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Biomechanical interactions of cancer cells with the microvasculature during hematogenous metastasis

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Abstract

Different aspects of hematogenous metastasis are discussed from the viewpoint of biomechanics. The processes considered include the role of primary tumor pressure, cell locomotor forces and degradation, in invasion of tissues and intravasation by cancer cells. Consideration of the fluid dynamics of cancer cell movement along capillaries lead to the view that *in vivo*, arrest is primarily due to mechanical trapping of cancer cells, and that the pathobiologic role of so-called adhesion molecules is not mainly in the arrest and adhesion of cancer cells, but rather in stimulating their proliferation by signal induction. As a consequence of deformation from spherical-to-cylindrical shape in the microvasculature, demands for increased surface membrane area leads to increases in surface membrane tension above critical levels for rupture, and the cancer cells are rapidly and lethally damaged. The possibility is briefly discussed of increasing the susceptibility of circulating cancer cells to mechanical trauma, as a form of anti-metastatic therapy.

Various interactions of cancer cells with the microvasculature are of major importance in determining the efficiency with which cohorts of circulating cancer cells form metastases [1, 2]. Some of these interactions will be considered primarily in terms of biomechanics, and although the 'mechanics' will be emphasized, the biology will not be ignored, but together they constitute only one aspect of some extremely complex processes.

Invasion/intravasation

A combination of factors contribute to invasion, including the generation of expansile forces ('vis a tergo') by growing tumors, and/or locomotor forces by individual cancer cells; the actions of these forces are resisted by the mechanical properties of the invaded tissues and, in the case of intravasation, by blood-pressure.

A simple manometric technique was used to measure the 'tissue pressures' in the normal rabbit testis, and in implanted Brown-Pearce carcinomas growing in the contralateral organ. The mean ($\pm$ S.D.) tissue pressure of 26,2 $\pm$ 8.2 cm H_2O (n = 100) in the tumors was significantly higher than in either the normal testis (11.3 $\pm$ 1.8) or in normal tissues surrounding tumors (12.7 $\pm$ 3.0). On the basis of these results, Young *et al.* [3] concluded that the entry of cancer cells into blood vessels was essentially due to increased extravascular or tissue pressure. The other side of the coin, namely blood-pressure resistance to intravasation, was revealed by the use of micro-occlusion techniques [4]. Thus, in subcutaneous AH109A Yoshida hepatomas, the microvascular pressures fell in the range of 5 to 10 cm H_2O, compared with the mean pressure of 12.0 $\pm$ 5.2, within 10 to 50 μm diameter venules in the normal subcutis. These measurements, which are of the same order as

those measured in other tissues and tumors by others (cited in [4]), indicate that cancer cell invasion of loose connective tissues and the imperfect neovasculature of tumors themselves, could be driven by pressure generated by growth-associated expansion in the parent tumor. However, it is doubtful that pressures of this order could, in themselves, be sufficient to drive invasion or intravasation through intact basement membranes.

In malignant tumors, it is difficult to assess the role of expansile forces alone in invasion, because growth is usually associated with histolysis due to enzymes released by cancer cells themselves. In addition, the damage inflicted on surrounding tissues by cancer cells often results in an inflammatory response with tissue degradation caused by enzymes released from leukocytes and tissue macrophages. However, the effects of expansile forces alone are perhaps best demonstrated by the convoluted shapes developed by benign tumors growing in mechanically heterogenous 'normal' tissues; for example, those seen when (benign) lipomas expand through surrounding soft tissues and bend around bone. The tendency of malignant tumors to grow along fascial planes, or in the bone marrow, which constitute pathways of least mechanical resistance, also indicates a role for expansile forces in tissue penetration. However, apart from the entry of cancer cells into the intratumoral neovasculature, expansile forces alone account for neither the initial nor the later steps in invasion which both involve the enzymatic degradation of basement membranes and connective tissues.

Invasion may also involve the active movement of individual cancer cells, or sheets of cancer cells as seen in epiboly during morphogenetic movements [5]. The absolute requirements for active movement of cancer cells are first, adhesion of parts of the cell periphery to the tissues over or through which movement occurs, to provide a fulcrum for locomotor forces, the generation of which constitutes the second requirement. Finally, as cancer cells are not infinitely extensible, their trailing edges must detach from the substratum for translocation movements to occur. Detachment is not the reverse of cell adhesion, but appears to occur in a different plane, because the adhesive forces holding cells to their substrata are usually less than the cohesive forces holding parts of the cell periphery to each other. This results in the non-lethal rupture of parts of cell peripheries during detachment, as evidenced by the presence of adherent, residual fragments on the substratum [5–8].

Factors decreasing adhesion or detachment below critical levels tend to totally or partially inhibit active cancer cell movement. From the biomechanical viewpoint, the same agents may produce opposing effects on cell movement; for example, on the one hand, enzyme activity at the cell surface may prevent effective adhesion by the lysis of focal contacts, with corresponding reduction in movement. On the other hand, collagenase and its tissue degradation-products may directly stimulate migration [9], and by degradative reduction of tissue 'viscosity', may indirectly promote movement [10]. Enzyme-facilitated cell detachment may promote detachment [11] and hence migration, and factors inhibiting cell migration may also inhibit detachment [12].

The actual locomotor forces generated by cancer cells have not been measured to date, although the late R.D. Allen observed that movement of the amoeba Chaos chaos along 50 to 100 μm diameter tubes which they filled in section, could be stopped by hydrostatic pressures of 1 to 2 cm H_2O. These correspond to maximal locomotor pressures of approximately 2×10^3 dynes/cm^2 [13]. Amoebae migrate faster than cancer cells, and their locomotor pressures may therefore be considerably higher, thus, while extrapolations from one to the other are conceptually attractive, they lack numerical verisimilitude. However, forces of this order can cause considerable cancer cell deformation [14], they would permit a cell process to move against venous pressure during intravasation, and could also permit cell movement through enzymatically-weakened matrices, although they appear too low for cellular penetration of intact tissue matrices.

Analysis of the biomechanical aspects of invasion is further complicated by observations that a number of peptide growth factors (e.g. EGF, PDGF, TGF-β) also affect cell motility [15], indicating a coupling of the two processes. It is there-

fore of interest that a morphometric analysis of invasive (vertical phase) melanomas indicated that an initial phase of invasion was associated with the active migration of melanoma cells towards the subcutis, and that after migrating several hundred micrometers, active cancer cell movement temporarily ceased the gaps between the cancer cells were 'filled-in' by proliferation. Invasion progressed by repetitive cycles of migration and proliferation [16].

Intravascular arrest and adhesion

By a combination of mechanisms, cancer cells enter the blood-stream by venous invasion. Many studies indicate that most circulating cancer cells are almost immediately arrested in the microvasculature of the first organ encountered. The greater the diameter of individual or clumps of cancer cells, the less likely it is that they will be diverted from larger to smaller vessels and, at first sight, it is more probable that they will pass directly through an organ in vascular shunts [17]. Indeed, arteriovenous shunting of glass spheres measuring up to several hundred micrometers in diameter has been reported in the liver, spleen and lungs [18]; however, studies of metastatic seeding-patterns indicate that successful shunting of viable cancer cells is uncommon [19–23].

Some clues on the mode of cancer cell arrest come from simplified, fluid dynamic models. Initially in this approach, cancer cells are regarded as viscoelastic spheres, moving along smooth-walled, fluid-filled tubes, driven by blood-pressure. As the cancer cells have greater diameters than capillaries, their entry must be associated with their deformation from spherical to cylindrical configuration or, alternatively, the capillaries will be deformed by the cancer cells; however, the latter has not been reported.

Passage of cancer cells along capillaries is associated with the formation of a thin film of plasma separating them from the vascular endothelium. During passage, hydrodynamic forces are generated which cause changes in pressure and plasma movement, in a pericellular region having approxi-

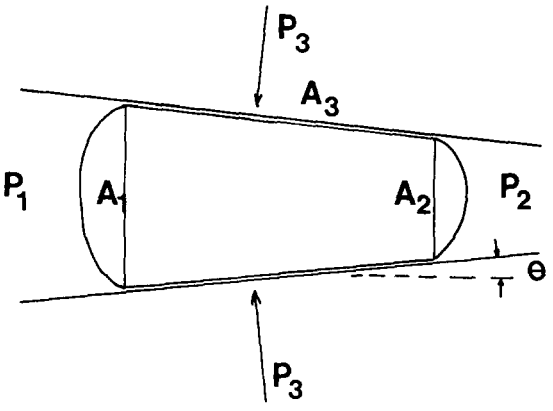

Fig. 1. Schematic of a cancer cell in the entry region of a capillary. The narrowing of the lumen is represented by the taper angle θ; P_1 and P_2 are the up-stream and down-stream pressures; P_3 is the 'squeeze' pressure compressing the cell, and A_1 and A_2 the up-stream and down-stream cell cross-sectional areas. From [25] by permission.

mately the same depth as cell radius. The rheologic properties of this plasma, and the relative mechanical properties of the cancer cells and the capillary walls are major factors regulating contact between them [24, 25]. Thus, when a cancer cell moves along a small vessel, when it is separated from the vessel wall by a distance exceeding cell radius, contact between them can only be accomplished by driving out interposed plasma, by pressure and viscous shear forces. As the separation distance decreases below cell radius, the pericellular hydrodynamic field will dominate motion, slowing down the approach of the cancer cell surface to the vessel wall.

The deformation of cancer cells is a prerequisite for their entry into capillaries, owing to the disparity between their diameters, and the deformation or 'squeeze' pressure (p_3) is a function of blood-pressure upstream (P_1) and down-stream (p_2) of the cells, the taper angle (θ), the up- and downstream cross-sectional areas (A_1 and A_2), and the area (A_3) of the cell in contact with the vessel wall, so that:

$$p_3 = (1/\sin\theta)\cdot(1/A_3)\cdot(p_1 A_1 - p_2 A_2)$$

During transit in capillaries, the elastic recoil of deformed cancer cells towards the capillary wall,

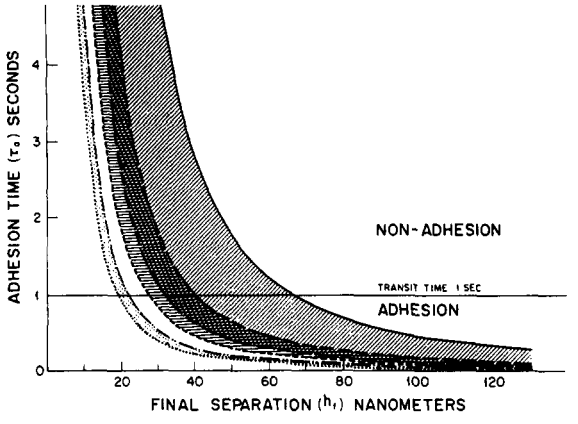

Fig. 2. Calculations of possible adhesion times, as a function of separation, h_f, between the cancer cells and capillary walls. With a transit time of 1 second, direct adhesive bonds cannot be formed between the two surfaces. From [26] with permission.

tends to drive out, and ultimately break the thin film of interposed plasma, which acts in some respects as a lubricant. Reduction in film thickness below a critical amount, will then permit interactive forces to occur between the two surfaces creating friction which, if in excess of the driving force due to blood-pressure, will result in cancer cell arrest. Attempts were made to assess the feasibility of this hypothesis, using well-accepted formulations from the field of fluid dynamics [26, 24]. Essentially, comparisons were made between cancer cell transit times through capillary segments, with the times taken to produce the necessary film-thinning, for the generation of interaction (arresting) forces.

Cancer cell velocity, u, was calculated from:

$$u = \delta p \cdot h \cdot R/2 \cdot \mu \cdot L$$

where δp is the pressure drop between the ends of a deformed cancer cell (0.1 Pa); h is average film thickness (10^{-6} cm); R is capillary internal radius (2.6×10^{-4} cm): μ is plasma viscosity (0.2 Pa.sec.), and L the length of cell opposed to the vessel wall (4×10^{-3} cm for a cancer cell having an original undeformed diameter of 15 μm). Under these conditions, the calculated cancer cell velocity is approximately 0.1 cm sec^{-1}, which corresponds to a transit time of 1 sec. in an 0.1 cm long capillary segment (Fig. 2).

Adhesion time, t, is given by:

$$t = (\mu \cdot R \cdot L^2) \div 2T\,(h_f)^2$$

where T is tension (2 to 5 dyne. cm^{-1} in the cancer cell membrane and h_f is film thickness. The results indicated adhesion times greatly in excess of transit times for all values of membrane tension, when h_f is less than 20 nm, which is the case for attractive forces.

Therefore, this model predicts that the transit times for cancer cells passing through capillary segments, are too short to permit direct adhesive bonding between the cell and capillary surfaces resulting in cancer cell arrest. However, the fact that cancer cells are rapidly arrested after entering capillaries, mandates reexamination of the model. A major assumption was that both cancer cells and capillaries had smooth, homogeneous surfaces; the fact that they do not, suggests that contact could well be made through fine surface extensions, and that initial arrest is mediated through mechanical trapping. An alternative is that initial arrest involves bridging by the various cell adhesion molecules with receptors (integrins) at the cancer cell surfaces. Although such bridging is demonstrable *in vitro*, where cancer cells are allowed to sediment onto coated dish surfaces over relatively long periods of time, the *in vivo* situation is much more complex, since receptor mediated adhesion occurs under conditions of viscous shear flow. Hammer and Lauffenberger [27] have described a dynamic model (Fig. 3) in which the occurrence of adhesion is considered in terms of dimensionless quantities, including bond formation rate, receptor-ligand affinity, fluid mechanical forces acting on the cell, receptor density and mobility, and contact area. Two processes are considered: A rate-controlled high affinity process and an affinity-controlled low affinity process. Whether or not arrest occurs depends upon the balance of adhesive and distractive forces, and the rate at which adhesive bonds break. Unfortunately, this model is incomplete and, while making a useful contribution to the dynamics of the adhesion process, does not answer the question of

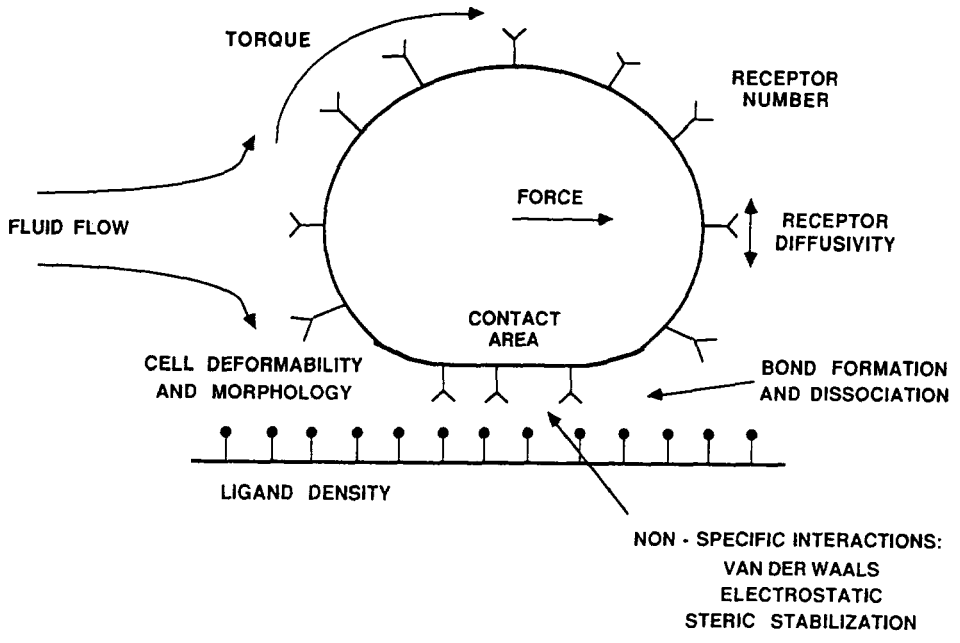

Fig. 3. Quantities expected to influence receptor-mediated cell adhesion to a surface include receptor number, the density of complementary surface ligands, the force and torque transmitted to the cell by the passing fluid, the mobility of receptors in the plane of the membrane, and the contact area in which cell to surface bonds may form. From [27] with permission.

whether or not the initial arrest of cancer cells in the microvasculature is mediated by mechanical trapping or specific ligand-receptor interactions. These considerations indicate a distinction between cancer cell arrest in the microvasculature, and cancer cell adhesion.

My own opinion based on present evidence, is that the pathobiologic importance of cell 'adhesion' molecules and their receptors is not primarily in connection with initial cancer cell arrest, and although they probably have a role in stabilizing the adhesion of arrested cancer cells, their main significance in the metastatic process lies in signal transduction from extracellular matrix to viable cancer cells, which serves as a stimulus for their intravascular proliferation at the arrest site and which, in combination with degradative processes, results in their extravasation by a 'bursting out' process [28].

Deformation-driven cancer cell destruction

A working hypothesis

The majority of cancer cell delivered to various target organs via the blood-stream, are trapped and rapidly and lethally damaged in the microvasculature; this makes a major contribution to 'metastatic inefficiency' [29].

In the larger blood-vessels, cancer cells are spherical, however, on entry into capillaries having smaller diameters than themselves, they are deformed into cylinders (Fig. 4). These sphere-to-cylinder shape transitions occur without statistically significant changes in cell volume. For example, MCG 1AA ascites sarcoma cells have mean diameter of 16.5 μm, corresponding to a mean volume ($\pm$ S.E.) of 2344 $\pm$ 40 μm^3; when these cells were deformed into cylindrical configuration within capillaries, their mean volumes were 2486 $\pm$ 212 μm^3 [30].

Under conditions of equal cell volume, sphere-to-cylinder transitions mandate a demand for increased cell surface area. For example, spherical

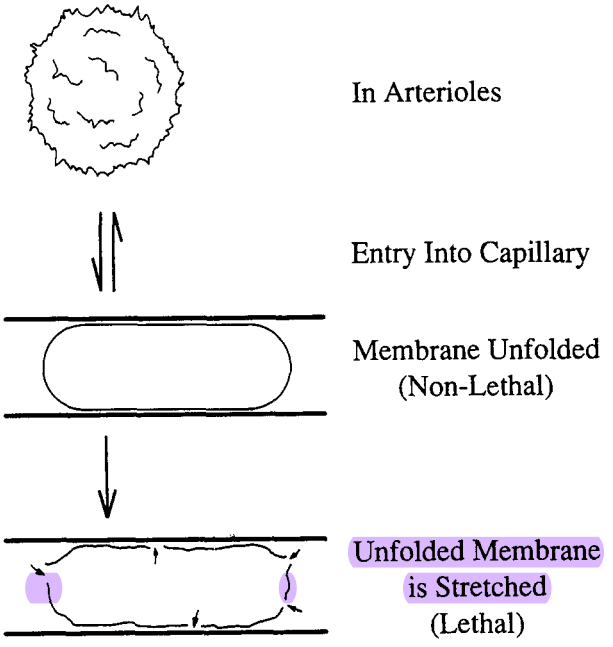

Fig. 4. Diagrammatic phases of deformation-driven, surface membrane rupture in a cancer cell. A cancer cell at equilibrium, in an arteriole, with membrane 'excess'. Inside a capillary, the cylindrical cell first undergoes non-lethal surface membrane unfolding, followed by lethal membrane-stretching.

MCG 1AA cancer cells have a mean, apparent surface area of $853 \pm 14.5\,\mu m^3$, compared with $1287 \pm 76\,\mu m^2$ for cells within capillaries.

Increases in cell surface area may be brought about by two distinct mechanisms: First, APPARENT increases may be accomplished by 'unfolding' of surface membrane 'excess', which requires less energy than membrane 'stretching', and therefore occurs first. Second, TRUE increases in area, accomplished by membrane-stretching.

Therefore, geometric demands for increased surface membrane area are mandated for cancer cells deformed in capillaries during hematogenous metastasis. When these demands cannot be met by apparent increases associated with non-lethal, reversible membrane 'unfolding', true increases follow, which involve membrane-stretching. However, in general, true increases in the surface area of biologic membranes cannot exceed 3 to 4% without rupture, due to increases in membrane tension beyond yield-point. The working hypothesis has therefore been advanced that deformation-driven, surface membrane-rupture, is an important mechanism in killing cancer cells within the microvasculature, and is an important rate-regulator for this phase of hematogenous metastasis.

It may be noted that although detailed theoretical examinations of this hypothesis have been limited to single cancer cells arrested in capillaries, analogous, mechanically-induced cell-killing is expected when multicellular clumps are arrested and deformed in larger vessels, but will be less efficient.

In vivo *observations*

Although a number of *in vitro* observations are consistent with the hypothesis outlined above [25, 31], only *in vivo* studies will be described here. *In vivo* observations of MCG 1AA sarcoma cells within capillary networks were made by vital videomicroscopy [30]. The transparent, membranous cremaster muscles of anesthetized mice were exteriorized and mounted in a perfusion chamber at 36° C, where their microvascular beds could be observed by fluorescence and higher resolution bright-field microscopy, and recorded on videotape. The contralateral femoral artery was cannulated and the mice were 'loaded' with ethidium bromide. This fluorochrome is excluded by intact cell surface membranes, but penetrates damaged membranes and reacts with intracellular nucleic acids, to give a bright red fluorescence, which is used to detect intravascular cancer cell death [32].

Measurements of the lengths and diameters of the cells trapped in capillaries were made from video images, and at the time of recording, it was noted whether or not individual cells were viable, on the basis of their ethidium bromide fluorescence.

Over 80% of the recorded trapped cells had damaged surface membranes, and cell fragments were visualized adherent to the capillary walls. Measurements revealed that the loss of viability was associated with a 51% increase in apparent cell surface area, of which no more than 4% could have been due to surface membrane stretching. That the increase could have been due to 'unfolding' was indicated by the presence of a mean linear mem-

brane excess of 80%, measured on transmission electron micrographs.

At the time of intra-arterial infusion, approximately 25% of the cancer cells had damaged membranes, as judged by trypan blue-exclusion tests. The question therefore arose of whether the observation that 80% of the trapped cancer cells were non-viable, indicated preferential trapping of the 25% with previously damaged membranes, or whether the membrane damage was a consequence of intravascular, cancer cell deformation.

That the latter explanation is correct, was demonstrated by aspirating cancer cells into micropipettes having internal diameters of 6.3 to 7.2 μm, in the presence of ethidium bromide. When protrusions having mean lengths of $23.0 \pm 2.45\,\mu$m were aspirated from cells (mean diameter 16.3 μm), when their nuclei were not drawn into the pipettes, they began to exhibit red, intracellular fluorescence. These lethal deformations corresponded to the observed mean total length of $53.3 \pm 2.25\,\mu$m, of whole, non-viable cells within capillaries.

Cell deformability

Although cell deformation is the driving force for lethal membrane rupture in cancer cells, deformability alone is not necessarily a predictor of surface membrane susceptibility to this type of mechanical trauma. For example, Sato and Suzuki [33] have shown that the ease with which certain rat hepatoma and sarcoma cells are aspirated into micropipettes, correlates with their survival on transcapillary passage. Cell survival, assessed by surface membrane integrity is also favored by increased surface rugosity and by decreased cell diameter. Large rigid cells tend to pass along shunts rather than capillaries, however, cancer cells cannot retain their viability indefinitely, while free in the circulation.

Cell deformation depends on the mechanical properties of whole cells, with the cytoskeleton and nucleus playing more dominant roles in resisting passive deformation than the surface membrane. However, in the case of lethal deformation, drug-induced disorganization of the cytoskeleton of Ehrlich ascites tumor (EAT) cells, produced no change in their susceptibility to mechanical (filtration) trauma [34], and that the nuclei of these cells are more resistant to deformation than whole cells. In addition, some agents acting at the cell periphery, including neuraminidase, make sarcoma 37 and EAT cells more deformable in micropipette-aspiration studies [35].

It will be of interest to explore the use of membrane-active and cell-rheotropic agents in augmentation of the deformation-associated killing of cancer cells, as a mode of antimetastatic therapy. Initial studies with doxorubicin, which acts on cancer cell surface membranes in addition to its better-known nuclear actions, augments cell susceptibility to rapid, mechanically induced trauma [36].

Compression by tissues

Cancer cells trapped in capillary beds in muscle are expected to be subject to addition mechanical trauma during muscle contraction; a suggestion supported by the relatively low incidence of metastasis in the myocardium and striated muscle in early metastatic disease [26], and by *in vivo* experiments.

In mice, it was shown [37] that following left ventricular injections (LVI), some 5% of injected cancer cells became arrested in the myocardium. However, by 5 minutes after injection, no intact cancer cells were detected in sectioned myocardium by light microscopy, using immunohistochemical enhancement. In mice which had carried the B16 melanoma for 3 weeks, greater quantities of cell-free melanin pigment were observed in the myocardium than in the other organs, indicating that large numbers of melanoma cells had been killed in the heart. In other experiments, in which the heart was removed immediately after LVI, bioassayed revealed that significantly smaller proportions of cancer cells delivered to the myocardium via the coronary arteries survived, than among those delivered to the lungs via the bronchial arteries. It was calculated that 95% of B16 and 80% of Ehrlich ascites tumor cells delivered to the myocardium were killed within 5 minutes. In control experiment, in which cancer cells were mixed with

minced heart muscle and then bioassayed, 2 orders of magnitude less killing was detected than after LVI.

Although details of the mechanical coupling between the myocardium, its capillaries and trapped cancer cells are not known, it appears that 'hoop' tensions in the muscle fibers are 4 to 5 orders of magnitude higher that the critical tensions required for the lethal rupture of cancer cell surface membranes. It was therefore suggested that the preferential, initial growth of metastases at myocardial surfaces, where pressure 'relief' is greatest, is a consequence of trauma of this type.

In skeletal muscle, cancer cell arrest is inhibited by vascular shunting [30]. Of those cancer cells arrested in the Quadriceps femoris muscles after LVI, bioassays indicated that the vast majority were lethally damaged within 5 minutes. However, when these muscles were made flaccid by section of the femoral nerve just prior to LVI, there was a 23-fold reduction in cell-killing, and when the resting muscles were made to contract by electrical stimulation of the femoral nerve just after LVI, there was a 28-fold increase in killing [38].

These experiments on muscle indicate that pressures generated in contractile organs can contribute to 'soil-hostility', underlying 'seed-and-soil' effects in the genesis of metastatic patterns.

Conclusions

The mechanical properties of cancer cells and host tissues are often overlooked in reviews of invasion and metastasis, although as indicated here, these properties may play an important role in permitting these processes to occur and in regulating their rates.

Limitations in space preclude a complete review of the rather large areas of biomechanics which appear relevant to the various aspects of metastasis covered elsewhere in this publication. These include the induction of 'dormancy' in cancer cells by mechanical deformation [37]: the modulation of metastatic potential by cell shape [38]; cellular mechanics as an indicator of cytoskeletal structure and function [39]; shear-associated platelet activation [40]; the effects of shear on prostacyclin production by endothelial cells [41]; the role of cell shape in growth control [42]; the role of tension and compression as determinants of cell function and form [43]; mechanochemical switching in angiogenesis [44]; the relation of cell shape to collagenase secretion [45] and finally, the effects of fluid shear stress on endothelial cell proliferation [46].

References

1. Weiss L, Orr FW, Honn KV: Interactions between cancer cells and the microvasculature: A rate-regulator for metastasis. Clin exp Metastasis 7: 127–167, 1980
2. Orr FW, Buchanan MR, Weiss L (eds): Microcirculation in Cancer Metastasis. CRC Press, Boca Raton, FL, 1991
3. Young JS, Lumsden CE, Stalker AL: The significance of the 'Tissue pressure' of normal testicular and of neoplastic (Brown-Pearce carcinoma) tissue in the rabbit. J Path Bact 62: 313–333, 1950
4. Hori K, Suzuki M, Abe I, Saito S, Sato H: A micro-occlusion technique for the measurement of the microvascular pressure in tumor and subcutis. Gann 74: 122–127, 1983
5. Trinkaus JP: Cells into organs. The forces that shape the embryo. 2nd ed. Prentice-Hall Inc, Englewood Cliffs, NJ, pp 370–414, 1984
6. Weiss L: Studies on cellular adhesion in tissue culture. IV. The alteration of substrata by cell surfaces. Exp Cell Res 25: 504–517, 1961
7. Weiss L, Coombs RRA: The demonstration of rupture of cell surfaces by an immunological technique. Exp Cell Res 30: 331–338, 1963
8. Weiss L, Lachmann PJ: The origin of an antigenic zone surrounding HeLa cells cultured on glass. Exp Cell Res 36: 86–91, 1964
9. Maslow DE: Collagenase effects on cancer cell invasiveness and motility. Invasion Metastasis 7: 297–310, 1987
10. Folger R, Weiss L, Glaves D, Subjeck JR, Harlos JP: Translational movements of macrophages through media of different viscosities. J Cell Sci 31: 245–257, 1978
11. Weiss L: Studies on cellular adhesion in tissue culture. V Some effects of enzymes on cell detachment. Exp Cell Res 30: 5409–5420, 1963
12. Weiss L, Glaves D: Effects on migration inhibiting factor(s) on the *in vitro* detachment of macrophages J Immunol 115: 1362–1365, 1975
13. Weiss L: Cellular locomotive pressure in relation to initial cell contacts. J Theor Biol 6: 275–281, 1964
14. Weiss L, Harlos JP, Elkin G: Measurements of compression of Ehrlich acites tumor cells and their relevance to hematogenous metastasis. Biorheology 28: 185–193, 1991
15. Rosen EM, Goldberg ID: Protein factors which regulate cell motility *in vitro*. Cell Devel. Biol. 25: 1079–1087, 1989
16. Suh O, Weiss L: The development of a technique for the

morphometric analysis of invasion in cancer. J Theor Biol 108: 547–562, 1984
17. Zeidman I, Buss JM: Transpulmonary passage of tumor cell emboli. Cancer Res 12: 731–733, 1952
18. Prinzmetal M, Ornitz EM, Sinkin B, Bergman HC: Arteriovenous anastomoses in liver, spleen and lungs. Am J Physiol 152: 48–52, 1948
19. Willis RA: The spread of tumours in the human body. Butterworth, London, 1973
20. Del Regato J: Physiopathology of metastasis. In: Weiss L, Gilbert HA (eds) Pulmonary Metastasis. GK Hall, Boston, pp 104–113, 1978
21. Bross IDJ, Viadana E, Pickren JW: Does generalized metastasis occur directly from the primary? J chronic Dis 28: 149–159, 1975
22. Weiss L, Grundmann E, Torhorst J, Hartveit F, Moberg I, Eder M, Fenoglio-Preiser CM, Napier J, Horne CHW, Lopez MJ, Shaw-Dunn RI, Sugar J, Davies JD, Day DW, Harlos JP: Hematogenous metastatic patterns in colonic carcinoma: An analysis of 1541 necropsies. J Pathol 150: 195–203, 1986
23. Weiss L: Metastatic inefficiency and regional therapy for liver metastases from colorectal carcinoma. Reg Cancer Treatment 2: 77–81, 1989
24. Dimitrov DS: Dynamic interactions between approaching surfaces of biological interest. Progr Surface Sci 14: 295–423, 1984
25. Weiss L, Schmid-Schonbein GW: Biomechanical interactions of cancer cells with the microvasculature during metastasis. Cell Biophys 14: 187–215, 1989
26. Weiss L, Dimitrov DS, Angelova M: The hemodynamic destruction of cancer cells in relation to myocardial metastasis. Proc nat Acad Sci USA 82: 5737–5741, 1985
27. Hammer DA, Lauffenburger DA: A dynamical model for receptor-mediated cell adhesion to surfaces in viscous shear flow. Cell Biophys 14: 139–173, 1989
28. Crissman JD, Hatfield J, Schaldenbrand J, Sloane BF, Honn KV: Arrest and extravasation of B16 amelanotic melanoma in murine lungs. Lab Invest 53: 470–478, 1985
29. Weiss L: Metastatic inefficiency. Adv Cancer Res 54: 159–211, 1990
30. Weiss L, Nannmark U, Johansson BR, Bagge U: Lethal deformation of cancer cells in the microcirculation: a potential rate-regulator of hematogenous metastasis. Int J Cancer 51: 103–113, 1992
31. Weiss L: The biomechanics of cancer cell traffic, arrest and intravascular destruction. In: Orr FW, Buchanan MR, Weiss L (eds) Microcirculation in cancer metastasis, CRC Press, Boca Raton, FL, pp 131–144, 1991
32. Blomqvist G, Scolnik G, Braide M, Bjursten LM, Blixt A, Bagge U: Differences in lodgement of tumour cells in muscle and liver. Clin exp Metastasis 6: 285–289, 1988
33. Sato H, Suzuki M: Deformability and viability of tumor cells by transcapillary passage with reference to organ affinity in metastasis in cancer. In: Weiss L (ed) Fundamental Aspects of Metastasis. North Holland, Amsterdam, pp 311–318, 1976
34. Weiss L, Asch BB, Elkin G: Effects of cytoskeletal perturbation on the sensitivity of ehrlich ascites tumor cell membranes to mechanical trauma. Invasion Metastasis 11: 93–101, 1991
35. Weiss L: Studies on cell deformability. II Effects of some proteolytic enzymes. J Cell Biol 30: 39–43, 1966
36. Weiss L, Bernacki RJ, Elkin G, Hillman M: Effects of Doxorubicin on the sensitivity of L1210 leukemia cells to deformation-associated trauma. Cell Biophys 18: 57–67, 1991
37. Weiss L: Biomechanical destruction of cancer cells in the heart: a rate-regulator for hematogenous metastasis. Invasion Metastasis 8: 228–237, 1988
38. Weiss L: Biomechanical destruction of cancer cells in skeletal muscle: a rate-regulator for hematogenous metastasis. Clin Exp Metastasis 7: 483–491, 1989
39. Gabor H, Weiss L: Mechanically induced trauma suffered by cancer cells in passing through pores in polycarbonate membranes. Invasion Metastasis 5: 71–83, 1985
40. Raz A, Ben-Ze'ev A: Modulation of the metastatic capability in B16 melanoma by cell shape. Science 221: 1307–1310, 1983
41. Elson EL: Cellular mechanics as an indicator of cytoskeletal structure and function. Ann Rev Biophys Biophys Chem 17: 397–430, 1988
42. Wurzinger LJ, Opitz R, Wolf M, Schmid-Schonbein H: 'Shear induced platelet activation' – A critical review. Biorheology 22: 399–413, 1985
43. Frangos JA, McIntyre LV, Ive CL: Flow effects on prostacyclin production by cultured human endothelial cells. Science 227: 1477–1479, 1985
44. Folkman J, Moscona A: Role of cell shape in growth control. Nature 273: 345–349, 1978
45. Ingber DE, Folkman J: Tension and compression as basic determinants of cell form and function: utilization of a cellular tensegrity mechanism. In: Stein WD, Bronner F (eds) Cell Shape: Determinants, Regulation, and Regulatory Role. Academic Press, New York, pp 3–31, 1989
46. Ingber DE, Folkman J: Mechanochemical switching between growth and differentiation during fibroblast growth factor-stimulated angiogenesis *in vitro*: role of extracellular matrix. J Cell Biol 109: 317–330, 1989
47. Kuter I, Johnson-Wint B, Beaupre N, Gross J: Collagenase secretion accompanying changes in cell shape occur only in the presence of a biologically active cytokine. J Cell Sci 92: 473–485, 1989
47. Ando J, Nomura H, Kamiya A: The effect of fluid shear stres on the migration and proliferation of cultured endothelial cells. Microvascular Res 33: 62–70, 1987

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