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DNA nanotechnology as a tool to develop molecular tension probes for bio-sensing and bio-imaging applications: An up-to-date review

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ABSTRACT

DNA is known to be a life material that has been explored as an exciting biomaterial for bio-sensing, bio-imaging, and analytical applications. The current review focuses on describing the general concept of DNA nanotechnology including linear DNA nanotechnology, short circular DNA nanotechnology, DNA origami, and the hybrid protein–DNA nanotechnology/supramolecular approaches. We will further describe the existing strategies for the development of DNA molecular tension probes to target the cell surface receptors (mainly integrin) for bio-imaging and bio-sensing applications. The surface activation of the cellular receptors by the DNA probes will elicit the mechanical responses to the cells for the analysis and bio-imaging of mechano-biological processes. The literature overview is obvious about the role of cell surface receptors in generating piconewton (pN) forces and carrying out mechano-transduction events necessary for the growth, development, and proper functioning of the cells. The last part of the review will briefly summarize our contribution as a latest advancement in this field, and to establish a further need for research.

Contents

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1. Introduction

The nano-science or nano-technology represents material particles having a size in the range of 1–100 nm prepared either semi-synthetically or artificially using physical, chemical, biochemical, or mechanical approaches [1–4]. DNA (Deoxyribonucleic acid) being a life material is well known as a comprehensive information-house in the form of genetic-codes [5–8]. During the last decades, synthetic DNA has been explored as an excellent material to fabricate specifically shaped nano-architects of 1D, 2D and 3D geometry by simple self-assembly of various DNA strands with the designed length and sequences of the nucleotides in the presence of cations (Mg^{++}/Na^{+}) and buffers (TE and TAE) [9–12]. DNA comprises of pentose-sugar and phosphate backbone linked to other strands through the base pairing of the nitrogenous bases in such a way that G forms triple hydrogen-bonds with the C, while A forms double hydrogen-bonds with the T of another antiparallel complementary strand as suggested by the Watson/Crick base-pairing model (1953) and Chargaff's rule [13–16].

2. Linear DNA-nanotechnology

The pioneering work by Nadrian C. Seeman in 1998 on the synthetic linear DNA nanotechnology (based on Watson–Crick/base-pairing model and Chargaff's rule) was accomplished to construct specifically designed nano-architects with definite shape and features [17–19]. After that different scientists designed DNA based materials for potential applications in drug delivery, bio-imaging, bio-sensing, bio-analysis, biomedicines, nano-electronics, and fabricating the nano-devices for biomedical engineering [20–24].

Double-stranded/B-form DNA (dsDNA) with the diameter of 2 nm is the most common feature of the linear DNA molecules having precise complementary base-pairing with the nanometer-sized dimensions [25–27]. B-form/dsDNA has a right twisted helical structure in which two half-turns constituting one complete helical-turn with a length of 3.4 nm and comprising of 10.5 base-pairs [28–30].

An example of the linear DNA nanotechnology is a design with four-arm junctions (holiday junctions) of the dsDNA. Due to the specific base pairing of the nucleotides (based on Watson/Crick base-pairing model), scientists are able to hybridize different linear DNA strands with predesigned sequences into DNA tiles that are self-assembled owing to the sticky ends mediated connectability forming specifically shaped nanostructures. Differently designed DNA tiles are synthesized from the self-assembly of the linear DNA-strands. The DNA tiles are equipped with the sticky ends to combine with the other tiles in a programmed way to make 2D DNA-nanoribbon lattices.

3. Circular DNA nano-technology

After scientists successfully used linear DNA strands to make specially designed nano-structures that however, lack the rigidity and mechanical strength required to be used for various potential applications [31–34]. Later, the circular DNA scaffold strand was introduced to assemble with the staple strands to synthesize stiffer nanostructures utilizing B-from/dsDNA (acting as a rigid rod) with better shape and size control for various biological applications [35–37]. The B-form/dsDNA based nano-materials made from circular-scaffolds add stiffness with the improved programmability to synthesize highly-ordered nano-architects with definite geometry [38–40].

3.1. DNA origami (semi-synthetic)

DNA origami involves the use of the large single-stranded circular template strand with the length of more than 7000 nucleotides extracted from a natural source such as M13 phage [41–43]. This large circular template (or scaffold strand) is mixed with the various staple strands that fold the circular scaffold strand into the specific shape after hybridizations and self-assembly (according to the precise Watson/Crick base-pairing model) [44–46]. The self-assembled structure got the exact shape as designed after the self-assembly of the strands with nanometer-size precision [47–49].

3.2. Short circular DNA nanotechnology (synthetic)

Short circular DNA nanotechnology (a synthetic technique) involves a series of steps to circularize the short linear strand of DNA into a circular scaffold ranging in length from 34 nucleotides to 128 nucleotides [50–52].

3.2.1. Short circular 1D and 2D DNA nanotechnology

After the circularization of the scaffold strand, it is self-assembled with the various short staple strands to make 2D DNA tiles [53–56]. These 2D DNA tiles are equipped with the sticky ends to make connections to the other DNA tiles and self-assemble into predesigned 1D or 2D lattices [57–60].

3.2.2. Short circular 2D and 3D DNA nanotechnology

Due to the increased rigidity and tensile strength of the DNA lattices, and due to the incorporation of a circular scaffold, and the intrinsic curvature of the double-stranded DNA, some 2D DNA lattices may fold on its own to form 3D nanotubes [61–63]. Especially the 2D lattices made from the triangular DNA tiles have the big possibility to undergo self-coiling and being converted to the 3D DNA nanotubes or nano-threads [50,64,65].

3.3. Hybrid protein-DNA nanotechnology and supramolecular approach

The DNA has become an established approach to design 1D, 2D and 3D nanostructures [66–68]. But this technique has become more fascinated with the addition of the programmability of different functional groups that might be attached to the DNA at special locations to form bio-conjugates with proteins, lipids or other compounds for various potential applications [63,69]. Furthermore, covalent linkages of DNA with proteins at delicate positions in the DNA nano-architects can further stabilize the nano-lattices to add suitable strength for various applications [70]. Special proteins attached to the DNA may find scope for the bio-imaging of the bio-processes or in facilitating the targeting of the DNA based delivery system to the precise cells [48, 71]. The nano-scale programmability of the protein–DNA hybrid materials has opened a new horizon to find solutions of unaddressed problems in the field of biomedicine and bio-imaging [21, 66]. Three or more different DNA strands can be attached to specific proteins through amino-modifications of the DNA strands and the reactive cysteine modifications of the proteins [72]. These protein–DNA complexes can be predesigned to make complementary pairing with the free DNA strands of the pre-assembled DNA nano-architects to make hybrid nanostructures [73].

4. Design of molecular probes with the linear DNA nanotechnology for bio-analysis

The programmability of small molecular DNA probes has led to breakthrough advancement to the analytical chemistry to detect mRNA, DNA sequences, proteins, gene sequencing and identification of genetic diseases as well as toxic compounds, mutagens and environmental pollutants [15,24,74]. Due to the sequence-specific folding and hybridization capability of linear DNA strands and its conjugation at precise locations to the functional moieties has established small DNA nano-probes to find vast applications in theranostics [69]. Small molecular linear DNA probes for analysis of specific DNA sequences are effective for the detection of target DNA sequence by separation of the fluorophore and quencher to produce fluorescence signals. Detection of target DNA sequence is achieved through the enhancement of the fluorescence of the acceptor fluorophore due to the emitted light from the donor fluorophore through the FRET phenomenon using a DNA sequencing with a padlock probe. The portion of the ped-lock probe which is complementary to specific genes in the DNA may hybridize with that portion of the gene. Remaining un-hybridized single-stranded DNA is cut using exonuclease [69].

4.1. Small molecular tension probes made from DNA to sense pN forces on cell surface

Small molecular linear DNA tension probes have been designed to sense the pN forces on the cell surface to understand the mechanical cell processes [72]. A ligand of interest is attached to one end of the linear DNA probe while the other end is fixed on some substrate [75]. Small molecular tension probes made from DNA appeared to be an effective tool to sense pN forces on cell Surface [68]. The surface of the glass slide was coated with the gold nanoparticles functionalized with the DNA tension probes as glowing molecular beacons to track cell movements. We can see that another end of the DNA tension probe is attached to the cell-surface integrin receptors to activate it. After integrin activation, it will stimulate cytoskeleton and cell contractions. We can measure the pN forces of the cells that cause unfolding of the hairpin portion of the DNA probe and separation of the fluorescent and the quencher generating fluorescence that can be imaged using double photon confocal microscopy. Matlab programming is designed with definite algorithms to process the data about force calculations. Also, the pixels changes after the fluorescence generation enable us to incorporate into Matlab programming.

The ligand interacts with the mechanical cell surface receptors that trigger cytoskeletal activation after binding to the intended receptor [69]. DNA tension probe is also equipped with the hairpin structure that is unfolded upon the pN forces generated by the fixed cells exerted on the DNA probe causing fluorophore and quencher to be separated generating fluorescence signals [76]. The images are processed according to the designed algorithms in MATLAB for pixels change to correlate with the pN force generation by the cells [77]. Integrin is one of the cell surface receptors that after activation initiates cell signal transduction pathways to stimulate cytoskeletal activation [78]. An aptamer or fibronectin/RGD protein can be attached to one end of the amino-modified DNA to bind and activate the integrin on cell surface [79].

4.2. A DNA tension probe to investigate TCR mediated pN forces on T cells after Ca^{++} intake

A similar approach was used to design the molecular tension probe by the same research group [76]. A DNA tension probe that was attached to the AuNPs fixed on the cover-slip was made to bind with T cells due to the TCR-antigen (ligand) attached on the other end. T cells exerted pN forces on the DNA probe resulting in the unfolding of its hairpin portion to separate the fluorophore and the quencher generating fluorescence enabling to track changes in the cell morphology, cytoskeleton activation, and the pN forces involved [80,81].

4.3. A chemical linker mediated fixation of DNA tension probe on the substrate to visualize cell traction pN forces

Instead of using gold nanoparticles to fix the DNA probes on the glass slide, the same research group at the Emory University reported a chemical linker method to fix similar type of DNA tension probe on the substrate surface to interact with the cell surface integrin molecule to investigate the activation of cytoskeleton and generation of pN forces [77]. A chemical linker method turned out to be an effective method to fix the DNA tension probe on the substrate to visualize cell traction pN forces [72]. The unfolded hairpin in response to the cellular pN forces produced fluorescence after the separation of fluorophore and quencher. More force can be calculated using longer hairpin. As longer hairpin requires more force to be unfolded. Similarly, by increasing the GC base pairing contents in the hairpin will require more force due to the triple hydrogen bonding as compared to AT base pairing that exhibits double hydrogen bonding [77].

4.4. DNA origami based multivalent digital tension probes to measure pN forces

The same research group from the Emory University under Khalid Salaita developed DNA origami-based multivalent tension probes decorated with multiple hairpin structures conjugated to fluorophore–quencher pairs. The origami body provided a platform to program the attachment of multiple hairpins and calculating forces and stress on the platelets as shown below in Fig. 1 [69].

Platelet aggregation depends on the mechanical processes that were sensed by the current study. Integrin is an important cell surface receptor to modulate cytoskeletal activation and signal transduction events [69]. Force/tension measurement

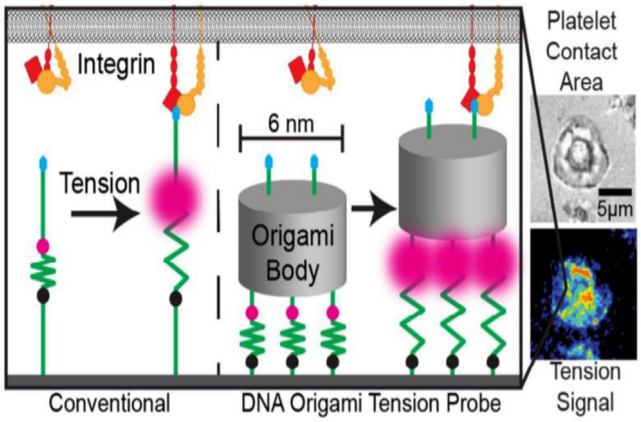

Fig. 1. Design of the DNA origami-based molecular tension probe with multiple hairpin functionalization capable of measuring force and stress with more precision, accuracy with an enhanced limit of detection.
Source: Image reproduced with permission of [69].
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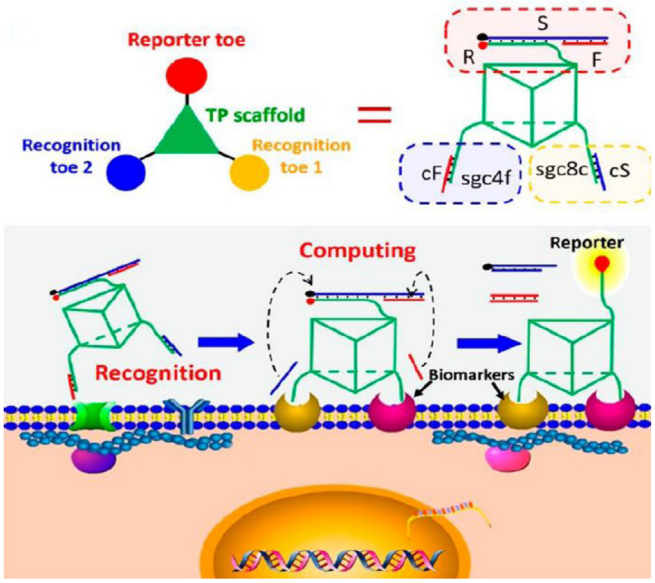

Fig. 2. Working on the 3D DNA nano-prism probe as a Boolean logic "AND" gate. DNA nano-prism acts as a scaffold for the probe, supporting recognition toe 1 and recognition toe 2 which are equipped with the two different sgc-aptamers to simultaneously bind two different protein receptors on the cancer cell surface acting as biomarkers. The strands complementary to the aptamers detach after recognition of specific biomarkers and recombine with the reporter region to separate the fluorophore–quencher to produce fluorescence "ON" signals.
Source: Images reproduced with permission of [63].
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was very sensitive using DNA-origami based molecular tension probe. The six-helix bundle makes the body of the DNA origami-based tension probe enabling the programmability of multiple hairpins with attached fluorophore–quencher pair to measure pN forces [64]. Force calculations were performed through designed algorithms and MATLAB simulations about hairpin unfolding with different GC contents.

4.5. Two receptors targeting logic gate probe as a 3D DNA nano-machine to identify specific cancer cell types

To better understand the behavior of the cancer cells and their increased mutagenicity, integrated recognition machines are required as logic gates and development of proper computing modules about the single-molecule structure and protein response. Weihong Tan and co-workers designed a three dimensional DNA nano-machine as a logic gate to target the overexpressed multiple cell surface receptors on the cancer cell to identify bispecific biomarkers with precision [63,82]. When both receptors are present on a cancer cell then DNA nano-machines undergo strands displacements and re-combinations of strands to generate the 'On' fluorescence signal. The response of bispecific activations on the cell membrane can also be observed by fluorescence spectroscopy, flow cytometry as well as confocal fluorescence microscopy. So for bispecific recognition, the designed DNA nano-machine act as an "AND" gate with two possible outcomes either 1 or 0. When both of the receptors are activated then the fluorescence signals of DNA Nanomachines turn on as Boolean operator 1 with a specific cell type with dual expression of surface protein receptors [63]. Thus this technique is an effective molecular targeting and for the rapid analysis of specific cancer cells compared to other approaches. DNA based probe based on 3D triangular prism exhibited outstanding performance, robust molecular recognition with ease of fabrication of as an effective tool for nanorobotics [63]. The visual representation of logic operation has been shown in Fig. 2.

4.6. Molecular tension probe computing and fluorescence mapping of the shear stress on the cell and calculation of involved pN forces

Brockman and coworkers from the group of Khalid Salaita developed computational tools and programs to efficiently map the pN forces on different portions of the cells after activating

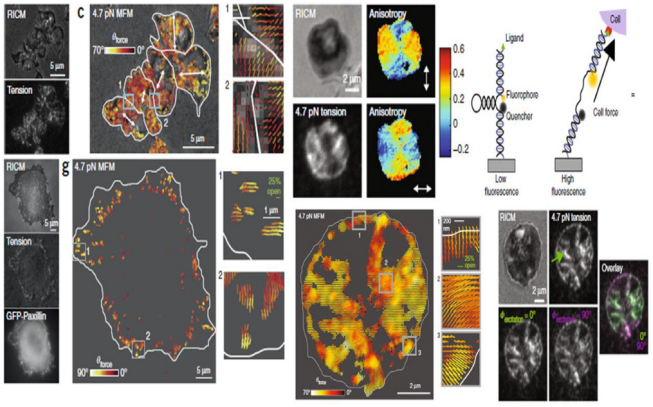

Fig. 3. Approaches to compute the polymerization of actin stress fiber in the cells. Computation was performed from the generated fluorescence signals after the unfolding of the hairpin on the DNA probe.
Source: Images reproduced with permission of [83].
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the cell surface integrin receptors [83]. The software can provide a 16 color map on the entire cell to investigate the shear stress and pN forces involved. They used a similar DNA hairpin probe as previously reported by the same research group that generated fluorescence after interacting and activating the cell surface integrin receptors [83]. The polymerization of actin stress fibers can be simulated from the computer programming according to the fluorescence pattern achieved after the interactions of the DNA probe with the cells as illustrated in Fig. 3 [83].

4.6.1. DNA tension probe applied for the imaging and treatment of lung disease (asthma) as an approach towards the mechanical pharmacy

Integrin is the cell surface receptors chiefly responsible for signal transduction events to activate the cytoskeleton to perform mechanical cell processes [84]. However same integrin stimulations can be intended for the treatment of some diseases in which cells adhere to the undesired place for their detachments. Such an attempt was made by Galior and coworkers to increase the cytoskeletal activation to treat human airway smooth muscle cells for the samples from the asthmatic patients [84]. A DNA nanoprobe was used to interact with the cell surface integrin receptors and fluorescence signals were achieved after the unfolding of the DNA hairpin. The results about fluorescence imaging of cells and mechanical signal transduction events to activate cytoskeletal and mechanical cell movements [84]. Mechanical imaging of human airway smooth muscle cells from asthmatic patients were made detached after mechanical stimulation as an approach towards the mechanical pharmacy.

4.7. DNA probes for the imaging of the integrin clustering and filopodia extensions causing high-level mechanical stimulations in the cells necessary for carrying out normal cell processes

Scientists used DNA probes to image the integrin clustering necessary to generate enough pN forces to perform specific functions [72,73,76,85]. DNA probes effectively imaged the integrin clustering enabling to calculate the enhanced pN force generation. Block-copolymer, Micelle nano-lithographic technique was employed to fabricate nano-sensors to investigate integrin clustering [73]. RGD functionalized DNA nano-trains were developed as the DNA probes for sensing integrin clustering on platelets to calculate large forces involved in platelet aggregations [67]. The MATLAB tools were designed to evaluate cell stress maps after integrin clustering and enhanced cytoskeletal activation [80]. Another study reports the development of special DNA probes to image the integrin activation that was found to be consistent with the filopodia extensions of the cells [77,86]. After successful activation of integrin, the length of filopodia was increased. Extension of filopodia after integrin activation on the cell surface was clearly visible in the confocal images [72,81].

4.8. Mechano-sensing using plasmonic nano-springs

Two gold nanoparticles were linked with an elastic linker [87]. The larger gold nanoparticle was fixed at the surface while smaller gold nanoparticle was functionalized with the RGD protein to interact and activate integrin receptors on the cell surface. The mechanical signal transduction was sensed after integrin activation through changes in the plasmonic coupling [87]. Scientists were able to image reactive oxygen species-mediated enhanced mechanical activity in cells [87]. The study design has been illustrated in Fig. 4.

4.9. DNA membrane interacting probes for intercellular imaging of forces

Cell–cell attachment is an important phenomenon in proper growth development and maintenance of proper cell density to control cell proliferation and programmed cell death [73]. Cells interact to perform normal physiological functions and even transport of micro-nutrients. Zhao and coworkers designed a DNA probe that anchored the lipid membrane on one cell and was designed to contain ligand for another cell on the other end of the probe [73]. So they designed a DNA probe that can attach two different cells and equipped with the hairpin part that successfully showed fluorescence under applied force due to cell–cell interactions as shown in Fig. 5 [73].

4.10. Using a DNA probe to image the cell surface receptors internalizations

DNA hairpin structure with attached fluorophore–quencher pair that is attached to the cell surface receptors in a quenched form [88]. After the activation of cell surface receptors, shear stress is generated due to the mechano-transduction events and cytoskeletal activations. These important mechanical processes give rise to cell internalizations of these membrane receptors [88]. After the co-internalization of the DNA probe and cell surface receptors, the hydrolytic opening of the hairpin structure causes the separation of fluorophore–quencher to show strong fluorescence [88]. With the increase of membrane receptors stimulations, an increase in the fluorescence, mechanical stimulations, and receptors internalizations are observed. The scheme and key findings of the study have been shown in Fig. 6.

5. Our contribution to this field

We have used short circular DNA nanotechnology to develop topologically stiffer molecular tension probe and to target two receptors simultaneously in a bi-specific manner as shown in Fig. 7. Circular DNA nanotechnology is a technique that involves the synthesis of a circular scaffold from the 5'-phosphate modified linear DNA strand, with the help of DNA ligase. The circular scaffold is combined to various staple strands to make stiffer nanostructures [50]. Circular DNA based molecular tension probes can be developed with the precisely tunable size, shape and ligand-targeting with two-arm, three-arm and four-arm (Holiday) junctions at vertices to target different proteins and receptors simultaneously [63]. The simultaneous targeting of receptors/proteins enables us to investigate the cooperative role of the ligand binding to study interactions between the cell surface receptors or other proteins and macromolecules in the cellular or biological systems [89].

We used a unique circular DNA nanotechnology using circular DNA scaffolds to self-assemble with the various staple and functionalizing strands to synthesize stiffer small molecular tension probes or nano-devices [50]. Designed DNA-nanodevices are functionalized with the gold nanoparticles [81], fluorophore /quenchers [20], and different ligands to interact with the cell surface receptors [76], and activate signal transduction events, cytoskeletal activation, and mechanical cell processes [79]. We attained stiffer probe employing circular DNA nanotechnology to image the interactions between the EGFR and integrin on cancer cell surface. We observed that bi-specific co-activations of EGFR and integrin caused enhanced cytoskeletal activations and biochemical signal transductions and killing of the cancer cells through mechanical exhaustion effect, turned out to be a novel tool for bio-imaging and mechano-pharmacology.

6. Conclusion

DNA nanotechnology has enabled us to develop molecular tension probes for bio-imaging, bio-analysis, and calculating pN forces involved in the important biological processes. Biochemical signaling pathways are coupled with the mechano-transduction events to properly perform the complex biological processes in the body. All the growth, development, differentiation, and cell maturation processes involve cytoskeletal activations to carryout mechanical events. Hence, measuring pN forces to better understand these processes becomes important. This review focused on the development of DNA molecular tension probes to activate cell surface receptors (mainly integrin) for initiating signal transduction events and the mechanical cell processes via cytoskeletal activation and actin stress fiber polymerization, as well as to

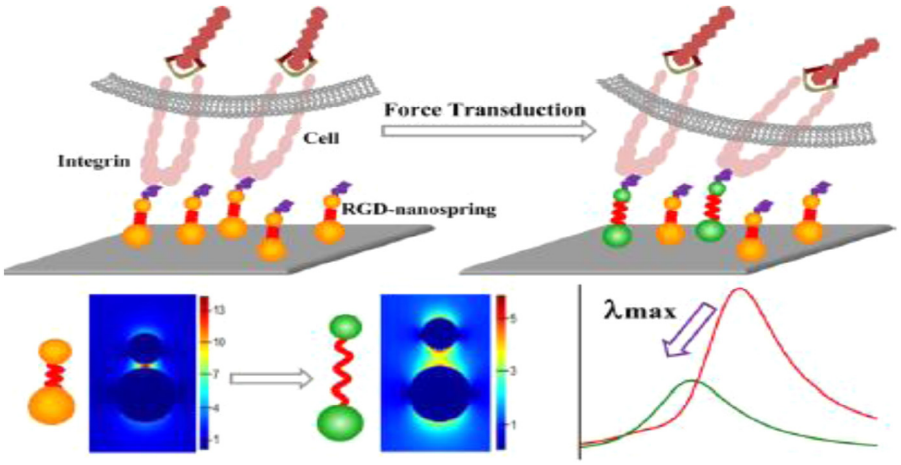

Fig. 4. Plasmonic nano-spring as mechanical sensing of cellular traction forces and mechanical signal transductions. The two ends of the nano-springs have different properties. One end is fixed on a surface through a larger gold nanoparticle. While another end is equipped with smaller gold nanoparticles with RGD functionalization to interact with cell surface integrin receptors to sense mechano-transduction events. Plasmonic coupling and change in UV signals are illustrated.
Source: Image reproduced with permission of [87].

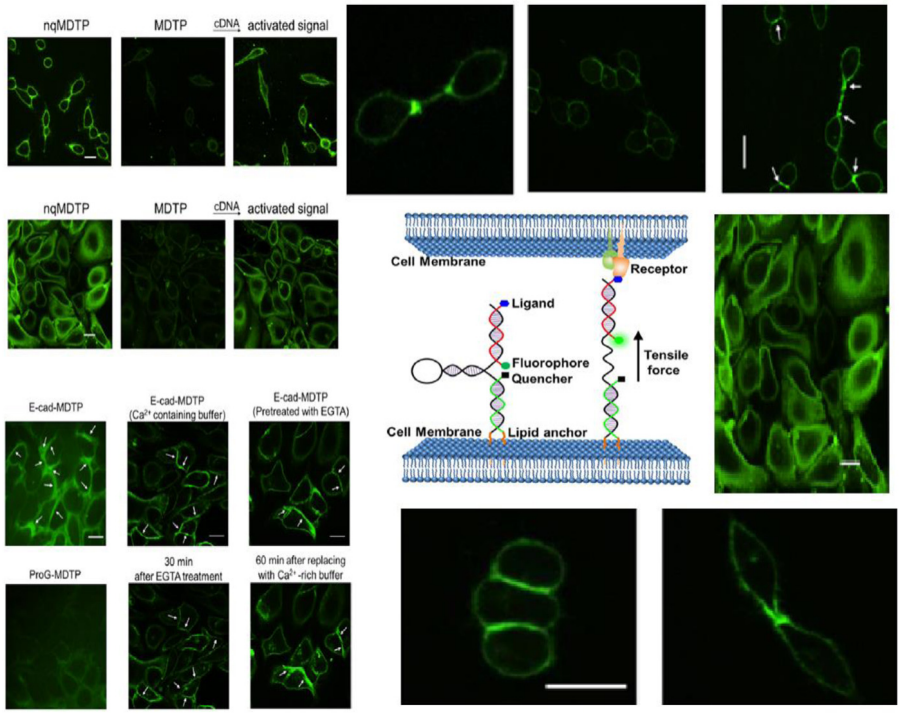

Fig. 5. A DNA probe to sense tensile forces due to cell–cell interactions.
Source: Images reproduced with permission of [73].

treat diseases as a novel tool towards **Mechanical Pharmacy** and **Medical Biophysics**. However, to image interactions between the multiple cell surface receptors, stiff molecular tension probes were required to interact with multiple receptors simultaneously and to attain stiff topology, capable of binding to the multiple receptors simultaneously.

7. Limitations and future prospects

So far, DNA molecular tension probes based on linear DNA strands have been developed to target only one type of receptors, with one end of the probe to be covalently fixed at the designed surface, and other end to interact precisely to the specific surface receptor of the target cell for bio-imaging of a receptor specific effects. However, mechano-transduction pathways depend on the multiple cell surface receptors (not only one type of receptors) in initiating and mediating effective mechanical response to carry out distinct growth and developmental processes in the cells. Therefore, probes are required to be developed for the bio-imaging of the adherent live cells in relation to the role of multiple cell surface receptors in cell proliferations, proper growth and development. Keeping this theme, DNA based molecular tension probes can be important to target multiple receptors capable of causing mono-, bi-specific or tri-specific activations on the adherent cell surface for bio-imaging

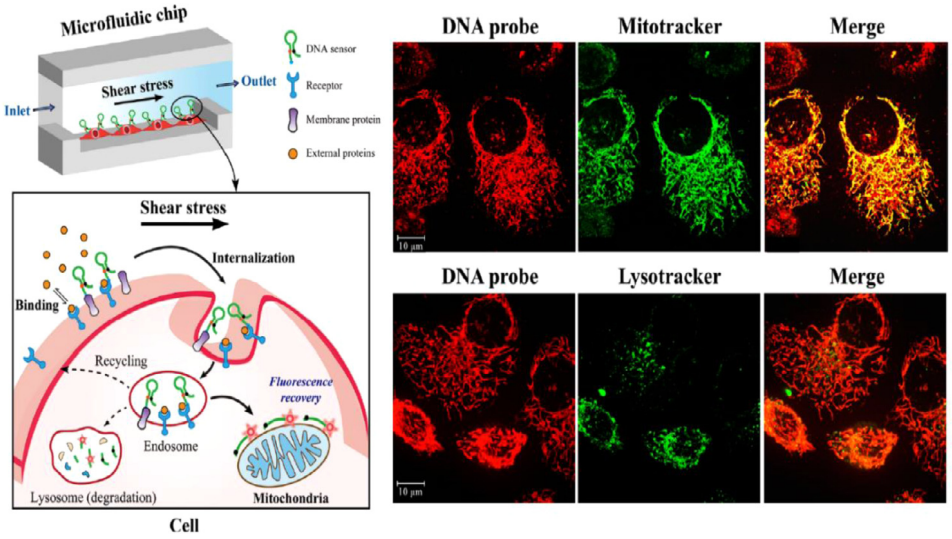

Fig. 6. Imaging of the internalization of cell surface receptors after mechanical stimulations. Cell surface receptors (integrin) were stimulated and mechanical cell processes caused the receptors-DNA probe to internalize into cells. We can see the presence of receptors attached to DNA probes in the mitochondria of cells.
Source: Images reproduced with permission of [88].

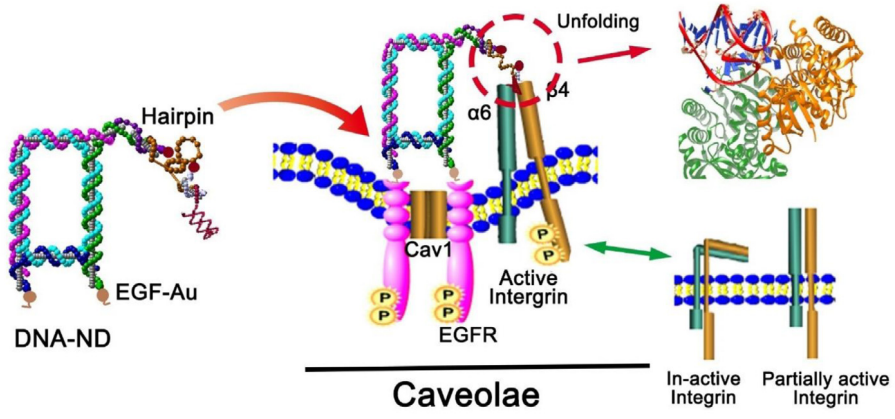

Fig. 7. Design of the bi-specific molecular tension probe to interact with EGFR and integrin receptors simultaneously on the caveolae of cancer cell surface.
Source: Image reproduced with permission of [3].

of mechanical cell events. In this way, we can be able to analyze interactions between the cell surface receptors and their impact on the important cellular processes. Such tension probes can be designed and synthesized primarily from the short circular DNA strand (as a scaffold strand) and a few staple strands. Molecular tension probes based on short circular scaffold strand could attain a firm 2D topology for ligand functionalization and to precisely target the multiple cell surface receptors simultaneously. In this way, scientists can explore the interactions of the cell surface receptors in initiating macho-transductions, enhanced cytoskeletal activations, and developmental cell processes. Due to enhanced mechano-transduction, there will be enhanced forces on the cell surface and changes in the configurations in the cell surface receptors that may exert pN forces on specially designed molecular tension probes to generate variations in the fluorescence or plasmon-coupling signals after mono-, bi- and tri-specifically activate the cell surface receptors for bio-imaging of the interactions between cell surface receptors. Based on the interactions between the multiple receptors, scientists can do research to understand their vital impacts on the cellular physiology and on the patterned growth and development.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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