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Biomechanics of transendothelial migration by cancer cells

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Abstract: Cancer metastasis is still a major social issue with limited knowledge of the formation of tumors and their growth. In addition the formation of metastases is very difficult to understand, since it involves very complex physical mechanisms such as cellular interactions and cell rheology, which are flow-dependent. Previous studies investigated transendothelial migration using sophisticated techniques such as microfluidics, traction force microscopy (TFM) or Atomic Force Microscopy (AFM), combined with physical modeling. Here we summarize recent results and suggest new ways to investigate the precise mechanisms used by cancer cells to undergo transendothelial migration.

Introduction

Cancer arises as tumors are formed within the body and grow in size because cells behave abnormally and divide rapidly. Tumors can be localized due to the pressure exerted on the surrounding medium (Deptuła *et al.*, 2020), and possibly can be destroyed using chemo- or radiotherapy. Unfortunately, before and after the operation, cancer cells manage to escape from the initial tumor and penetrate into the blood stream where they can be transported for large distances, until they reach a distant organ (colon, breast, skin, bladder, bone), i.e., a soil (Fidler, 2003; Yang *et al.*, 2020). Once in this location, cancer cells (CCs) interact with the vessel walls covered by endothelial cells (ECs) as shown in Fig. 1. It is known from other works on leukocytes that rolling motion (Alon *et al.*, 1997) can first occur due to weak interactions between ligands on ECs and receptors on leukocytes or CCs (Dabagh *et al.*, 2020). After rolling has taken place, the next step is secondary adhesion when strong forces are produced to balance the flow forces. Then new bonds are formed involving integrins, immunoglobulins (Laurent *et al.*, 2014; Jin *et al.*, 2021) leading to larger forces through catch bonds (Kong *et al.*, 2009; Yeoman *et al.*, 2021). The activation of these adhesion proteins can be long, up to hours (Haddad *et al.*, 2010). One of the important questions is to determine which molecules are involved and whether they are common to all cancers. The final two steps are CC migration towards the endothelial junctions, and extravasation through the gap. This process involves both chemical signaling and mechanical effects (Mierke, 2021; Arefi *et al.*, 2020), but is not so well understood. Due to the interest of biophysicists, new tools are now available to quantify the interactions involved in these dynamic processes (Michor *et al.*, 2011), as well as the measurement of cell mechanical properties (Cross *et al.*, 2008; Lekka *et al.*, 2012; Rianna and Radmacher, 2017; Zbiral *et al.*, 2022). The viewpoint is organized as follows. Recent results concerning new techniques developed for the investigation of transendothelial migration are presented in the next part, while future promising researches are proposed, in relation with essential biological needs. Finally, conclusions are drawn.

Recent Developments

As discussed above, it seems essential to understand what mechanisms are used by cancer cells to **a)** resist the flow in order to adhere to the endothelium; **b)** form strong bonds, i.e., receptor-ligand ones; **c)** migrate along the soft endothelium; **d)** be able to deform in order to pass through tight junctions, in other words to modify their rheological properties rapidly.

Flow chambers and microfluidics

Flow chambers or microfluidics devices have been designed since the 80's. Usually microchannels are made of PDMS (typical dimensions between 5 to 200 μm) where fluid is driven at constant flow rate or imposed pressure. Different geometries are used. Surfaces can be coated with proteins or cells under such confinement so that it is possible to study cell-surface or cell-cell interactions. In particular interactions

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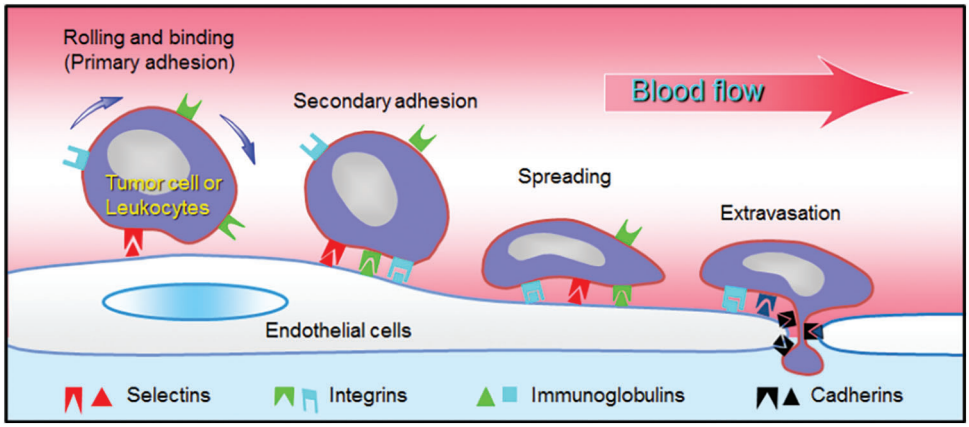

FIGURE 1. Extravasation process. Different steps used by leukocytes or tumor cells to interact with the endothelium. Sketch of the possible molecules involved.

between the endothelium and circulating cells (leukocytes or cancer cells) can be studied.

The role of flow was initially found important for the binding of cells at low shear rates, but for higher rates, the lift force detaches cells and they are unable to adhere to the endothelium (Lawrence *et al.*, 1987; Couzon *et al.*, 2009). Another important aspect is the alignment of endothelial cells under flow. Usually, after 12 to 24 hours, ECs align in the direction of flow, depending on the shear stress (typically 0.2 to 2 Pa) and the actin cytoskeleton follows this trend (Chien, 2006). However, signaling pathways involving CCM proteins and β1-integrins can actually produce an opposite effect with ECs aligned perpendicular to the flow direction (Jilkova *et al.*, 2014). Regarding cancer cells, the role of higher flow rate is decisive to enhance axial spreading of cancer cells within the endothelium, as compared to radial spreading (Chotard-Ghodsnia *et al.*, 2007). Finally, flow affects the overexpression of cellular adhesion molecules (CAMs) like E-selectins, ICAM-1 and VCAM-1, through the NFκB pathway, but this effect is ruled out at higher shear stresses (Haddad *et al.*, 2010).

Finally, new platforms enable to control and measure forces, while visualising cancer cell extravasation (Coughlin and Kamm, 2020) and promise to become outstanding tools for therapy.

Cell-cell interactions using AFM

AFM (Atomic Force Microscopy) in liquid environment can be used in Single Cell Force Spectroscopy (SCFS) mode to measure adhesion of living cells in near-physiological conditions. Cell-substrate or cell-cell interactions can be measured directly The cell is attached to the cantilever and comes in contact with another cell, then is pulled away after a given contact time. This is a good method to probe the presence of receptor-ligand interactions and it enables to characterize how force rates can affect the dissociation of bonds (i.e., detachment forces).

For example, cell-cell interactions involving receptor-ligand bonds have shown the role of LFA-1 and ICAMs (Wojcikiewicz *et al.*, 2006). In the case of adhesion of tumor cells to the endothelium, the expression of ICAM-1 on CCs has been confirmed (Laurent *et al.*, 2014) and CD43 and MUC1 were shown to be the relevant ligands (Rajan *et al.*, 2017). It appears that more invasive bladder cancer cells use the latter CAMs simultaneously in order to bind more efficiently and a reduction of around 70% of cancer cell adhesion has been obtained when blocking these two molecules with antibodies. Moreover, CD43 and MUC1 are associated with ICAM-1 with a stronger connection with the cytoskeleton in the case of CD43, whereas MUC1 is more likely to form tethers when detaching. However other molecules are involved in CC adhesion to the endothelium, so no general trend can be proposed. Ultimately, as CCs transmigrate through the endothelium, they express β1 integrins or P-selectins that bind with Extra-Cellular Matrix (ECM) proteins to migrate further (Mierke *et al.*, 2011; Le Cigne *et al.*, 2016; Dao *et al.*, 2021).

Altogether, AFM-based measurements have possible clinical implications, since they allow to characterize adhesion molecules relevant during the transmigration process.

Traction Force Microscopy and cell migration

Another possible way to explore the physics of cancer is to find how invasive cells can exert forces on the surrounding medium. Such methods–called Traction Force Microscopy (TFM)–have been developed in the years 2000 on two-dimensional substrates using the displacement of beads embedded in elastic gels onto which cells adhere, then an inverse problem is solved to determine traction stresses (Butler *et al.*, 2002; Schwarz *et al.*, 2002; Ambrosi *et al.*, 2009).

This is important here, since invasive cancer cells migrate differently as compared to normal cells and exert less stress in order to move faster (Peschetola *et al.*, 2013). This technique also proved to be quite efficient to determine the forces exerted by cancer cells as they transmigrate through an endothelium layer (grown as a circular patch on a 10 kPa gel, see Figs. 2A and 2B). In such a case, the horizontal (shear) forces exerted by CCs are small compared to other ones at the edges of the patch (Figs. 2C and 2D). This reveals that forces crucial for transmigration are vertical ones, necessary to pull the cell through the junction. They can be related to the strength of bonds between CAMs located at the cell invadopodium (intense green levels in Fig. 2A, Rajan, 2016) and ECM proteins on the gel surface below (fibronectin in this case).

Therefore, it is important to continue in this direction and explore this process using 3D TFM developed in recent studies, using elastic gels (Legant *et al.*, 2013; Fertin *et al.*, 2019) or nonlinear matrices (Jorge-Peñas *et al.*, 2017; Song *et al.*, 2020). Clinical applications could also benefit from these *in vitro* studies, allowing to test various drugs.

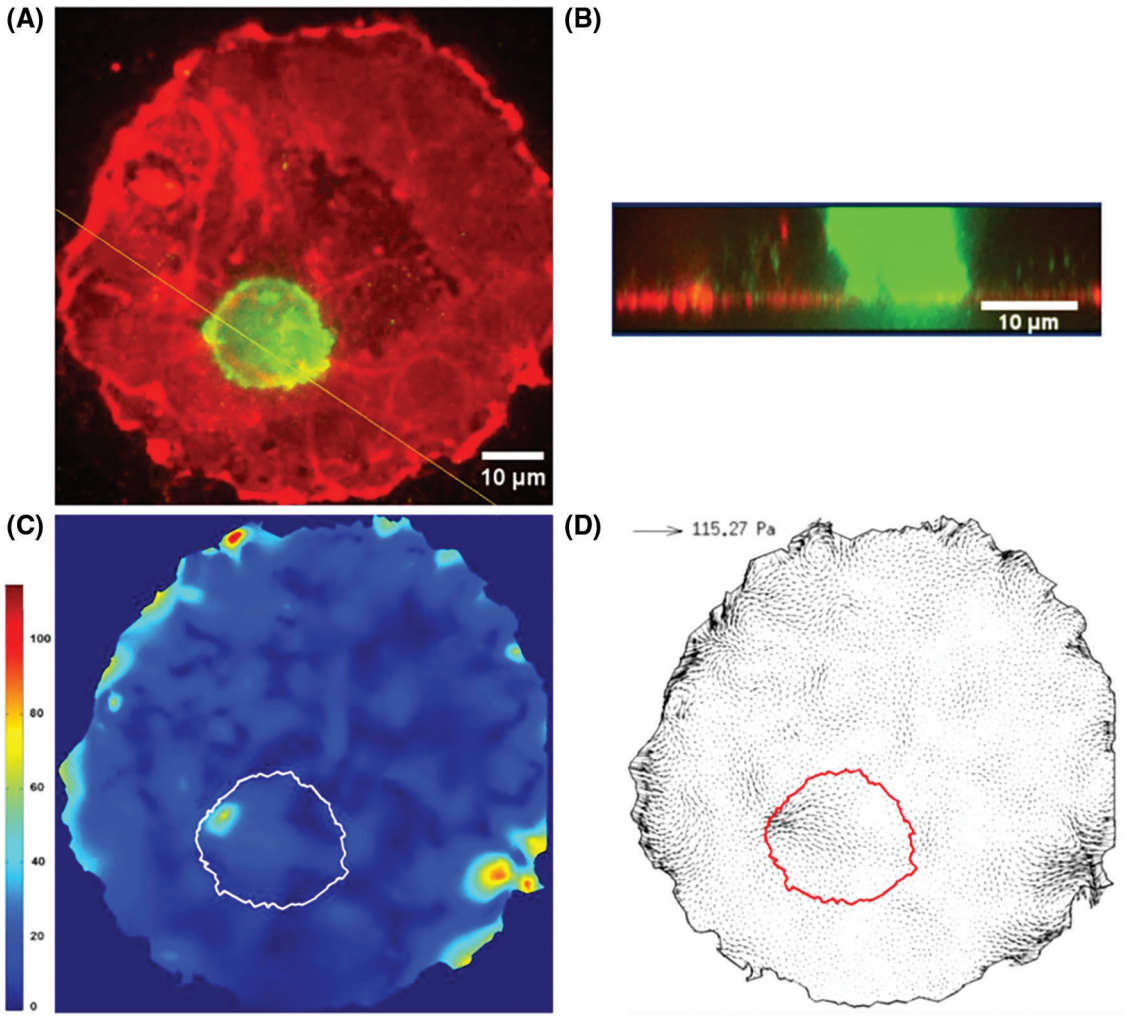

FIGURE 2. 2D Traction Force Microscopy performed when a CC interacts with the EC monolayer. A) Fluorescence image of ECs (red) and CC (green). B) Confocal side view, following the yellow line in A. C) Traction stresses (Pa), the white line represents the cell contour. D) Stress vectors with maximum value indicated. The cell contour is in red (Rajan, 2016).

Cell deformability and AFM

AFM has another added value, which is its ability to indent soft substrates and obtain force curves. AFM cantilevers built with a specific tip (pyramid, sphere, etc.) probe cells in a controlled manner. The analysis of such force curves allows to calculate the elastic (or viscoelastic) moduli. This is particularly relevant in this study as cancer cells have been known to be less rigid as compared to usual cells (Cross *et al.*, 2008; Lekka *et al.*, 2012). On the other hand, cells need to be rigid enough to push through the EC junctions. Therefore precise viscoelastic measurements (G', elastic modulus, G", loss modulus) of CCs in contact with various substrates are to be carried out.

Earlier results have shown the adaptation of CC stiffness when plated on different elastic gels: cells usually spread more, with a higher elasticity, on stiffer substrates (Solon *et al.*, 2007). Similarly, viscoelastic effects are enhanced (Abidine *et al.*, 2021) and f_T, the typical crossover frequency (such that $G'(f_T) = G''(f_T)$) is reduced for low elasticity substrates or when in contact with the endothelium (Abidine *et al.*, 2018). This demonstrates how the microenvironment (i.e., the endothelium) leads to a glassy-like cell response. Thus cancer cells use this key mechanism to modify their rheology quite rapidly (see Fig. 2A) and relocalize their rigid actin domains to push through the endothelial junction. Nuclear stiffness is also an important determinant of the ability of cancer cells to undergo transmigration. By combining Brillouin confocal microscopy (BCM) and confocal reflectance quantitative phase microscopy (QPM), Roberts *et al.*, 2021 found that the cells and their nuclei soften upon extravasation while the nuclear membranes remain soft for at least 24 hours.

Finally, the ability of cancer cells to extravasate through the tight endothelial junctions depends on crosstalk between CCs and ECs during contact (Haddad *et al.*, 2010; Stojak *et al.*, 2020), implies β-catenins, E-cadherins, tight junction proteins and is mediated by reactive oxygen species (Haidari *et al.*, 2013). There has been attempts to block TEM of breast cancer cells using cadherins or tight junction protein inhibitors (Bednarek *et al.*, 2020).

To conclude, AFM is a versatile tool enabling to carry out precise cell rheological measurements in close-to physiological environments. It can be adapted to study physiological/pathological processes and therefore promises to answer questions relevant for clinical studies.

Modeling cell rheology processes

Modeling cell mechanical processes has been a source of interest within the biophysics community for a very long time so only a few features will be addressed here. There is a large number of cellular models, going from vesicles, composite or deformable objects (Jadhav *et al*., 2005), tensegrity models (Ingber, 1993), active drops (Joanny *et al*., 2013) that can be used to model cells depending on the problem. Flow effects are also included (Verdier *et al*., 2009) and cell interactions are usually treated using the stochastic behavior of cell bonds that can form or break based on previous theories (Kramers, 1940; Evans and Ritchie, 1997). This results in a force *vs*. loading rate relationship, being able to explain AFM data as well as flow effects. Such models are therefore particularly relevant for the study of transmigration of cancer cells through the endothelial wall.

Attempts considering cell-cell interactions (i.e., the contact of cells) and deformations using chemo-mechanical models, have been proposed (Arefi *et al*., 2020) but are too few, probably because they involve numerous mechanical aspects, such as the dynamics of invadopodia protrusions (Kim *et al*., 2022). These simulations lead to a vast number of parameters to be determined experimentally or tuned, and this remains a major challenge.

Therefore, future models and simulations could use deep learning to try and identify the model parameters roles in order to build a smaller parameter landscape and get a deeper understanding of the transmigration process.

Conclusion

New physical tools (microfluidics, AFM, force-based methods, enriched modeling) have been developed or improved in the past twenty years and promise to give a better understanding of the mechanisms at play during cancer cell transmigration. New platforms are now available, capable of measuring forces under flow, with simultaneous microscopic observations of the mechanisms involved in such processes. These new tools bring a higher added value for clinical applications, because they allow to test various drugs *in vitro*, using organ-on-a chip devices. Recently, the quantification of 3D forces (TFM) developed during cell interactions in complex media has made significant progresses. Still more *in vitro* experimental data is necessary, and needs to be collected in view of models better adapted to a 3D cell environment. Such models have reached a state of sophistication that should help select the relevant parameters sometimes hidden within the vast biological data pool.

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