after nephrectomy[78,79]. This reversed behavior has often been explained by von Hippel Landau mutations in clear cell RCC, which are purported to enhance angiogenesis in the primary as well as in metastatic deposits[80], such that removal of the primary eliminates the sources of proangiogenic substances for the metastases rather than releasing them from postulated anti-angiogenic inhibition (i.e., the more usual case). How might the monocyte competition model accommodate this paradoxical behavior of RCC?

If, as Mantovani et al.[11] have suggested, the effects of anti-angiogenic and other treatments are truly mediated by effects on MDCs,[81] it is possible that the usual course of events following removal of primary tumour is that, along with cancer cells being released into the bloodstream, tumour-associated MDCs are also freed into circulation[82], such cells constituting as much as 50% of the tumour bulk. In melanomas, sarcomas and breast cancers, these circulating MDCs would then travel to metastases, enhancing their growth through angiogenic and other means. However, in RCC, the route to dissemination is abruptly cut off due to the highly unusual intervention of removal of an entire organ containing the tumour usually in its cortex, followed by tying off the blood supply from the aorta and to the vena cava. Although the surgical procedure itself would damage the peritoneum to some extent and cause inflammation there, which might compete with that occurring in lung and other metastatic sites, the usual pathway for tumour-associated MDCs to travel to other deposits would be blocked. There are also published cases of metastatic regression of RCC that occur in conjunction with flares of inflammatory diseases[2,83].

In the case of melanoma, the case best studied from an immunological standpoint on an abscopal effect is that of Postow et al.[84] The patient had been on the anti-CTLA-4 monoclonal antibody, Ipilimumab, for several months with metastatic progression until radiotherapy of a single deposit led to complete regression of all the metastases. No antigen-specific tumour vaccine had been included in the protocol. The mechanism of the regression therefore would not be expected to be clearly immunological in the usual sense. Nonetheless, Postow et al.

contend that their data suggest that anti-tumour immunity eliminated the metastatic deposits; the notion of immunogenic cell death is cited,[85-87] which derives from the danger model.[88,89] However, the actual data in the report are more consistent with our monocyte competition idea than with an immunological effect. His Supplementary Figure 2 in ref. 67 shows that IFN-gamma producing CD4+ and CD8+ T lymphocytes, which would have been expected to increase following radiotherapy if they had been involved in tumour cell killing, actually plummeted to their lowest levels. The levels of activated T lymphocytes (CD4+ ICOShigh) increased slightly following radiotherapy, but were much lower than they had been during Ipilimumab therapy alone. Autoantibody levels rose and fell, but the authors do not argue that these were involved in any immune-mediated destruction of tumour.

But by far and away the most dramatic positive effect was on levels of blood monocytes; as shown in Postow's Fig. 3 B and C[67], following radiotherapy levels of "bad" HLA-DR low monocytes dropped, while numbers of "good" HLA-DR high monocytes rose sharply. In addition, internally corroborating the inverse relation between the 2 monocyte subsets, it can be seen from these 2 panels that the HLA-DRhigh and HLA-DRlow numbers were reciprocal at every measured time point prior to the radiotherapy, creating an almost perfect inverted mirror-image (seeAppendix). It is apparent that, whatever the mechanism of the regressions, monocytes and not T lymphocytes are principally involved.

Discussion and conclusions

Based on the best available immunological measurements during regression of metastatic melanoma, viewed through the backdrop of cancer resistance data and the danger model, there are 2 mechanisms for metastatic regression that are most tenable in explaining how interventions/infections that enhance inflammation remote from any tumour and its deposits might induce regressions: 1) by drawing in MDCs to such an extent that too few MDCs are left to continue an attempted healing of those lesions, which might then die cataclysmically mainly by primary and secondary necrosis, leading to immune sequelae that are only epiphenomenal to the mechanism mediating tumour destruction; or 2) by drawing in MDCs to such an extent that too few myeloid-derived suppressor cells remain at the tumour site, which then frees any activated CD4 or CD8 lymphocytes to kill the tumour. This latter explanation integrates monocyte competition with current immunological thinking, and preserves some role for anti-tumour immunity in regression.

Perhaps the outstanding question for research to address is: What is it about the poising of the patient's overall marrow capacity and immunological state/reserves that primes them to respond to remote inflammation with such extraordinary metastatic regressions as have been documented? We might suspect, based on Rosenberg's work on total body irradiation and lympho-depletion as preparation for immunotherapy with tumour infiltrating lymphocytes, that

regimens which abruptly reduce marrow reserves and favour genesis of autoimmunity[90,91] may also facilitate metastatic regressions. Just why concurrent autoimmune phenomena are by far the strongest correlate of effective cancer immunotherapy remains unknown, but may be explained by monocyte or possibly other inflammatory cell competition, with immune-mediated mechanisms as a secondary phenomenon or epiphenomenal. Further research of a principally quantitative nature involving diverse disciplines is clearly much needed.

Acknowledgements

I thank Roger Day, Michael Retsky, John Kirkwood, and Lisa Butterfield for criticisms and thought-provoking discussions about the general idea of monocyte competition, and Bard Ermentrout for providing a preliminary mathematical model. In addition, I thank Polly Matzinger for allowing me to get my feet wet as an experimentalist, and to begin to explore the implications of the danger model for healing and regeneration.

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Appendix:

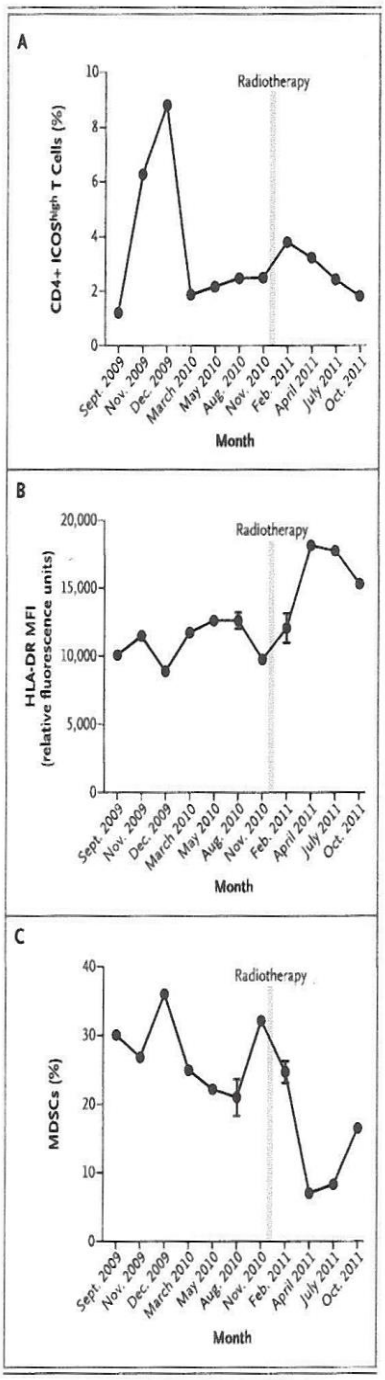
A
Radiotherapy
CD4+ ICOS^high T Cells (%)
0
2
4
6
8
10
Sept. 2009
Nov. 2009
Dec. 2009
March 2010
May 2010
Aug. 2010
Nov. 2010
Feb. 2011
April 2011
July 2011
Oct. 2011
Month
B
Radiotherapy
HLA-DR MFI
(relative fluorescence units)
0
5,000
10,000
15,000
20,000
Sept. 2009
Nov. 2009
Dec. 2009
March 2010
May 2010
Aug. 2010
Nov. 2010
Feb. 2011
April 2011
July 2011
Oct. 2011
Month
C
Radiotherapy
MDSCs (%)
0
10
20
30
40
Sept. 2009
Nov. 2009
Dec. 2009
March 2010
May 2010
Aug. 2010
Nov. 2010
Feb. 2011
April 2011
July 2011
Oct. 2011
Month

Figure 3. Results of Flow Cytometry of Peripheral-Blood Mononuclear Cells.

Panel A shows that levels of CD4+ ICOS^{high} cells increased during ipilimumab induction but decreased before radiotherapy; after radiotherapy, there was a second increase in the levels. Panel B shows an increase in HLA-DR expression on monocytes, expressed as mean fluorescence intensity (MFI), after radiotherapy. Panel C shows a decline in levels of myeloid-derived suppressor cells (MDSCs) (CD14+ HLA-DR^{low})[9] after radiotherapy. Data in Panel A are a representative sample from two independent determinations; data in Panels B and C are the means from two determinations. I bars indicate standard deviations.

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