EDITORIAL OPEN ACCESS

Nanostructured substrates for biomedical applications

Valentina Mussi

The starting point for a discussion on biomedical applications of nanostructured substrates may well be the obvious observation that properties of materials change dramatically down to the nanoscale, so that a change of methodologies is required for their production and assembly, a change of analytical instruments is needed for their characterization, and novel tools can be designed with special way of functioning. In fact, nanostructured materials are able to probe and influence processes at cellular and molecular level, and their application is potentially able to deeply modify the way in which we perform environmental and clinical monitoring, tissue engineering, biomarking, drug delivery.

In particular, biomedical applications of nanostructured systems rely on the development of innovative devices and materials able to interact with sub cellular elements with a high degree of specificity, so to maximize the diagnostic/therapeutic effect but with minimal invasiveness. Clearly, such different perspective requires a complex reshuffling and mixing of diverse disciplines and expertise in order to work at the frontier between physics, biology, chemistry and engineering, as already envisioned by Feynman in 1963*.

Microparticles and nanoparticles realized with various materials (metals, silica, polymers, carbon nanotubes, proteins, lipids) have been until now the most frequently suggested and studied diagnostic and therapeutic agent, even if, apart from few exceptions [1], a translation to commercial clinical use has not yet occurred. This is mainly due to difficulties in obtaining a sufficient size and shape uniformity (strongly affecting the overall properties), in optimizing pharmacokinetic behaviour, and in overcoming general concerns about toxicity, biodegradation and excretion [2]. However, a different strategy can be pursued because industrial nanofabrication methods permit nowadays to control the surface texture of materials at the nanoscale, enabling to realize nanostructured substrates to investigate, understand and manipulate cell and molecular response. When surface topographical features become comparable with those of cellular surface components (microvilli, filopodia) and extra-cellular matrix elements (ECM), they can influence cell adhesion [3] and proliferation [4], cell morphology [5] and alignment [6], cell differentiation [7] and migration [8], but can also affect actin formation [9] and cause alkaline phosphatase [10] and gene upregulation [11]. Man-made nanotopography has thus enormous potential application in implant design and tissue engineering, allowing to realize scaffolds and biodegradable structures mimicking microscale and nanoscale natural tissue organization and enhancing vascularization and in vivo tissue regeneration [12]. In this context, some interesting attempts have been recently made to push further forward the similarity with naturally occurring structures [13]. In taking inspiration from insect wings, bioinspired randomly oriented anisotropic nanostructures have been produced by reactive ion etching on titanium to impart an additional bactericide property to the scaffold, improving the performance for orthopedic in vivo applications [14].

In tissue engineering applications, a relevant role seems to be played also by a certain degree of nanoscale disorder which appears to be able to stimulate cell differentiation at such a degree that the use of osteogenic media could be avoided, with implications for cell therapies [15, 16]. The order-disorder transition has the clear advantage of reducing fabrication costs and enhancing production throughput, thus increasing the overall interest on nanostructuring processes for commercial realization of biomedical devices. For example, the combination of bioactive ingredients to be released, such as antimicrobial, antibacterial and anti-inflammatory agents, with fibrous nanostructured

*If our small minds, for some convenience, divide this glass of wine, this universe, into parts—physics, biology, geology, astronomy, psychology, and so on—remember that nature does not know it!, The Feynman Lectures on Physics, volume I; lecture 3, "The Relation of Physics to Other Sciences"; section 3–7.

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materials is considered for next generation of smart wound dressings and healing [17, 18], while 3D anisotropic Silicon nanostructures produced by wet chemical etching have been inserted into microfluidic platforms to efficiently capture circulating tumor cells (CTC) from whole blood samples, with the aid of a proper target-oriented functionalization, the key elements being an increased CTC-substrate contact frequency and duration [19]. Even more appealing appears the possibility to produce capturing nanostructures on soft polymeric substrates by means of template assisted methods [20], or replica molding manufacturing [21]. In this last case, nano-cavities on PDMS surface has been successfully used to enhance the adsorption of miRNA molecules, usually present in low concentration in biological fluids, even in the absence of surface functionalization with specific probes. Considering the ascertained role of miRNA as biomarker for several degenerative, contagious or inflammatory illnesses, a similar topography-based trapping mechanism can have a notable application in the field of diagnostic tools for early and not invasive disease detection. Actually, the same elastic properties of polymeric deformable materials can be exploited to tune the nanometric dimension of the realized structures in order to obtain advanced manipulation and sensing capabilities, up to single molecule level [22, 23].

A separate discussion must be devoted to approaches where 'active properties' of nanostructured substrates are involved. Laser excitation of nanoscale roughened metal surfaces (typically gold or silver) is able to give rise to strong localized surface plasmon resonances that can cause a considerable enhancement of the electromagnetic field. When a target molecule lies in close proximity to the metal surface, a correspondingly large increase of the scattered Raman signal can be observed. This surface enhancement Raman scattering effect (SERS) makes it possible to analyse low concentration samples without the need for fluorescent labelling. Several biosensing frameworks based on SERS substrates have been proposed, both for chemical analysis of cells in routine diagnostic monitoring and for molecular recognition [24], but obtained through different strategies: direct growth of a nanostructured metal film [25, 26], by decorating surface nanostructures with metal nanoparticles [27, 28], or by covering a nanopatterned layer with a thin metal film [29]. This last solution appears particularly promising because, being based on a low cost-low temperature CVD fabrication process of disordered nanowires, it is compatible with industrial Si based technology, it can be coupled with others analytical methodologies in multi-transduction devices (i.e. Raman plus electrochemical sensing), and it can be applied on polymeric and glass supports to be exploited in standard and endoscopic read-out devices. In fact, multifunctional platforms could play an important role for less invasive biomedical applications, combining imaging, diagnostic and therapeutic capabilities [30]. For instance, as recently demonstrated [31, 32], metal covered or decorated nanostructures (gold on silicon nanowires, Au-SiNWs) can also generate significant amount of heat upon irradiation in the near-infrared (NIR) region, where biological tissues and systems are almost transparent, which can be successfully used for inducing thermal drug release or cell death. In principle, it is therefore possible to design and develop specific endoscopic devices based on fiber optic integrated nanostructured interface for NIR photothermal treatment of cancer cells and simultaneous SERS monitoring of the process evolution [33], or to use layered structures for capture and plasmonic phothermal therapy of circulating tumour cells [34].

After all, it can be foreseen that exactly the integration of morphological, mechanical and multifuctional 'active' properties will be the future of nanostructured substrates for biomedical applications, as proposed to realize a sort of electronic skin made of wearable or implantable nanostructured devices and sensors for continuous diagnostic monitoring and therapeutic activity [35–37]. An open challenge for all those who want to contribute to future progress in this incredible field of research.

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Keywords: Biomedicine, Cells, Nanostructures, Substrate, Surface enhancement Raman scattering effect (SERS), Tissues

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REFERENCES

1. www.nanospectra.com
2. Kiessling F, Mertens ME, Grimm J, Lammers T. Nanoparticles for imaging: Top or flop? Radiology 2014 Oct;273(1):10–28.
3. Zhukova Y, Hiepen C, Knaus P, et al. The role of titanium surface nanostructuring on preosteoblast morphology, adhesion, and migration. Adv Healthc Mater 2017 Aug;6(15).
4. Dolatshahi-Pirouz A, Jensen T, Kraft DC, et al. Fibronectin adsorption, cell adhesion, and proliferation on nanostructured tantalum surfaces. ACS Nano 2010 May 25;4(5):2874–82.

5. Nguyen AT, Sathe SR, Yim EK. From nano to micro: Topographical scale and its impact on cell adhesion, morphology and contact guidance. J Phys Condens Matter 2016 May 11;28(18):183001.
6. Sousa MP, Caridade SG, Mano JF. Control of cell alignment and morphology by redesigning ECM-mimetic nanotopography on multilayer membranes. Adv Healthc Mater 2017 Aug;6(15).
7. Wu KC, Tseng CL, Wu CC, et al. Nanotechnology in the regulation of stem cell behavior. Sci Technol Adv Mater 2013 Oct 11;14(5):054401.
8. Liang EI, Mah EJ, Yee AF, Digman MA. Correlation of focal adhesion assembly and disassembly with cell migration on nanotopography. Integr Biol (Camb) 2017 Feb 20;9(2):145–55.
9. Guo Z, Jiang N, Chen C, Zhu S, Zhang L, Li Y. Surface bioactivation through the nanostructured layer on titanium modified by facile HPT treatment. Sci Rep 2017 Jun 23;7(1):4155.
10. Vercellino M, Ceccarelli G, Cristofaro F, et al. Nanostructured TiO2 surfaces promote human bone marrow mesenchymal stem cells differentiation to osteoblasts. Nanomaterials (Basel) 2016 Jun 24;6(7). pii: E124.
11. Guduru D, Niepel M, Vogel J, Groth T. Nanostructured material surfaces--preparation, effect on cellular behavior, and potential biomedical applications: A review. Int J Artif Organs 2011 Oct;34(10):963–85.
12. Limongi T, Tirinato L, Pagliari F, et al. Fabrication and applications of micro/nanostructured devices for tissue engineering. Nano-Micro Lett 2017;9:1.
13. Green DW, Ben-Nissan B, Yoon KS, Milthorpe B. Jung HS. Bioinspired materials for regenerative medicine: Going beyond the human archetypes. J Mater Chem B 2016;4:2396.
14. Hasan J, Jain S, Chatterjee K. Nanoscale topography on black titanium imparts multi-biofunctional properties for orthopedic applications. Sci Rep 2017 Jan 23;7:41118.
15. Dalby MJ. Nanostructured surfaces: Cell engineering and cell biology. Nanomedicine (Lond) 2009 Apr;4(3):247–8.
16. Dalby MJ, Gadegaard N, Tare R, et al. The control of human mesenchymal cell differentiation using nanoscale symmetry and disorder. Nat Mater 2007 Dec;6(12):997–1003.
17. Andreu V, Mendoza G, Arruebo M, Irusta S. Smart dressings based on nanostructured fibers containing natural origin antimicrobial, anti-inflammatory, and regenerative compounds. Materials (Basel) 2015 Aug 11;8(8):5154–93.
18. Zahedia P, Rezaeiana I, Ranaei-Siadatb SO, Jafaria SH, andSupaphol P. A review on wound dressings with an emphasis on electrospunnanofibrous polymeric bandages. Polym Adv Technol 2010;21(2):77–95.
19. Wang S, Wang H, Jiao J, et al. Three-dimensional nanostructured substrates toward efficient capture of circulating tumor cells. Angew Chem Int Ed Engl 2009;48(47):8970–3.
20. Liu X, Chen L, Liu H, et al. Bio-inspired soft polystyrene nanotube substrate for rapid and highly efficient breast cancer-cell capture. NPG Asia Materials 2013;5;e63.
21. Guida P, Lo Savio R, Potrich C, et al. Enhancing miRNAs capture on polydimethylsiloxane surface with nanostructuration. J Nanomed Nanotechnol.2017;8(2):1–5.
22. Angeli E, Mussi V, Fanzio P, et al. Micro and nanofluidic platforms for advanced diagnostics. Edorium J Nanotechnol 2014;1:1–7.
23. Fanzio P, Manneschi C, Angeli E, et al. Modulating DNA translocation by a controlled deformation of a PDMS nanochannel device. Sci Rep 2012;2:791.
24. Cao Y, Zhang J, Yang Y, Huang Z, Long NV, Fu C. Engineering of SERS substrates based on noble metal nanomaterials for chemical and biomedical applications. Applied Spectroscopy Reviews 2015;50(6):499–525.
25. Zhang S, Tian X, Yin J, et al. Rapid, controllable growth of silver nanostructured surface-enhanced Raman scattering substrates for red blood cell detection. Sci Rep 2016 Apr 20;6:24503.
26. Yang YC, Huang TK, Chen YL, et al. Electrochemical growth of gold nanostructures for surface-enhanced Raman scattering. J Phys Chem C 2011;115(5):1932–9.
27. Lee BS, Lin DZ, Yen TJ. A Low-cost, highly-stable surface enhanced Raman scattering substrate by Si nanowire arrays decorated with Au nanoparticles and au backplate. Scientific Reports 2017;7(1):4604.
28. Convertino A, Cuscunà M, Martelli F, Manera MG, Rella R. Silica nanowires decorated with metal nanoparticles for refractive index sensors: Three-dimensional metal arrays and light trapping at plasmonic resonances. J Phys Chem C 2013;118(1):685–90.
29. Convertino A, Mussi V, Maiolo L. Disordered array of Au covered Silicon nanowires for SERS biosensing combined with electrochemical detection. Sci Rep 2016 Apr 26;6:25099.
30. Lee H, Lee Y, Song C, et al. An endoscope with integrated transparent bioelectronics and theranostic nanoparticles for colon cancer treatment. Nat Commun 2015 Nov 30;6:10059.
31. Chen J, Li X, Wu X, et al. Au-Silica nanowire nanohybrid as a hyperthermia agent for photothermal therapy in the near-infrared region. Langmuir 2014 Aug 12;30(31):9514–23.
32. Peng F, Su Y, Zhong Y, Fan C, Lee ST, He Y. Silicon nanomaterials platform for bioimaging, biosensing, and cancer therapy. Acc Chem Res 2014 Feb 18;47(2):612–23.
33. Convertino A, Mussi V, Maiolo L, Ledda M, Lolli MG, Fortunato G. Gold coated silicon nanowires for combined near-infrared photothermal treatment of cancer cells and Raman monitoring of the process evolution. Under publication.
34. Park GS, Kwon H, Kwak DW, et al. Full surface embedding of gold clusters on silicon nanowires for efficient capture and photothermal therapy of circulating tumor cells. Nano Lett 2012 Mar 14;12(3):1638–42.
35. Park J, Lee Y, Ha M, Cho S, Ko H. Micro/nanostructured surfaces for self-powered and multifunctional electronic skins. J Mater Chem B 2016;4(8):2999–3018.

36. Solovei D, Žák J, Majzlíková P, Sedlácek J, Hubálek J. Chemical sensor platform for non-invasive monitoring of activity and dehydration. Sensors (Basel) 2015 Jan 14;15(1):1479–95.
37. Liu Y, Pharr M, Salvatore GA. Lab-on-Skin: A review of flexible and stretchable electronics for wearable health monitoring. ACS Nano 2017 Oct 24;11(10):9614–35.

SUGGESTED READING

- AZoNano. Review of current concepts on convergence of nanotechnology with biology. AZojomo Journal of Materials online 2005. [Available at: https://www.azonano.com/article.aspx?ArticleID=1242]
- Ertorer E. Fabricating cost-effective nanostructures for biomedical applications. Electronic Thesis and dissertation repository. 1706. 2013. [Available at: http://ir.lib.uwo.ca/etd/1706]
- Fernandez-Fernandez A, Manchanda R, McGoron AJ. Theranostic applications of nanomaterials in cancer: Drug delivery, image-guided therapy and multifunctional platforms. Appl Biochem Biotechnol 2011;165(7–8):1628–51.
- Hasan J, Raj S, Yadav L, Chatterjee K. Engineering a nanostructured "super surface" with superhydrophobic and superkilling properties. RSC Adv 2015;5:44953–9.
- Krishnamoorthy S. Nanostructured sensors for biomedical applications: A current perspective. Current Opinion in Biotechnology 2015;34:118–24.
- Leszczak V, Smith BS, Popat KC. Hemocompatibility of polymeric nanostructured surfaces. J Biomater Sci Polym Ed 2013;24(13):1529–48.
- Leszczak V, Smith BS, Popat KC. Hemocompatibility of polymeric nanostructured surfaces. PNAS 2015;112(47):14444–51.
- Malsch I. Biomedical applications of nanotechnology. The Industrial Physicist 2002. [Available at: https://bwn.ece.gatech.edu/nanos/papers/biomedical%20applications%20of%20nanotechnology.pdf]
- Martins GV, Mano JF, Alves NM. Dual responsive nanostructured surfaces for biomedical applications. Langmuir 2011;27:8415–23.
- Mpoyi EN, Cantini M, Reynolds PM, Gadegaard N, Dalby MJ, Salmero´n-Sa´nchez M. Protein adsorption as a key mediator in the nanotopographical control of cell behavior. ACS Nano 2016;10:6638–47.
- Ramos AP, Cruz MAE, Tovani CB. Ciancaglini P. Biomedical applications of nanotechnology. Biophys Rev 2017;9:79–89.
- Shi H, Tsai WB, Garrison MD, Ferrari S, Ratner BD. Template-imprinted nanostructured surfaces for protein recognition. Nature 1999;398:593–7.
- Sortino S. Light-Responsive Nanostructured Systems for Applications in Nanomedicine. Series Title: Topics in Current Chemistry; Series Volume: 370. Switzerland: Springer International Publishing; 2016.
- Srichan C, Ekpanyapong M, Horprathum M, et al. Highly-sensitive surface-enhanced Raman spectroscopy (SERS)-based chemical sensor using 3D graphene foam decorated with silver nanoparticles as SERS substrate. Scientific Reports 2016;6:23733.
- Strnad G, Petrovan C, Russu O, Jakab-Farkas L. TiO2 nanostructured surfaces for biomedical applications developed by electrochemical anodization. IOP Conf. Ser.: Mater Sci Eng 2016;161:012051.
- Tibbitta MW, Rodellb CB, Burdick JA, Ansethc KS. Progress in material design for biomedical applications. Appl Biochem Biotechnol 2011;165(7–8):1628–51.
- Tripathy A, Sen P, Suc B, Brisco WH. Natural and bioinspired nanostructured bactericidal surfaces. Advances in Colloid and Interface Science 2017;248:85–104.

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Valentina Mussi – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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Author declares no conflict of interest.

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