Application of atomic force microscope in diagnosis of single cancer cells

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Abstract

Changes in mechanical properties of cells are closely related to a variety of diseases. As an advanced technology on the micro/nano scale, atomic force microscopy is the most suitable tool for information acquisition of living cells in human body fluids. AFMs are able to measure and characterise the mechanical properties of cells which can be used as effective markers to distinguish between different cell types and cells in different states (benign or cancerous). Therefore, they can be employed to obtain additional information to that obtained via the traditional biochemistry methods for better identifying and diagnosing cancer cells for humans, proposing better treatment methods and prognosis, and unravelling the pathogenesis of the disease. In this report, we review the use of AFMs in cancerous tissues, organs, and cancer cells cultured in vitro to obtain cellular mechanical properties, demonstrate and summarize the results of AFMs in cancer biology, and look forward to possible future applications and the direction of development.

1 Introduction

In recent years, the number of deaths caused by cancer has increased from 7.58 million in 2006 to 9.6 million in 2018[1-2]. Despite some successful cancer treatment methods, including traditional surgical resection[3-4], chemotherapy[5-8], radiotherapy[9-11], immunotherapy[12-14] and gene therapy[15-17], cancer has been the second most common cause of death in chronic non-communicable diseases. The reason is that cancer cells can transfer in human body, proliferate and divide indefinitely, and can pretend to evade immune system attacks.

The size of human somatic cells is mostly between 10-20 μm. At this microscopic scale, unlike the inertial forces such as gravity at the macroscopic scale, adhesion and capillary forces between cells cannot be ignored[18-20]. Because the mechanical properties of cells are closely related to many diseases, such as blood diseases[21-22], malaria[23] and mucolipidosis type II or I-cell disease[24]. With regards to the acquisition of cellular information, such as cell morphology, surface roughness, adhesion and Young's

modulus, the most widely used instruments are Scanning Electron Microscope (SEM)[25-27], Transmission Electron Microscope (TEM)[28-29] and Atomic Force Microscope (AFM)[30-32]. SEM is based on the interaction of electrons and matter[33]. It scans samples with a highly focused high-energy electron beam that excites various physical information. The observation of the surface topography of the test specimen is obtained by imaging, amplifying and displaying the information[34]. TEM uses scatter imaging produced by accelerated and concentrated electron beams colliding into atoms in a sample[35]. AFM mainly relies on the interaction between atoms to obtain sample information. It converts the force of the probe into a characteristic parameter that can characterize the surface information of the sample[36-37].

AFMs are originally developed to capture cellular information, but now are also used to manipulate cells with their probe tips. AFM has already attracted widespread attentions in cancer treatment from both biomedicine and engineering perspectives. Since AFM can be used in liquid phase[38], nanomanipulation of cancer cells based on AFM can directly contact living cells to obtain multiple information of living cells in physiological conditions[39], including physical parameter such as cell height, surface roughness and adhesion[40-42]. The information of living cells, in particular, adhesion and Young's modulus, are believed being able to help to more accurately classify different kinds of cancer cells[43] and to differentiate between cancer cells and benign cells[44-45]. Furthermore, the mechanical properties of cells can be used to predict the location of metastases and can help to gain comprehensive understanding of the metastatic characteristics of cancer cells[46], which are of great significance for the diagnosis, analysis and treatment of cancer cells[47].

Here we give a review of the application of atomic force microscopy in the diagnosis of single cancer cells. First, we will introduce the basic structure and basic working mode of AFM. Then we will focus on the report of AFM in the diagnosis of single cancer cells. Finally, we will discuss the prospects of AFM and the future applications.

2 Basic structure and working modes of AFM

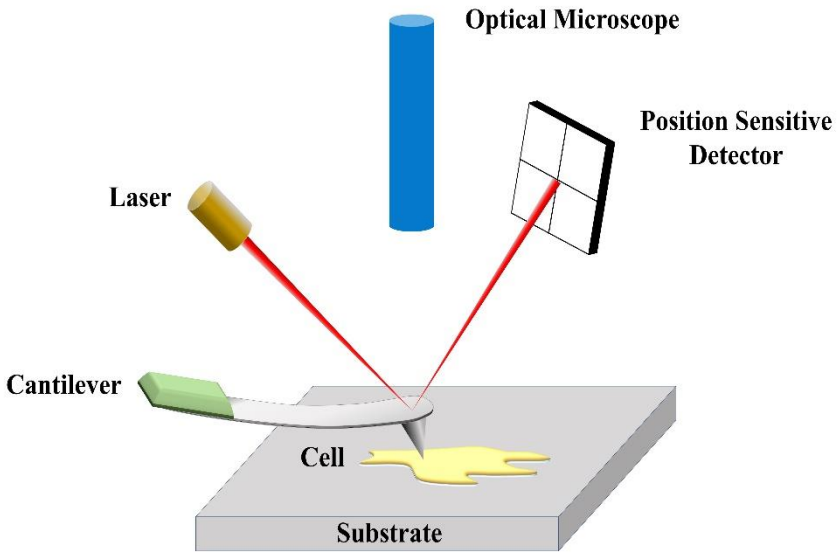

Fig. 1 Basic structure diagram of AFM[198].

Atomic Force Microscope (AFM), as shown in Fig. 1[198], as an important tool widely used in micron and nanoscale research in recent years, was successfully developed in 1986[48], providing new ideas for microscopic research. In an Atomic Force Microscope system, a tiny cantilever could sense the interaction between the tip and the sample being tested, and these forces could cause tiny displacements of the cantilever. When the laser is irradiated to the end of the cantilever, the displacement of the cantilever will cause the laser beam to shift, which is recorded by the laser detector (Position Sensitive Detector) and fed back to the system, and finally presented as an image[49-50].

With the development of science and technology, existing Atomic Force Microscopes have been equipped with the contact mode[51], non-contact mode[52] and tapping mode[53] to achieve the detection of microstructures on the surface of rigid objects such as nanomaterials[54-55].The three modes of operations of the AFM are based on the interaction between the tip and the sample[56]. When using the contact mode measurement, the probe and the sample to be tested are kept in a continuous contact state, and atomic force interaction is used to obtain information on the surface of the sample[57]. When the sample is measured using the non-contact mode, the probe is not in contact with the sample, and the sample information is obtained by the attraction of long distances between atoms[58-59]. The tapping mode works between the contact mode and the non-contact mode. The probe follows the cantilever to oscillate together at the resonant frequency, but ~~periodically~~ contacts the surface of the sample periodically[60-61]. On this basis, two new modes, PeakForce tapping (PFT) mode[62] and PeakForce Quantitative NanoMechanics (PF-QNM) mode[63], were derived. The PFT mode is similar to the tapping mode. The difference between the two is that the force in this mode is directly controlled by the applied force (applied maximum force) as a feedback parameter[64]. In the PF-QNM mode, the piezoelectric transducer uses high-frequency oscillation (approximately 0.25-8 kHz) to drive the engagement of the Z-axis tip, so that the tip contacts the sample surface at a speed close to 0, while the oscillation frequency of the cantilever is much lower than the resonance frequency , and achieve precise control of the press-in force[65]. A comparison of these three modes is shown in the table below.

Table 1 Comparison of characteristics of three working modes of AFM

Item \ Mode	Contact Mode	Non-contact Mode	Tapping Mode
Advantages	Fast scanning speed.	No force acting on the surface of the sample.	High image resolution; Does not damage the surface of soft samples.
Disadvantages	Image quality will be affected by lateral forces; Soft	Low horizontal resolution; Scanning speed is	Scan speed is lower than contact mode.

	samples may be damaged by the tip.	lower than the other two modes; Easy to cause feedback instability.	

In addition to detecting information such as nanomaterials, AFM can also detect flexible objects such as cells[66-67], viruses[68-69], proteins[70-71], and even DNA molecules[72-73], and obtain their physical information like their appearance. Due to its excellent measurement capability, such as accurate data acquisition, multi-mode selection of gas and liquid phases and convenient operations, at the micro-nano scale, AFM has often been used as an important experimental testing tool in various physical, chemical and life science experiments[74-77] in the last few years, especially at the cell scale level.

3 Single cancer cells and AFM

Together with the traditional surgical resection[78-79], chemotherapy[80-81], radiotherapy[82-84], there are some emerging therapies in recent years, such as immunotherapy[85-86] and gene therapy[87-89], focusing on specific organs using different schemes when dealing with specific types of cancers. However, these therapies have various problems. For example, they can hardly completely remove the lesions[90-94]. The chemotherapy and radiotherapy require very long period of time causing tremendous physical and psychological damages to patients and their families[95-105]. The immune therapy and the gene therapy are not very effective and have their limited scope of applications[106-110].

To overcome the deficiencies, it has been suggested that the treatments must be based on a full understanding of cancer, the most basic of which is cancer cells[111-112]. As an individual with a complete cellular structure, cancer cells have the same structure and life processes[113] as ordinary cells, including cell division, differentiation, senescence and apoptosis[114-115].

It has been found that the division of cancer cells is different from that of ordinary cells[116], though both rely on division to achieve the continuation of genetic material[117]. The division of the ordinary cells is limited by the number of cell divisions, Cancer cells, on the other hand, are the only subpopulations of cells that can achieve malignant proliferation[118]. They can almost continuously uninterrupted division under appropriate conditions. It is these abnormal divisions that make cancer a disease that is difficult to cure[119]. In addition, cancer cells are able to move and invade other tissues and organs through blood vessels. This large transfer can occur throughout the body, which adds on the further difficulty cancer treatment[46, 120]. The fully understanding of the mechanism of division and movement of cancer cells[121] requires multi-faceted testing of cancer cells to gather as much information as possible.

Because of subtle or large differences between individual cells (for example, between healthy cells, between healthy cells and cancer cells), single-cell level information makes it easier to describe these differences compared to post-summary batch analysis in traditional analytical methods.

The production and development of tumours lead to the gradual loss of the biomechanical balance of cancer cells and surrounding healthy cells, resulting in significant changes in their mechanical properties[122]. AFM has a natural advantage in detecting the changes. It precisely controls the forces exerted on cancer cells and their stromal cells, as well as the mechanical properties of the cells themselves (such as Young's modulus, and adhesion), cell-matrix, and cell-cell interactions[123].

In recent years, AFM has been widely used in the detection of cancer cells, and has made great contributions to the in-depth understanding of cancer cells. When AFM acquires cancer cell information, it acquires physical information related to cancer cells, such as cell height, cell adhesion, and Young's modulus. Changes in these single traits or multiple traits in cell characteristics can be used as a diagnostic basis for physiological and pathological conditions[116, 124-131].

Atomic force microscope technology has three main applications in research, namely imaging, measurement and manipulation of samples, and some studies also use imaging and measurement functions at the same time. Whether in the process of manipulating nano-scale particles or imaging and measurement, the atomic force microscope relies on the interaction force between the probe and the sample, Van der Waals force, to fulfill various requirements.

3.1 AFM in manipulation

When AFM is used in the manipulation of atom-level particles, the tip of an atomic force microscope can adsorb atoms, and the atomic exchange can be accomplished during the scanning process when the directional driving force generated by the tip of the atomic force microscope is greater than the threshold of interaction between the tip and the surface[132-133]. Besides that, nanomanipulation is able to manipulate atoms, molecules and other nanoscale objects, such as placement, orientation, assembly and bending, through nano-scale operations of push-pull, shear, and pick-up[134-136]. Yoshiaki[133] first demonstrated that near-contact atomic force microscope[56, 137] can also be used for well-controlled lateral manipulation of individual atoms at room temperature and can be used as a template for nanoscale devices. Junno[138] controlled a single adsorption particle with nano-precision to form a nanostructure composed of GaAs particles with a size of 30 nm on the GaAs surface, and determines the true lateral size of the GaAs nanoparticles, as shown in Fig. 2.

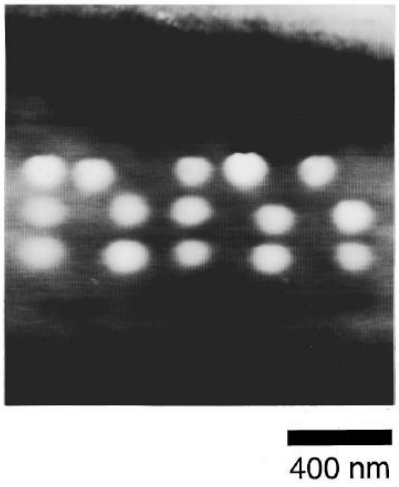

Fig. 2 Artificial nanostructure, the letters "nm", made by atomic force microscope[138].

However, the atomic force microscope relies on interatomic forces[132], and the adsorption energy of some metal adsorbents and some molecules on the insulating surface is very small[139,] which makes it difficult to manipulate atoms at normal or even high temperature[140-141] and large insulator surfaces[142].

3.2 AFM in imaging and detecting

The atomic force microscope uses the weak force between the probe tip and the sample to drive the cantilever to deform the cantilever when imaging the sample. These movements and deformations are transformed into position changes that are detected by the detector, and then the structure of the sample surface information is presented at the nanometre resolution. In addition to the structure information of the sample surface, since the working principle of the atomic force microscope is based on the interaction forces between the tip and the atoms, these forces are recorded, and the characteristic physics of the sample is calculated according to the models[143-145] (such as Hertz model and JKR model) applied under different conditions parameters, such as the Young's Modulus, which is widely used in cell biology. Therefore, the use of atomic force microscope to image and measure the sample can be achieved simultaneously on the basis of a certain model. Due to its excellent imaging capabilities and measurement precision[30], AFM is widely used in cell biology research, especially in adherent cells[32], such as various cancer cell research in recent years.

Cancer cells used in AFM information acquisition experiments usually have two acquisition methods. One is obtained directly from the patient's tissue or body fluid, and the other is purchased from the cell bank. The difference between the two is that the characteristics of the cancer cells obtained by the first method are closer to those of the human body, and the cancer cells obtained by the second method can be continuously cultured by means of passage and the like, and are more suitable for repetitive experiments. Whether the cancer cells obtained by the two methods lead to different or even the opposite conclusion is still inconclusive[146-147]. In 2008, Cross[45] et al. isolated mesothelial cells from pleural effusions of cancer patients. After AFM testing, metastatic tumour cells were found to be 80% softer than benign cells and had 33% lower cell adhesion than normal cells. Similarly, Lekka[148] et al. isolated three metastatic prostate cancer cell lines (PC-3, Du145 and LNCaP) and two breast cancer cell lines (T47D and MCF-7) from the patient's organs, which were examined by atomic force microscopy, as shown in Fig. 3. It was found that the Young's modulus value of cancer cells was significantly lower than that of cells derived from benign tissues. Plodinec[44] used IT-AFM to measure normal, benign, and aggressive cancerous breast tissue. In terms of stiffness distribution, both normal and benign tissue show a uniform distribution, while malignant tissue is widely distributed and has a low stiffness. After obtaining tissue in patients with cirrhosis and liver cancer, Tian[149] discussed the lowest elastic peak (LEP) of the tissue and found that the LEP of the tumour tissue (0.42 ± 0.17 kPa) was about half of the adjacent tissues' LEP (1.10 ± 0.20 kPa). In addition, although the mechanical characteristics and tissue structure of these liver cancer tissues were diverse, they all had similar LEP (0.33-0.65 kPa). Similar conclusions were found in Ding's cervical epithelial cells obtained from patients[150]. By comparing the cells obtained in the inflammation group and the cancer group, it was shown that the stiffness

of the cervical epithelial cells gradually increased as the severity of the cervical lesion increased. In addition, Minelli[151] et al. found through experiments that necrotic tissue lacked rigidity and elastic structure. On the contrary, non-necrotic brain tumours (GBM and MM cell lines) are more rigid than healthy tissues. In organs that have developed cancer lesions, the volume of the lesion has a large impact on whether cancer can metastasize in the future. In prostate cancer, when the volume exceeds 4 cc, it is easy to transfer from the transition zone to the outer peripheral zone[152]. Therefore, AFM has technical advantages in clinical practice, and has the potential to combine pathological analysis with surgically resected tissues[74].

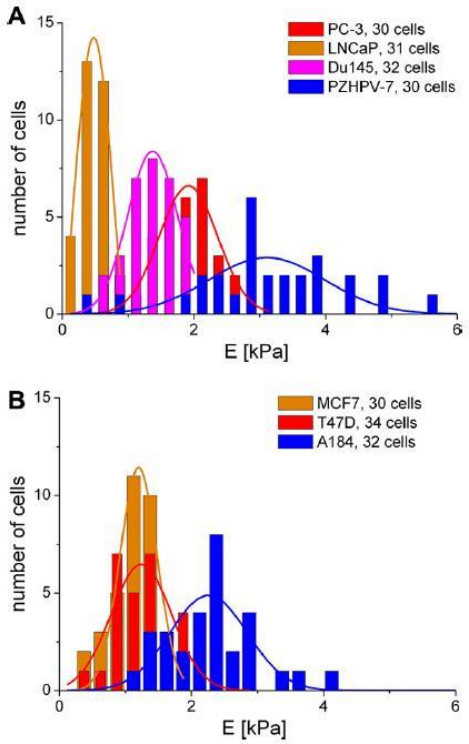

Fig. 3 The Young's modulus of the cells obtained from the (A)mammary gland (MCF7, T47D and A184) and the cells obtained from the (B) prostate (PC -3, LNCaP, Du145 and PZHPV-7) fit Gaussian function distribution[148].

Since the direct acquisition of tissues and body fluids from patients involves more complicated ethical issues, most of the existing cancer cells used are derived from cell banks, and after daily culture, and relevant information is obtained. The problems encountered during the experiment and the experimental results improve the experimental and data processing methods, laying a foundation for the clinical application of AFM[153-154]. Young's modulus, which is the modulus of elasticity along the longitudinal direction, refers to the ability of cells to resist external deformation. It means that the larger the Young's modulus of the cell, the less easily the shape of the cell changes. In the experiments in which AFM is applied to cancer cell detection, Young's modulus is often focused on alone or in combination with other physical quantities (such as cell adhesion) as diagnostic criteria. At physiological temperature (37 ºC), Li[155] found that the Young's modulus of the malignant breast cancer cell line MCF-7 was significantly lower than that of its homologous non-malignant cell line MCF-10A. In addition, Calzado[43] tested the MB-231 breast cancer cell line, further confirming that the Young's modulus of healthy cells is greater than the Young's modulus of its homologous cancer cells, while the difference between two cancer cell

lines (MCF-7 and MB-231) is not big. This conclusion was also confirmed in the non-malignant bladder cell line (HCV29) and cancer cell lines (HTB-9, HT1376 and T24)[156]. Furthermore, Young's modulus has also been proved to be associated with cell invasiveness. Li[157] used AFM to detect red blood cells (RBC) and three invasive cells (Raji, Hut and K562), and the results (in Fig. 4) showed that invasive cancer cells were softer and easier to migrate than inert red blood cells. Similar experimental results also appeared in the ovarian cancer cell lines HEY A8 and HEY. Compared with HEY cells, HEYA8 cells had increased invasion and migration ability, while cell stiffness was reduced[158]. Similarly, in the relevant experiments of prostate cell line (BPH) and its homologous cancer cell line (PC-3, LNCap)[159], human lymphocyte lineage (normal lymphatic cancer cells and Jurkat cells)[160], bladder cancer cell lines (RT112, T24 and J82)[161] and human pancreatic cancer cell lines (PaTu8988S and PaTu8988T)[162], the Young's model of benign cells has been confirmed to be higher than the Young's modulus of homologous cancer cell lines, while cancer cells with high invasiveness are softer than cancer cells with less invasiveness. At the level of cell differentiation, Young's modulus can also be used as a reference. For example, well differentiated T24 cells and poorly differentiated RT4 cells have similar diameters, but well differentiated cells have a lower Young's modulus [163], and at the same time, similar conclusions have been made in Efremov's research[164].

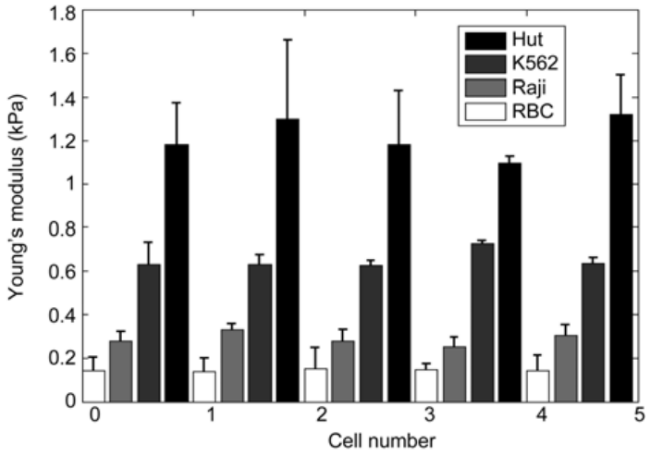

Fig. 4 Histogram of Young's modulus for RBCs, Raji, Hut, and K562 cells[157].

The cell elastic modulus is also used as one of the indicators for measuring whether a cell is cancerous. Experiments have shown that malignant cells are softer than primary normal cells[165-168], which is shown in Fig. 5, and the cellular elasticity of benign cells is more susceptible to temperature[169]. Meantime, cancer cells with higher metastatic potential have lower elastic modulus than metastatic cancer cells [170].

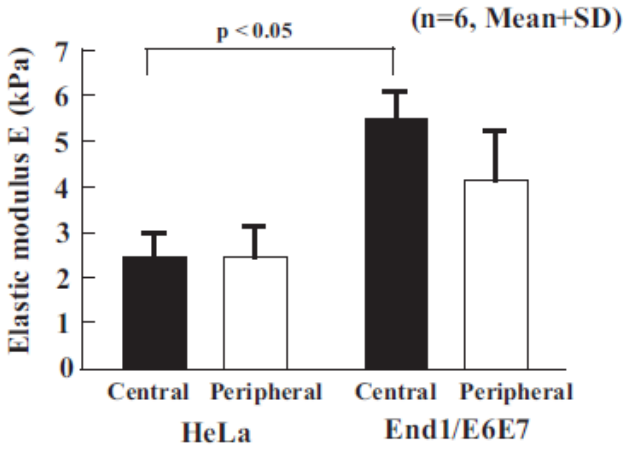

Fig. 5 Elastic modulus of the central and surrounding areas of cancer cells (Hela) and healthy cells (End1 / E6E7)[167].

In addition to the physical parameters that characterize cell elasticity，in some studies, adhesion is also used as a criterion for discriminating the cancer cell grade and cancer cell invasion. Experiments have shown that the adhesion between high-grade cancer cells is significantly lower than that between low-grade cancer cells[171], and the interaction between cancer cells and endothelial cells is positively correlated with the aggressiveness of cancer cells[172], as shown in Fig. 6.

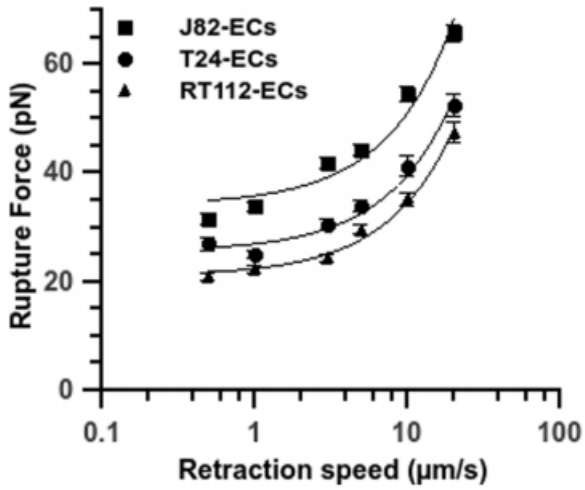

Fig. 6 Schematic diagram of interaction between three bladder cancer cell lines (T24, J82 and RT112) and endothelial cells [172].

In addition to a single parameter, a combination of two physical quantities is often used to characterize cancer cells. Ketene's research targeted mouse ovarian surface epithelial cells (MOSE). The results showed that the elastic modulus of advanced MOSE cells was significantly lower than that of the early counterparts, and the apparent cell viscosity also decreased significantly[173]. But not in all cases, the degree of malignancy of cancer cells is positively correlated with cell elasticity and apparent viscosity. In human chondrosarcoma cell lines (JJ012, FS090 and 105KC), JJ012 cells have the lowest modulus of the cell line tested, while FS090 typically has the highest modulus.

At this time, the apparent viscosity changes as the degree of malignancy of the cancer cells increases, as shown in Fig. 7[174]. The three human prostate cancer cell lines studied by Bastatas[175] showed that the elastic moduli of the two high metastatic cell lines (CL-1 and CL-2) were higher than those of the low metastatic cell line LNCaP, and the results of adhesion were also the same as that, which might mean that the enhancement of adhesion was conducive to the invasion of malignant cells and the establishment of additional blood vessels. However, Omidvar[176] had different conclusions in the study of breast cancer cell lines (MCF-7, T47D and MDA-MB-231). The results showed that the adhesion between cells was opposite to that of invasion, and the Young's modulus was positively correlated with adhesion. Comparably, Rebelo[47] also had the same conclusions for experiments with renal cancer cell lines (A-498, ACHN) and non-tumorigenic cell lines (RC-124). Therefore, for cancer cells derived from different organs, the mechanical properties and metastatic potential may not be the same, but the correlation between mechanical characteristics and metastatic potential is unique[177].

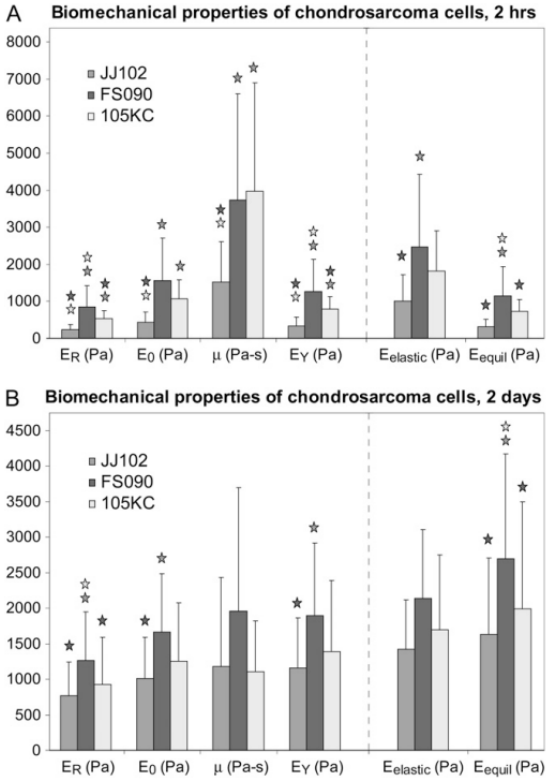

Fig. 7 Biomechanical properties (elastic modulus and apparent viscosity) of JJ012, FS090 and 105KC chondrosarcoma cell lines cultured for 2 h (A) and 2 days (B)[174].

Young's modulus can be obtained by force curve fitting and calculation, and the force curve can also be used as a physical quantity to independently discuss cancer cell features in some experiments. Fuhrmann[178] found that in cell experiments (ECP2, CP-A and CP-D), the force-indentation curve showed a non-monotonic discontinuity similar to a jagged line, and the incidence of such events was related to whether the cells were normally development. Meanwhile, dysplastic CP-D cells had the lowest Young's modulus.

In addition, based on the measurement mode and measurement results of the atomic

force microscope, there are some custom parameters like elastic shear platform moduli (G_N^0), glass transition frequency (f_T) and loss tangent (G"/G') as indicators for evaluating the invasiveness of cancer cells, such as Abidine[179] in bladder cell lines (Experiments in RT112, T24, J82) demonstrated a decrease in both invasive cell elastic platform modulus and transition frequency. Rother[180] experiments in breast cell lines (MCF-10A and MDA-MB-231) demonstrated that G"/G' increased with increasing malignancy, as shown in Fig. 8.

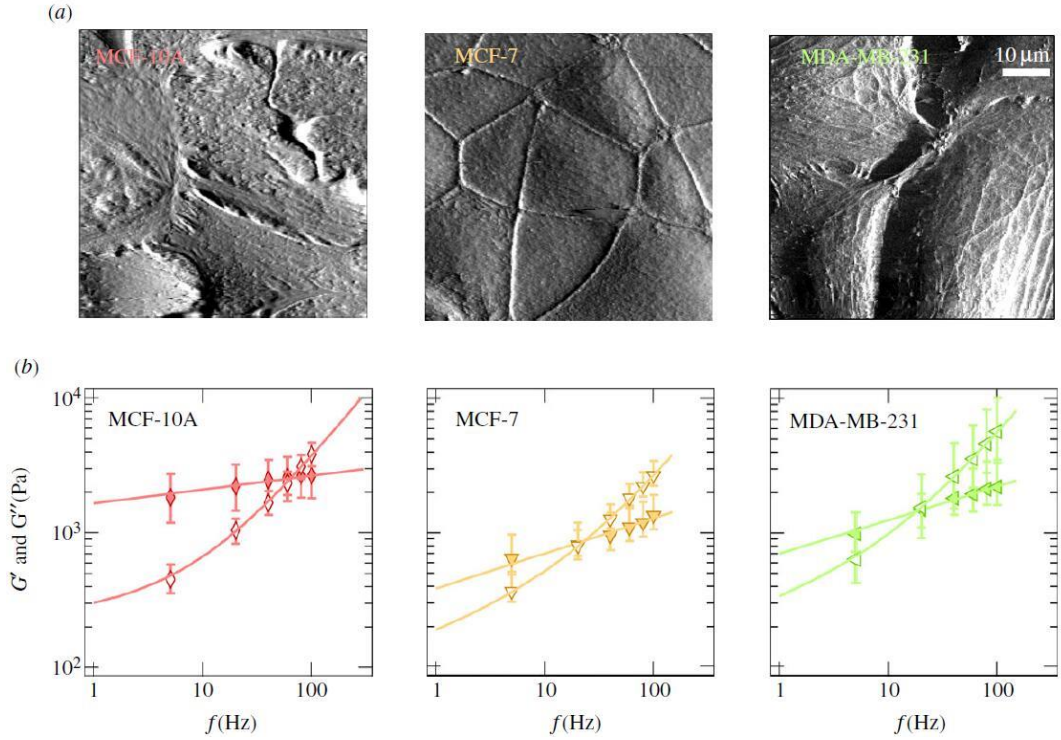

Fig. 8 (a) Images of MCF-10A, MCF-7 and MDA-MB-231 cell lines obtained using AFM measurement. (b) The median values of storage modulus G'(filled symbol) and loss modulus G"(hollow symbol) as a function of oscillation frequency (complex shear modulus data is fitted using a power-law structure damping model)[180].

However, because it needs to contact or be close to the cells during the measurement, it is impossible to obtain the characteristic quantities of suspended cells (such as the H22 cell line[181] and the K562 cell line[182]). Therefore, the detection of some blood-like cancer cells is difficult, so it is necessary to use a special technique, such as electrospinning[183-184] (shown in Fig. 9), to capture and fix cells in a liquid, after which could be measured using an AFM.

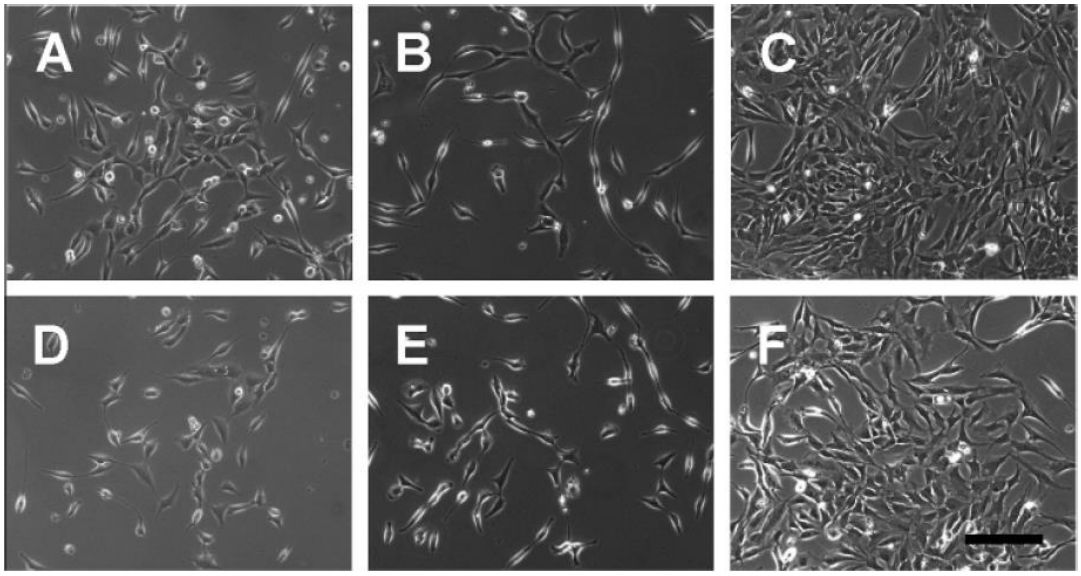

Fig. 9 (A-F) Pictures of cell characteristics within 9 days of culture. (A-C) are control cells. (D-F) were electrospun cells. Among them, the culture time of cells in (A, D), (B, E) and (C, F) was respectively 55 hours, 80 hours and 6 days[183].

Summary and Prospects

AFM's unique advantages including imaging in liquid phase conditions, direct contacting with cells, and precise adjustment of applied forces, which make it widely used in the life sciences. High-resolution imaging of living cells in the physiological environment of the human body and further in-depth research and analysis have become hot spots and challenging topics. The complexity of the liquid environment, including solution perturbations, the complexity of living cells themselves, and the interaction between cells and probes, results in the inability to obtain high-precision images[74], and also leads to the inaccuracy of the results obtained by the processing and analysis of cellular information. In addition, in order to more accurately describe the characteristics of cells, a large number of repeated experiments are usually carried out, which brings a huge amount of information to be processed, and increases the time for information processing and analysis[185]. The mechanical properties of cells, to a certain extent, can serve as markers for human health and diseases. The use of AFM to determine the mechanical properties of a single cancer cell can provide a new way for cancer diagnosis, on the basis of which to achieve better cancer treatment. The occurrence and development of tumours is accompanied by a gradual loss of biomechanical homeostasis, leading to significant changes in the mechanical properties of cancer and surrounding cells, which can be well monitored by AFM[122]. In the process of carcinogenesis, in order to facilitate the transfer and the establishment of blood vessels, the characteristics of Young's modulus (increased softness) and decreased adhesion are accompanied. In terms of invasiveness, more aggressive cells usually have lower Young's modulus and adhesion, but may have different conclusions in different organs and cancer cells derived from different organs. These changes may be due to the collagen content and cytoskeleton that the cells suddenly change during the process of carcinogenesis[165, 186]. It is worth noting that some studies have shown that cells with higher motility are softer (usually cancer cells)[75-76], but in some research, cells with increased mobility have higher Young's moduli[187-188]. Therefore, stiffness is not necessarily the standard for identifying cells and cancer cells, but also the criteria for

identifying different benign cells and different cancer cells, which are mainly reflected in the migration ability of cells[147].

AFM can be used as a precise measuring instrument when used alone, and it can fully exploit the potential of AFM when combined with other technologies. At this time, multiple complementary information can be acquired at the same time, so that the physiological activities of cells can be understood from many aspects. For example, by combining AFM and confocal fluorescence microscopy, information on the mechanical properties of cells and tissues and fluorescence images can be obtained simultaneously[189]. Because AFM can detect changes in the mechanical properties of cells, it can be used to observe the difference in cells before and after drug action, and play an important role in drug toxicity testing, drug development and drug screening[190-191].

In addition to cell mechanics, the resting potential and dynamic potential of the cell are also important factors to measure the cell state. Through the modification of AFM[192], or in combination with Scanning Probe Microscope (SPM)[193] and Scanning Ion Conductance Microscope (SICM)[194], the measurement of cell surface charge can be achieved. Besides oncology, AFM can also be used to study the vascular-related diseases, diabetic complications, kidney diseases, cataracts, Alzheimer's diseases[195-196], and cardiomyopathies[197], even applying AFM to the clinical surgery for the rehabilitation and prognosis of more diseases, to bring the gospel to human health.

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R. L.; Torre, L. A.; Jemal, A., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians* **2018,** *68* (6), 394-424.

2. Naghavi, M.; Abajobir, A. A.; Abbafati, C.; Abbas, K. M.; Abd-Allah, F.; Abera, S. F.; Aboyans, V.; Adetokunboh, O.; Afshin, A.; Agrawal, A., Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic

analysis for the Global Burden of Disease Study 2016. *The Lancet* **2017,** *390* (10100), 1151-1210.
3. Tuttle, T. M.; Habermann, E. B.; Grund, E. H.; Morris, T. J.; Virnig, B. A., Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. *Journal of Clinical Oncology* **2007,** *25* (33), 5203-5209.
4. Serizawa, T.; Saeki, N.; Higuchi, Y.; Ono, J.; Iuchi, T.; Nagano, O.; Yamaura, A., Gamma knife surgery for brain metastases: indications for and limitations of a local treatment protocol. *Acta neurochirurgica* **2005,** *147* (7), 721-726.
5. Greenberg, P.; Hortobagyi, G. N.; Smith, T. L.; Ziegler, L. D.; Frye, D. K.; Buzdar, A. U., Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *Journal of Clinical Oncology* **1996,** *14* (8), 2197-2205.
6. Seymour, M. T.; Maughan, T. S.; Ledermann, J. A.; Topham, C.; James, R.; Gwyther, S. J.; Smith, D. B.; Shepherd, S.; Maraveyas, A.; Ferry, D. R., Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *The Lancet* **2007,** *370* (9582), 143-152.
7. Sherif, A.; Holmberg, L.; Rintala, E.; Mestad, O.; Nilsson, J.; Nilsson, S.; Malmström, P.-U., Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. *European urology* **2004,** *45* (3), 297-303.
8. Poultsides, G. A.; Servais, E. L.; Saltz, L. B.; Patil, S.; Kemeny, N. E.; Guillem, J. G.; Weiser, M.; Temple, L. K.; Wong, W. D.; Paty, P. B., Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *Journal of Clinical Oncology* **2009,** *27* (20), 3379-3384.
9. Kapiteijn, E.; Marijnen, C. A.; Nagtegaal, I. D.; Putter, H.; Steup, W. H.; Wiggers, T.; Rutten, H. J.; Pahlman, L.; Glimelius, B.; van Krieken, J. H. J., Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *New England Journal of Medicine* **2001,** *345* (9), 638-646.
10. Tepper, J.; Krasna, M. J.; Niedzwiecki, D.; Hollis, D.; Reed, C. E.; Goldberg, R.; Kiel, K.; Willett, C.; Sugarbaker, D.; Mayer, R., Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* **2008,** *26* (7), 1086-1092.
11. Hoskin, P. J.; Rojas, A. M.; Bownes, P. J.; Lowe, G. J.; Ostler, P. J.; Bryant, L., Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiotherapy and Oncology* **2012,** *103* (2), 217-222.
12. Mellman, I.; Coukos, G.; Dranoff, G., Cancer immunotherapy comes of age. *Nature* **2011,** *480* (7378), 480-489.
13. Abken, H.; Hombach, A.; Reinhold, U.; Ferrone, S., Can combined T-cell-and antibody-based immunotherapy outsmart tumor cells? *Immunology today* **1998,** *19* (1), 2-5.
14. Pardoll, D. M., The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer* **2012,** *12* (4), 252-264.
15. Roth, J. A.; Cristiano, R. J., Gene therapy for cancer: what have we done and where are we going? *Journal of the National Cancer Institute* **1997,** *89* (1), 21-39.
16. Cross, D.; Burmester, J. K., Gene therapy for cancer treatment: past, present and

future. *Clinical medicine & research* **2006,** *4* (3), 218-227.
17. Mohammadi, M.; Jaafari, M.; Mirzaei, H.; Mirzaei, H., Mesenchymal stem cell: a new horizon in cancer gene therapy. *Cancer gene therapy* **2016,** *23* (9), 285-286.
18. Menciassi, A.; Eisinberg, A.; Izzo, I.; Dario, P., From" macro" to" micro" manipulation: models and experiments. *IEEE/ASME Transactions on mechatronics* **2004,** *9* (2), 311-320.
19. Fearing, R. S. In *Survey of sticking effects for micro parts handling*, Proceedings 1995 IEEE/RSJ International Conference on Intelligent Robots and Systems. Human Robot Interaction and Cooperative Robots, IEEE: 1995; pp 212-217.
20. Sitti, M. In *Micro-and nano-scale robotics*, Proceedings of the 2004 American Control Conference, IEEE: 2004; pp 1-8.
21. Rosenbluth, M. J.; Lam, W. A.; Fletcher, D. A., Analyzing cell mechanics in hematologic diseases with microfluidic biophysical flow cytometry. *Lab on a Chip* **2008,** *8* (7), 1062-1070.
22. Zhou, Z.; Han, H.; Cruz, M. A.; López, J. A.; Dong, J.-F.; Guchhait, P., Haemoglobin blocks von Willebrand factor proteolysis by ADAMTS-13: a mechanism associated with sickle cell disease. *Thrombosis and haemostasis* **2009,** *101* (06), 1070-1077.
23. LIM, C. T., Single cell mechanics study of the human disease malaria. *Journal of Biomechanical Science and Engineering* **2006,** *1* (1), 82-92.
24. Wiesmann, U.; Herschkowitz, N., Studies on the pathogenetic mechanism of I-cell disease in cultured fibroblasts. *Pediatric Research* **1974,** *8* (11), 865-870.
25. Keller, R., The cellular basis of epiboly: an SEM study of deep-cell rearrangement during gastrulation in Xenopus laevis. *Development* **1980,** *60* (1), 201-234.
26. Handel, K.; Grünfelder, C. G.; Roth, S.; Sander, K., Tribolium embryogenesis: a SEM study of cell shapes and movements from blastoderm to serosal closure. *Development genes and evolution* **2000,** *210* (4), 167-179.
27. Ahmad, M. R.; Nakajima, M.; Kojima, S.; Homma, M.; Fukuda, T., In situ single cell mechanics characterization of yeast cells using nanoneedles inside environmental SEM. *IEEE Transactions on Nanotechnology* **2008,** *7* (5), 607-616.
28. Iguchi, K. S., Hideo Yamane, Kazuo Konishi, Masahiro Takayama, Yoshiaki Nakai, Takayuki Nakagawa, Shigetaro Shibata, Keizo Nishimura, Hiroyoshi, Apoptotic cell death in Kikuchi's disease: a TEM study. *Acta Oto-Laryngologica* **1998,** *118* (540), 250-253.
29. Martins-Green, M.; Erickson, C., Basal lamina is not a barrier to neural crest cell emigration: documentation by TEM and by immunofluorescent and immunogold labelling. *Development* **1987,** *101* (3), 517-533.
30. Puech, P.-H.; Poole, K.; Knebel, D.; Muller, D. J., A new technical approach to quantify cell–cell adhesion forces by AFM. *Ultramicroscopy* **2006,** *106* (8-9), 637-644.
31. Sen, S.; Subramanian, S.; Discher, D. E., Indentation and adhesive probing of a cell membrane with AFM: theoretical model and experiments. *Biophysical journal* **2005,** *89* (5), 3203-3213.
32. Alsteens, D.; Dague, E.; Rouxhet, P. G.; Baulard, A. R.; Dufrêne, Y. F., Direct measurement of hydrophobic forces on cell surfaces using AFM. *Langmuir* **2007,** *23* (24), 11977-11979.
33. Bogner, A.; Jouneau, P.-H.; Thollet, G.; Basset, D.; Gauthier, C., A history of scanning electron microscopy developments: towards “wet-STEM” imaging. *Micron* **2007,** *38* (4), 390-401.
34. Vasiliev, A.; Kovalchuk, M.; Yatsishina, E., Electron microscopy methods in studies of cultural heritage sites. *Crystallography Reports* **2016,** *61* (6), 873-885.

35. Fultz, B.; Howe, J. M., *Transmission electron microscopy and diffractometry of materials*. Springer Science & Business Media: 2012.
36. Morris, V. J.; Kirby, A. R.; Gunning, A. P., *Atomic force microscopy for biologists*. World Scientific: 1999.
37. Eaton, P.; West, P., *Atomic force microscopy*. Oxford university press: 2010.
38. Fotiadis, D.; Scheuring, S.; Müller, S. A.; Engel, A.; Müller, D. J., Imaging and manipulation of biological structures with the AFM. *Micron* **2002,** *33* (4), 385-397.
39. Ohnesorge, F.; Hörber, J.; Häberle, W.; Czerny, C.; Smith, D.; Binnig, G., AFM review study on pox viruses and living cells. *Biophysical journal* **1997,** *73* (4), 2183-2194.
40. Yang, R.; Xi, N.; Kar, C.; Fung, M.; Wai, K.; Lai, C.; Seiffert-Sinha, K.; Sinha, A. A. In *Analysis of keratinocytes stiffness after desmosome disruption using atomic force microscopy based nanomanipulation*, 2009 9th IEEE Conference on Nanotechnology (IEEE-NANO), IEEE: 2009; pp 640-643.
41. Engel, A.; Müller, D. J., Observing single biomolecules at work with the atomic force microscope. *Nature structural biology* **2000,** *7* (9), 715-718.
42. Fung, C. K. M.; Xi, N.; Yang, R.; Seiffert-Sinha, K.; Lai, K. W. C.; Sinha, A. A., Quantitative analysis of human keratinocyte cell elasticity using atomic force microscopy (AFM). *IEEE transactions on nanobioscience* **2011,** *10* (1), 9-15.
43. Calzado-Martín, A.; Encinar, M.; Tamayo, J.; Calleja, M.; San Paulo, A., Effect of actin organization on the stiffness of living breast cancer cells revealed by peak-force modulation atomic force microscopy. *ACS nano* **2016,** *10* (3), 3365-3374.
44. Plodinec, M.; Loparic, M.; Monnier, C. A.; Obermann, E. C.; Zanetti-Dallenbach, R.; Oertle, P.; Hyotyla, J. T.; Aebi, U.; Bentires-Alj, M.; Lim, R. Y., The nanomechanical signature of breast cancer. *Nature nanotechnology* **2012,** *7* (11), 757-765.
45. Cross, S. E.; Jin, Y.-S.; Tondre, J.; Wong, R.; Rao, J.; Gimzewski, J. K., AFM-based analysis of human metastatic cancer cells. *Nanotechnology* **2008,** *19* (38), 384003.
46. Chambers, A. F.; Groom, A. C.; MacDonald, I. C., Dissemination and growth of cancer cells in metastatic sites. *Nature Reviews Cancer* **2002,** *2* (8), 563-572.
47. Rebelo, L. M.; de Sousa, J. S.; Mendes Filho, J.; Radmacher, M., Comparison of the viscoelastic properties of cells from different kidney cancer phenotypes measured with atomic force microscopy. *Nanotechnology* **2013,** *24* (5), 055102.
48. Binnig, G.; Quate, C. F.; Gerber, C., Atomic force microscope. *Physical review letters* **1986,** *56* (9), 930-933.
49. Meyer, G.; Amer, N. M., Erratum: Novel optical approach to atomic force microscopy [Appl. Phys. Lett. 5 3, 1045 (1988)]. *Applied physics letters* **1988,** *53* (24), 2400-2402.
50. Putman, C. A.; De Grooth, B. G.; Van Hulst, N. F.; Greve, J., A detailed analysis of the optical beam deflection technique for use in atomic force microscopy. *Journal of Applied Physics* **1992,** *72* (1), 6-12.
51. Le Grimellec, C.; Lesniewska, E.; Giocondi, M.-C.; Finot, E.; Vié, V.; Goudonnet, J.-P., Imaging of the surface of living cells by low-force contact-mode atomic force microscopy. *Biophysical journal* **1998,** *75* (2), 695-703.
52. Meyer, E., Atomic force microscopy. *Progress in surface science* **1992,** *41* (1), 3-49.
53. Kasas, S.; Longo, G.; Dietler, G., Mechanical properties of biological specimens explored by atomic force microscopy. *Journal of Physics D: Applied Physics* **2013,** *46* (13), 133001.
54. Jurečka, S.; Matsumoto, T.; Imamura, K.; Kobayashi, H., Multifractal analysis and

optical properties of nanostructured silicon layers. *Applied Surface Science* **2017,** *395*, 150-156.
55. Wang, Y.; Wang, Z.; Liu, J.; Hou, L., Differential magnetic force microscope imaging. *Scanning* **2015,** *37* (2), 112-115.
56. Giessibl, F. J., Advances in atomic force microscopy. *Reviews of modern physics* **2003,** *75* (3), 949-983.
57. Magonov, S.; Elings, V.; Whangbo, M.-H., Phase imaging and stiffness in tapping-mode atomic force microscopy. *Surface science* **1997,** *375* (2-3), L385-L391.
58. Jalili, N.; Dadfarnia, M.; Dawson, D. M., A fresh insight into the microcantilever-sample interaction problem in non-contact atomic force microscopy. *J. Dyn. Sys., Meas., Control* **2004,** *126* (2), 327-335.
59. Tello, M.; García, R., Nano-oxidation of silicon surfaces: Comparison of noncontact and contact atomic-force microscopy methods. *Applied Physics Letters* **2001,** *79* (3), 424-426.
60. Zhong, Q.; Inniss, D.; Kjoller, K.; Elings, V., Fractured polymer/silica fiber surface studied by tapping mode atomic force microscopy. *Surface Science Letters* **1993,** *290* (1-2), L688-L692.
61. Garcia, R.; San Paulo, A., Attractive and repulsive tip-sample interaction regimes in tapping-mode atomic force microscopy. *Physical Review B* **1999,** *60* (7), 4961-4967.
62. Schillers, H.; Medalsy, I.; Hu, S.; Slade, A. L.; Shaw, J. E., PeakForce Tapping resolves individual microvilli on living cells. *Journal of Molecular Recognition* **2016,** *29* (2), 95-101.
63. Smolyakov, G.; Pruvost, S.; Cardoso, L.; Alonso, B.; Belamie, E.; Duchet-Rumeau, J., AFM PeakForce QNM mode: Evidencing nanometre-scale mechanical properties of chitin-silica hybrid nanocomposites. *Carbohydrate polymers* **2016,** *151*, 373-380.
64. Walczyk, W.; Schön, P. M.; Schönherr, H., The effect of PeakForce tapping mode AFM imaging on the apparent shape of surface nanobubbles. *Journal of physics: Condensed matter* **2013,** *25* (18), 184005.
65. Hu, J.; Chen, S.; Huang, D.; Zhang, Y.; Lü, S.; Long, M., Global mapping of live cell mechanical features using PeakForce QNM AFM. *Biophysics Reports* **2020,** *6* (1), 9-18.
66. Obataya, I.; Nakamura, C.; Han, S.; Nakamura, N.; Miyake, J., Nanoscale operation of a living cell using an atomic force microscope with a nanoneedle. *Nano letters* **2005,** *5* (1), 27-30.
67. Gavara, N., A beginner's guide to atomic force microscopy probing for cell mechanics. *Microscopy research and technique* **2017,** *80* (1), 75-84.
68. Kuznetsov, Y. G.; Malkin, A.; Lucas, R.; Plomp, M.; McPherson, A., Imaging of viruses by atomic force microscopy. *Journal of General Virology* **2001,** *82* (9), 2025-2034.
69. Kuznetsov, Y. G.; Victoria, J.; Robinson, W.; McPherson, A., Atomic force microscopy investigation of human immunodeficiency virus (HIV) and HIV-infected lymphocytes. *Journal of virology* **2003,** *77* (22), 11896-11909.
70. Guo, S.; Zhu, X.; Jańczewski, D.; Lee, S. S. C.; He, T.; Teo, S. L. M.; Vancso, G. J., Measuring protein isoelectric points by AFM-based force spectroscopy using trace amounts of sample. *Nature nanotechnology* **2016,** *11* (9), 817-823.
71. Dong, Y.; An, R.; Zhao, S.; Cao, W.; Huang, L.; Zhuang, W.; Lu, L.; Lu, X., molecular interactions of protein with TiO2 by the AFM-measured adhesion force. *Langmuir* **2017,** *33* (42), 11626-11634.
72. Wang, D.; Song, J.; Wang, P.; Pan, V.; Zhang, Y.; Cui, D.; Ke, Y., Design and operation of reconfigurable two-dimensional DNA molecular arrays. *Nature protocols*

2018, *13* (10), 2312-2329.
73. Bose, K.; Lech, C. J.; Heddi, B.; Phan, A. T., High-resolution AFM structure of DNA G-wires in aqueous solution. *Nature communications* **2018,** *9* (1), 1-9.
74. Cross, S. E.; Jin, Y.-S.; Rao, J.; Gimzewski, J. K., Nanomechanical analysis of cells from cancer patients. *Nature nanotechnology* **2007,** *2* (12), 780-783.
75. Kam, N. W. S.; O'Connell, M.; Wisdom, J. A.; Dai, H., Carbon nanotubes as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction. *Proceedings of the National Academy of Sciences* **2005,** *102* (33), 11600-11605.
76. Pan, D.; Turner, J. L.; Wooley, K. L., Folic acid-conjugated nanostructured materials designed for cancer cell targeting. *Chemical communications* **2003,** (19), 2400-2401.
77. Tao, Y.; Lin, Y.; Huang, Z.; Ren, J.; Qu, X., Incorporating graphene oxide and gold nanoclusters: A synergistic catalyst with surprisingly high peroxidase‐like activity over a broad pH range and its application for cancer cell detection. *Advanced materials* **2013,** *25* (18), 2594-2599.
78. Yamada, E.; Miyaishi, S.; Nakazato, H.; Kato, K.; Kito, T.; Takagi, H.; Yasue, M.; Kato, T.; Morimoto, T.; Yamauchi, M., The surgical treatment of cancer of the stomach. *International surgery* **1980,** *65* (5), 387-399.
79. Tulenko, J.; Priore, R.; Hoffmeister, F., Cancer of the tongue: Comments on surgical treatment. *The American Journal of Surgery* **1966,** *112* (4), 562-568.
80. Debatin, K.-M.; Krammer, P. H., Death receptors in chemotherapy and cancer. *Oncogene* **2004,** *23* (16), 2950-2966.
81. Farber, S.; Toch, R.; Sears, E. M.; Pinkel, D., Advances in chemotherapy of cancer in man. In *Advances in cancer research*, Elsevier: 1956; Vol. 4, pp 1-71.
82. Delaney, G.; Jacob, S.; Featherstone, C.; Barton, M., The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence‐based clinical guidelines. *Cancer: Interdisciplinary International Journal of the American Cancer Society* **2005,** *104* (6), 1129-1137.
83. Barton, M. B.; Frommer, M.; Shafiq, J., Role of radiotherapy in cancer control in low-income and middle-income countries. *The lancet oncology* **2006,** *7* (7), 584-595.
84. Wilbur, D. S.; Hadley, S. W.; Hylarides, M. D.; Abrams, P. G.; Beaumier, P. A.; Morgan, A. C.; Reno, J. M.; Fritzberg, A. R., Development of a stable radioiodinating reagent to label monoclonal antibodies for radiotherapy of cancer. *Journal of nuclear medicine* **1989,** *30* (2), 216-226.
85. Gattinoni, L.; Powell, D. J.; Rosenberg, S. A.; Restifo, N. P., Adoptive immunotherapy for cancer: building on success. *Nature Reviews Immunology* **2006,** *6* (5), 383-393.
86. Kirkwood, J. M.; Butterfield, L. H.; Tarhini, A. A.; Zarour, H.; Kalinski, P.; Ferrone, S., Immunotherapy of cancer in 2012. *CA: a cancer journal for clinicians* **2012,** *62* (5), 309-335.
87. Morille, M.; Passirani, C.; Vonarbourg, A.; Clavreul, A.; Benoit, J.-P., Progress in developing cationic vectors for non-viral systemic gene therapy against cancer. *Biomaterials* **2008,** *29* (24-25), 3477-3496.
88. Culver, K. W.; Blaese, R. M., Gene therapy for cancer. *Trends in Genetics* **1994,** *10* (5), 174-178.
89. Zhang, W.-W., Development and application of adenoviral vectors for gene therapy of cancer. *Cancer gene therapy* **1999,** *6* (2), 113-138.
90. Kaminishi, M.; Yamaguchi, H.; Shimizu, N.; Nomura, S.; Yoshikawa, A.; Hashimoto, M.; Sakai, S.; Oohara, T., Stomach-partitioning gastrojejunostomy for

unresectable gastric carcinoma. *Archives of Surgery* **1997,** *132* (2), 184-187.
91. Keereweer, S.; Van Driel, P. B.; Snoeks, T. J.; Kerrebijn, J. D.; de Jong, R. J. B.; Vahrmeijer, A. L.; Sterenborg, H. J.; Löwik, C. W., Optical image-guided cancer surgery: challenges and limitations. *Clinical Cancer Research* **2013,** *19* (14), 3745-3754.
92. Frangioni, J. V., New technologies for human cancer imaging. *Journal of clinical oncology* **2008,** *26* (24), 4012-4021.
93. Keereweer, S.; Kerrebijn, J. D.; Van Driel, P. B.; Xie, B.; Kaijzel, E. L.; Snoeks, T. J.; Que, I.; Hutteman, M.; Van der Vorst, J. R.; Mieog, J. S. D., Optical image-guided surgery—where do we stand? *Molecular Imaging and Biology* **2011,** *13* (2), 199-207.
94. Weissleder, R.; Pittet, M. J., Imaging in the era of molecular oncology. *nature* **2008,** *452* (7187), 580-589.
95. Leonard, G. D.; Brenner, B.; Kemeny, N. E., Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. *Journal of Clinical Oncology* **2005,** *23* (9), 2038-2048.
96. Group, I. A. L. C. T. C., Cisplatin-based adjuvant chemotherapy in patients with completely resected non–small-cell lung cancer. *New England Journal of Medicine* **2004,** *350* (4), 351-360.
97. Herskovic, A.; Martz, K.; Al-Sarraf, M.; Leichman, L.; Brindle, J.; Vaitkevicius, V.; Cooper, J.; Byhardt, R.; Davis, L.; Emami, B., Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *New England Journal of Medicine* **1992,** *326* (24), 1593-1598.
98. Kondziolka, D.; Patel, A.; Lunsford, L. D.; Kassam, A.; Flickinger, J. C., Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *International Journal of Radiation Oncology* Biology* Physics* **1999,** *45* (2), 427-434.
99. Forastiere, A. A.; Goepfert, H.; Maor, M.; Pajak, T. F.; Weber, R.; Morrison, W.; Glisson, B.; Trotti, A.; Ridge, J. A.; Chao, C., Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *New England Journal of Medicine* **2003,** *349* (22), 2091-2098.
100. Sakuramoto, S.; Sasako, M.; Yamaguchi, T.; Kinoshita, T.; Fujii, M.; Nashimoto, A.; Furukawa, H.; Nakajima, T.; Ohashi, Y.; Imamura, H., Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *New England Journal of Medicine* **2007,** *357* (18), 1810-1820.
101. Sasako, M.; Sakuramoto, S.; Katai, H.; Kinoshita, T.; Furukawa, H.; Yamaguchi, T.; Nashimoto, A.; Fujii, M.; Nakajima, T.; Ohashi, Y., Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol* **2011,** *29* (33), 4387-4393.
102. Lau, P. M.; Stewart, K.; Dooley, M., The ten most common adverse drug reactions (ADRs) in oncology patients: do they matter to you? *Supportive care in cancer* **2004,** *12* (9), 626-633.
103. Chopra, D.; Rehan, H. S.; Sharma, V.; Mishra, R., Chemotherapy-induced adverse drug reactions in oncology patients: a prospective observational survey. *Indian journal of medical and paediatric oncology: official journal of Indian Society of Medical & Paediatric Oncology* **2016,** *37* (1), 42-46.
104. Sawaya, H.; Sebag, I. A.; Plana, J. C.; Januzzi, J. L.; Ky, B.; Cohen, V.; Gosavi, S.; Carver, J. R.; Wiegers, S. E.; Martin, R. P., Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. *The American journal of cardiology* **2011,** *107* (9), 1375-1380.
105. Verstappen, C. C.; Heimans, J. J.; Hoekman, K.; Postma, T. J., Neurotoxic

complications of chemotherapy in patients with cancer. *Drugs* **2003,** *63* (15), 1549-1563.
106. Boon, T.; Coulie, P. G.; Eynde, B. J. V. d.; Bruggen, P. v. d., Human T cell responses against melanoma. *Annu. Rev. Immunol.* **2006,** *24*, 175-208.
107. Segal, N. H.; Parsons, D. W.; Peggs, K. S.; Velculescu, V.; Kinzler, K. W.; Vogelstein, B.; Allison, J. P., Epitope landscape in breast and colorectal cancer. *Cancer research* **2008,** *68* (3), 889-892.
108. El-Aneed, A., An overview of current delivery systems in cancer gene therapy. *Journal of Controlled Release* **2004,** *94* (1), 1-14.
109. Annan, A. C.; Fisher, P. B.; Dent, P.; Siegal, G. P.; Curiel, D. T., Gene therapy in the treatment of human cancer. In *The Molecular Basis of Human Cancer*, Springer: 2017; pp 811-841.
110. Mishra, P. J.; Merlino, G., MicroRNA reexpression as differentiation therapy in cancer. *The Journal of clinical investigation* **2009,** *119* (8), 2119-2123.
111. Li, C.; Heidt, D. G.; Dalerba, P.; Burant, C. F.; Zhang, L.; Adsay, V.; Wicha, M.; Clarke, M. F.; Simeone, D. M., Identification of pancreatic cancer stem cells. *Cancer research* **2007,** *67* (3), 1030-1037.
112. Warburg, O., On the origin of cancer cells. *Science* **1956,** *123* (3191), 309-314.
113. Weaver, A. M., Invadopodia: specialized cell structures for cancer invasion. *Clinical & experimental metastasis* **2006,** *23* (2), 97-105.
114. Evan, G. I.; Vousden, K. H., Proliferation, cell cycle and apoptosis in cancer. *Nature* **2001,** *411* (6835), 342-348.
115. Collins, K.; Jacks, T.; Pavletich, N. P., The cell cycle and cancer. *Proceedings of the National Academy of Sciences* **1997,** *94* (7), 2776-2778.
116. Suresh, S., Biomechanics and biophysics of cancer cells. *Acta biomaterialia* **2007,** *3* (4), 413-438.
117. Ruchaud, S.; Carmena, M.; Earnshaw, W. C., Chromosomal passengers: conducting cell division. *Nature reviews Molecular cell biology* **2007,** *8* (10), 798-812.
118. Visvader, J. E., Cells of origin in cancer. *Nature* **2011,** *469* (7330), 314-322.
119. Preston-Martin, S.; Pike, M. C.; Ross, R. K.; Jones, P. A.; Henderson, B. E., Increased cell division as a cause of human cancer. *Cancer research* **1990,** *50* (23), 7415-7421.
120. Chaffer, C. L.; Weinberg, R. A., A perspective on cancer cell metastasis. *science* **2011,** *331* (6024), 1559-1564.
121. Malumbres, M.; Barbacid, M., To cycle or not to cycle: a critical decision in cancer. *Nature Reviews Cancer* **2001,** *1* (3), 222-231.
122. Goetz, J. G.; Minguet, S.; Navarro-Lérida, I.; Lazcano, J. J.; Samaniego, R.; Calvo, E.; Tello, M.; Osteso-Ibáñez, T.; Pellinen, T.; Echarri, A., Biomechanical remodeling of the microenvironment by stromal caveolin-1 favors tumor invasion and metastasis. *Cell* **2011,** *146* (1), 148-163.
123. Stylianou, A.; Lekka, M.; Stylianopoulos, T., AFM assessing of nanomechanical fingerprints for cancer early diagnosis and classification: from single cell to tissue level. *Nanoscale* **2018,** *10* (45), 20930-20945.
124. Henderson, E.; Haydon, P.; Sakaguchi, D., Actin filament dynamics in living glial cells imaged by atomic force microscopy. *Science* **1992,** *257* (5078), 1944-1946.
125. Schneider, S. W.; Sritharan, K. C.; Geibel, J. P.; Oberleithner, H.; Jena, B. P., Surface dynamics in living acinar cells imaged by atomic force microscopy: identification of plasma membrane structures involved in exocytosis. *Proceedings of the National Academy of Sciences* **1997,** *94* (1), 316-321.
126. Siegel, R. L.; Miller, K. D.; Jemal, A., Cancer statistics, 2015. *CA: a cancer*

journal for clinicians **2015,** *65* (1), 5-29.
127. Woodhouse, E. C.; Chuaqui, R. F.; Liotta, L. A., General mechanisms of metastasis. *Cancer: Interdisciplinary International Journal of the American Cancer Society* **1997,** *80* (S8), 1529-1537.
128. Mantovani, A., Inflaming metastasis. *Nature* **2009,** *457* (7225), 36-37.
129. Fidler, I. J., Critical determinants of cancer metastasis: rationale for therapy. *Cancer chemotherapy and pharmacology* **1999,** *43* (1), S3-S10.
130. Hou, H. W.; Li, Q.; Lee, G.; Kumar, A.; Ong, C.; Lim, C. T., Deformability study of breast cancer cells using microfluidics. *Biomedical microdevices* **2009,** *11* (3), 557-564.
131. Cavallaro, U.; Christofori, G., Cell adhesion and signalling by cadherins and Ig-CAMs in cancer. *Nature Reviews Cancer* **2004,** *4* (2), 118-132.
132. Custance, O.; Perez, R.; Morita, S., Atomic force microscopy as a tool for atom manipulation. *Nature nanotechnology* **2009,** *4* (12), 803-810.
133. Sugimoto, Y.; Abe, M.; Hirayama, S.; Oyabu, N.; Custance, Ó.; Morita, S., Atom inlays performed at room temperature using atomic force microscopy. *Nature materials* **2005,** *4* (2), 156-159.
134. Du, E.; Cui, H.; Zhu, Z., Review of nanomanipulators for nanomanufacturing. *International Journal of Nanomanufacturing* **2006,** *1* (1), 83-104.
135. Xie, H.; Onal, C.; Régnier, S.; Sitti, M., Automated control of AFM based nanomanipulation. In *Atomic force microscopy based nanorobotics*, Springer: 2011; pp 237-311.
136. Diankov, R., Automated construction of robotic manipulation programs. **2010**.
136. R. Diankov, PhD thesis, Carnegie Mellon University, United States of America (2010).
137. Garcıa, R.; Perez, R., Dynamic atomic force microscopy methods. *Surface science reports* **2002,** *47* (6-8), 197-301.
138. Junno, T.; Deppert, K.; Montelius, L.; Samuelson, L., Controlled manipulation of nanoparticles with an atomic force microscope. *Applied Physics Letters* **1995,** *66* (26), 3627-3629.
139. Hakala, M.; Pakarinen, O.; Foster, A. S., First-principles study of adsorption, diffusion, and charge stability of metal adatoms on alkali halide surfaces. *Physical Review B* **2008,** *78* (4), 045418.
140. Repp, J.; Meyer, G.; Olsson, F. E.; Persson, M., Controlling the charge state of individual gold adatoms. *Science* **2004,** *305* (5683), 493-495.
141. Heinrich, A.; Gupta, J.; Lutz, C.; Eigler, D., Single-atom spin-flip spectroscopy. *Science* **2004,** *306* (5695), 466-469.
142. Hirth, S.; Ostendorf, F.; Reichling, M., Lateral manipulation of atomic size defects on the CaF2 (111) surface. *Nanotechnology* **2006,** *17* (7), S148.
143. Mahaffy, R.; Park, S.; Gerde, E.; Käs, J.; Shih, C.-K., Quantitative analysis of the viscoelastic properties of thin regions of fibroblasts using atomic force microscopy. *Biophysical journal* **2004,** *86* (3), 1777-1793.
144. Tu, Y.-O.; Gazis, D., The contact problem of a plate pressed between two spheres. *Journal of Applied Mechanics* **1964,** *31* (4), 659-666.
145. Chen, W., Computation of stresses and displacements in a layered elastic medium. *International Journal of Engineering Science* **1971,** *9* (9), 775-800.
146. Chin, L.; Xia, Y.; Discher, D. E.; Janmey, P. A., Mechanotransduction in cancer. *Current opinion in chemical engineering* **2016,** *11*, 77-84.
147. Luo, Q.; Kuang, D.; Zhang, B.; Song, G., Cell stiffness determined by atomic force microscopy and its correlation with cell motility. *Biochimica et Biophysica Acta*

(BBA)-General Subjects **2016,** *1860* (9), 1953-1960.
148. Lekka, M.; Gil, D.; Pogoda, K.; Dulińska-Litewka, J.; Jach, R.; Gostek, J.; Klymenko, O.; Prauzner-Bechcicki, S.; Stachura, Z.; Wiltowska-Zuber, J., Cancer cell detection in tissue sections using AFM. *Archives of biochemistry and biophysics* **2012,** *518* (2), 151-156.
149. Tian, M.; Li, Y.; Liu, W.; Jin, L.; Jiang, X.; Wang, X.; Ding, Z.; Peng, Y.; Zhou, J.; Fan, J., The nanomechanical signature of liver cancer tissues and its molecular origin. *Nanoscale* **2015,** *7* (30), 12998-13010.
150. Ding, Y.-x.; Cheng, Y.; Sun, Q.-m.; Zhang, Y.-y.; You, K.; Guo, Y.-l.; Han, D.; Geng, L., Mechanical characterization of cervical squamous carcinoma cells by atomic force microscopy at nanoscale. *Medical Oncology* **2015,** *32* (3), 71.
151. Minelli, E.; Ciasca, G.; Sassun, T. E.; Antonelli, M.; Palmieri, V.; Papi, M.; Maulucci, G.; Santoro, A.; Giangaspero, F.; Delfini, R., A fully-automated neural network analysis of AFM force-distance curves for cancer tissue diagnosis. *Applied Physics Letters* **2017,** *111* (14), 143701.
152. McNeal, J. E.; Haillot, O., Patterns of spread of adenocarcinoma in the prostate as related to cancer volume. *The Prostate* **2001,** *49* (1), 48-57.
153. Schillers, H.; Rianna, C.; Schäpe, J.; Luque, T.; Doschke, H.; Wälte, M.; Uriarte, J. J.; Campillo, N.; Michanetzis, G. P.; Bobrowska, J., Standardized nanomechanical atomic force microscopy procedure (SNAP) for measuring soft and biological samples. *Scientific reports* **2017,** *7* (1), 1-9.
154. Sokolov, I., Atomic force microscopy in cancer cell research. *Cancer nanotechnology* **2007,** *1*, 1-17.
155. Li, Q.; Lee, G. Y.; Ong, C. N.; Lim, C. T., AFM indentation study of breast cancer cells. *Biochemical and biophysical research communications* **2008,** *374* (4), 609-613.
156. Ramos, J. R.; Pabijan, J.; Garcia, R.; Lekka, M., The softening of human bladder cancer cells happens at an early stage of the malignancy process. *Beilstein journal of nanotechnology* **2014,** *5* (1), 447-457.
157. Li, M.; Liu, L.; Xi, N.; Wang, Y.; Dong, Z.; Xiao, X.; Zhang, W., Atomic force microscopy imaging and mechanical properties measurement of red blood cells and aggressive cancer cells. *Science China Life Sciences* **2012,** *55* (11), 968-973.
158. Xu, W.; Mezencev, R.; Kim, B.; Wang, L.; McDonald, J.; Sulchek, T., Cell stiffness is a biomarker of the metastatic potential of ovarian cancer cells. *PloS one* **2012,** *7* (10), e46609.
159. Faria, E. C.; Ma, N.; Gazi, E.; Gardner, P.; Brown, M.; Clarke, N. W.; Snook, R. D., Measurement of elastic properties of prostate cancer cells using AFM. *Analyst* **2008,** *133* (11), 1498-1500.
160. Cai, X.; Xing, X.; Cai, J.; Chen, Q.; Wu, S.; Huang, F., Connection between biomechanics and cytoskeleton structure of lymphocyte and Jurkat cells: An AFM study. *Micron* **2010,** *41* (3), 257-262.
161. Abidine, Y.; Constantinescu, A.; Laurent, V. M.; Rajan, V. S.; Michel, R.; Laplaud, V.; Duperray, A.; Verdier, C., Mechanosensitivity of cancer cells in contact with soft substrates using AFM. *Biophysical journal* **2018,** *114* (5), 1165-1175.
162. Kim, J. H.; Riehemann, K.; Fuchs, H., Force Spectroscopy on a Cell Drum: AFM Measurements on the Basolateral Side of Cells via Inverted Cell Cultures. *ACS applied materials & interfaces* **2018,** *10* (15), 12485-12490.
163. Liu, H.; Tan, Q.; Geddie, W. R.; Jewett, M. A.; Phillips, N.; Ke, D.; Simmons, C. A.; Sun, Y., Biophysical characterization of bladder cancer cells with different metastatic potential. *Cell biochemistry and biophysics* **2014,** *68* (2), 241-246.

164. Efremov, Y. M.; Lomakina, M.; Bagrov, D.; Makhnovskiy, P.; Alexandrova, A.; Kirpichnikov, M.; Shaitan, K., Mechanical properties of fibroblasts depend on level of cancer transformation. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* **2014,** *1843* (5), 1013-1019.
165. Prabhune, M.; Belge, G.; Dotzauer, A.; Bullerdiek, J.; Radmacher, M., Comparison of mechanical properties of normal and malignant thyroid cells. *Micron* **2012,** *43* (12), 1267-1272.
166. Reeves, K. J.; Hou, J.; Higham, S. E.; Sun, Z.; Trzeciakowski, J. P.; Meininger, G. A.; Brown, N. J., Selective measurement and manipulation of adhesion forces between cancer cells and bone marrow endothelial cells using atomic force microscopy. *Nanomedicine* **2013,** *8* (6), 921-934.
167. Hayashi, K.; Iwata, M., Stiffness of cancer cells measured with an AFM indentation method. *Journal of the mechanical behavior of biomedical materials* **2015,** *49*, 105-111.
168. Zhao, X.; Zhong, Y.; Ye, T.; Wang, D.; Mao, B., Discrimination between cervical cancer cells and normal cervical cells based on longitudinal elasticity using atomic force microscopy. *Nanoscale research letters* **2015,** *10* (1), 1-8.
169. Li, Q.; Lee, G.; Ong, C.; Lim, C. In *Probing the elasticity of breast cancer cells using AFM*, 13th international conference on biomedical engineering, Springer: 2009; pp 2122-2125.
170. Zhou, Z.; Zheng, C.; Li, S.; Zhou, X.; Liu, Z.; He, Q.; Zhang, N.; Ngan, A.; Tang, B.; Wang, A., AFM nanoindentation detection of the elastic modulus of tongue squamous carcinoma cells with different metastatic potentials. *Nanomedicine: Nanotechnology, Biology and Medicine* **2013,** *9* (7), 864-874.
171. Andolfi, L.; Bourkoula, E.; Migliorini, E.; Palma, A.; Pucer, A.; Skrap, M.; Scoles, G.; Beltrami, A. P.; Cesselli, D.; Lazzarino, M., Investigation of adhesion and mechanical properties of human glioma cells by single cell force spectroscopy and atomic force microscopy. *PLoS one* **2014,** *9* (11), e112582.
172. Laurent, V. M.; Duperray, A.; Rajan, V. S.; Verdier, C., Atomic force microscopy reveals a role for endothelial cell ICAM-1 expression in bladder cancer cell adherence. *PLoS One* **2014,** *9* (5), e98034.
173. Ketene, A. N.; Schmelz, E. M.; Roberts, P. C.; Agah, M., The effects of cancer progression on the viscoelasticity of ovarian cell cytoskeleton structures. *Nanomedicine: Nanotechnology, Biology and Medicine* **2012,** *8* (1), 93-102.
174. Darling, E. M.; Zauscher, S.; Block, J. A.; Guilak, F., A thin-layer model for viscoelastic, stress-relaxation testing of cells using atomic force microscopy: do cell properties reflect metastatic potential? *Biophysical journal* **2007,** *92* (5), 1784-1791.
175. Bastatas, L.; Martinez-Marin, D.; Matthews, J.; Hashem, J.; Lee, Y. J.; Sennoune, S.; Filleur, S.; Martinez-Zaguilan, R.; Park, S., AFM nano-mechanics and calcium dynamics of prostate cancer cells with distinct metastatic potential. *Biochimica et Biophysica Acta (BBA)-General Subjects* **2012,** *1820* (7), 1111-1120.
176. Omidvar, R.; Tafazzoli-Shadpour, M.; Shokrgozar, M. A.; Rostami, M., Atomic force microscope-based single cell force spectroscopy of breast cancer cell lines: an approach for evaluating cellular invasion. *Journal of biomechanics* **2014,** *47* (13), 3373-3379.
177. Park, S.; Lee, Y. J., AFM-based dual nano-mechanical phenotypes for cancer metastasis. *Journal of biological physics* **2014,** *40* (4), 413-419.
178. Fuhrmann, A.; Staunton, J.; Nandakumar, V.; Banyai, N.; Davies, P.; Ros, R., AFM stiffness nanotomography of normal, metaplastic and dysplastic human esophageal cells. *Physical biology* **2011,** *8* (1), 015007.

179. Abidine, Y.; Laurent, V. M.; Michel, R.; Duperray, A.; Verdier, C., Local mechanical properties of bladder cancer cells measured by AFM as a signature of metastatic potential. *The European Physical Journal Plus* **2015,** *130* (10), 202.
180. Rother, J.; Nöding, H.; Mey, I.; Janshoff, A., Atomic force microscopy-based microrheology reveals significant differences in the viscoelastic response between malign and benign cell lines. *Open biology* **2014,** *4* (5), 140046.
181. Bao, F.; Qiu, J.; Zhang, H., Potential role of β-elemene on histone H1 in the H22 ascites hepatoma cell line. *Molecular medicine reports* **2012,** *6* (1), 185-190.
182. Klein, E.; Vánky, F.; Ben‐Bassat, H.; Neumann, H.; Ralph, P.; Zeuthen, J.; Polliack, A., Properties of the K562 cell line, derived from a patient with chronic myeloid leukemia. *International journal of cancer* **1976,** *18* (4), 421-431.
183. Townsend-Nicholson, A.; Jayasinghe, S. N., Cell electrospinning: a unique biotechnique for encapsulating living organisms for generating active biological microthreads/scaffolds. *Biomacromolecules* **2006,** *7* (12), 3364-3369.
184. Jayasinghe, S. N.; Irvine, S.; McEwan, J. R., Cell electrospinning highly concentrated cellular suspensions containing primary living organisms into cell-bearing threads and scaffolds. *Future Medicine* **2007,** *2* (4), 555-567.
185. Nitta, N.; Sugimura, T.; Isozaki, A.; Mikami, H.; Hiraki, K.; Sakuma, S.; Iino, T.; Arai, F.; Endo, T.; Fujiwaki, Y., Intelligent image-activated cell sorting. *Cell* **2018,** *175* (1), 266-276. e13.
186. Provenzano, P. P.; Inman, D. R.; Eliceiri, K. W.; Knittel, J. G.; Yan, L.; Rueden, C. T.; White, J. G.; Keely, P. J., Collagen density promotes mammary tumor initiation and progression. *BMC medicine* **2008,** *6* (1), 11.
187. Chaki, S. P.; Barhoumi, R.; Berginski, M. E.; Sreenivasappa, H.; Trache, A.; Gomez, S. M.; Rivera, G. M., Nck enables directional cell migration through the coordination of polarized membrane protrusion with adhesion dynamics. *Journal of cell science* **2013,** *126* (7), 1637-1649.
188. Luo, Q.; Wu, K.; Zhang, B.; Song, G., Mechano growth factor E peptide promotes rat bone marrow-derived mesenchymal stem cell migration through CXCR4-ERK1/2. *Growth Factors* **2015,** *33* (3), 210-219.
189. Jorba, I.; Uriarte, J. J.; Campillo, N.; Farré, R.; Navajas, D., Probing micromechanical properties of the extracellular matrix of soft tissues by atomic force microscopy. *Journal of cellular physiology* **2017,** *232* (1), 19-26.
190. Liu, J.; Qu, Y.; Wang, G.; Wang, X.; Zhang, W.; Li, J.; Wang, Z.; Li, D.; Jiang, J., Study of morphological and mechanical features of multinuclear and mononuclear SW480 cells by atomic force microscopy. *Microscopy research and technique* **2018,** *81* (1), 3-12.
191. Xiao, L.; Tang, M.; Li, Q.; Zhou, A., Non-invasive detection of biomechanical and biochemical responses of human lung cells to short time chemotherapy exposure using AFM and confocal Raman spectroscopy. *Analytical Methods* **2013,** *5* (4), 874-879.
192. Liu, C.; Han, X.; Yang, X.; Tian, L.; Wang, Y.; Wang, X.; Yang, H.; Ge, Z.; Hu, C.; Liu, C., Self-repair behaviour of the neuronal cell membrane by conductive atomic force indentation. *IET nanobiotechnology* **2019,** *13* (9), 891-895.
193. Cunningham, S.; Larkin, I. A.; Davis, J. H., Noncontact scanning probe microscope potentiometry of surface charge patches: Origin and interpretation of time-dependent signals. *Applied physics letters* **1998,** *73* (1), 123-125.
194. Klausen, L. H.; Fuhs, T.; Dong, M., Mapping surface charge density of lipid bilayers by quantitative surface conductivity microscopy. *Nature communications* **2016,** *7* (1), 1-10.

195. Ulrich, P.; Zhang, X., Pharmacological reversal of advanced glycation end-product-mediated protein crosslinking. *Diabetologia* **1997,** *40* (2), S157-S159.
196. Castellani, R. J.; Harris, P. L.; Sayre, L. M.; Fujii, J.; Taniguchi, N.; Vitek, M. P.; Founds, H.; Atwood, C. S.; Perry, G.; Smith, M. A., Active glycation in neurofibrillary pathology of Alzheimer disease: Nε-(carboxymethyl) lysine and hexitol-lysine. *Free Radical Biology and Medicine* **2001,** *31* (2), 175-180.
197. Bucala, R.; Cerami, A., Advanced glycosylation: chemistry, biology, and implications for diabetes and aging. In *Advances in pharmacology*, Elsevier: 1992; Vol. 23, pp 1-34.
198. Y Qu, PhD thesis, Changchun University of Science and Technology, China (2019).