Toward chemical communication between nanodevices

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ABSTRACT: Although many nanodevices have been described in recent years, nanoparticles capable of communicating with each other have been barely reported. Traditional communication technologies cannot be applied on the nanoscale, but a potential approach to achieve this goal is to mimic how nature communicates by exchanging information using molecules. Based on these concepts, some examples using DNA, enzymes and small molecules for information processing, nanoparticles capable of modulating chemical communication between cells and nanoparticles that can communicate with each another have been reported. Communication between nanodevices may find applications in different areas and a number of future new results are envisioned in this research field.

Ever since Richard Feynman gave his famous lecture "There's plenty of Room at the Bottom" in 1959 [1], significant advances in the nanotechnology field have been made. Nanotechnology is a highly multidisciplinary field with a steadily growing number of applications in different areas, such as medicine [2] electronics [3], chemistry [4] and computing [5]. Nanotechnologists work on developing devices that range from one to a few hundred nanometers capable of performing certain tasks, with examples such as nanomemories [6], nanobatteries [7], nanocarriers [8] and nanomotors [9] already having been developed. To date, these nanomachines have been studied mainly as single isolated units, and relatively very few examples are available in which human-made nanoconstructs communicate with one another. However, this is an appealing research field, and communication or interconnection between nanosystems is expected to lead to a number of new and advanced functionalities [10].

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Communication has become essential to human technology, but has barely been studied on the nanoscale. However, traditional communication technologies cannot be applied nanometrically as transmitters and receivers are still too big to fit on a nanoparticle. In line with this, the development of technologies to communicate nanodevices requires new ideas and concepts that can be applied on the nanoscale. Such technologies should employ components that can be easily incorporated into nanoparticles and to provide communication with minimum energy use. In this scenario, a potential approach to establish communication at the nanometric level is to mimic how nature communicates. In fact, a number of biological processes are governed by communication between cells. This form of communication, also called molecular communication, consists in information exchange using molecules. Thus neurons propagate information by means of neurotransmitter molecules [11]. For instance, acetylcholine is released from synaptic vesicles and is recognized by cholinergic receptors on muscle cells, which triggers muscle contraction. In the pancreas, β-cells respond to high levels of glucose and secret insulin, which travels through the blood to receptors on distant cells [12]. Activation of enzymes and vital processes, such as digestion, respiration and sleep, are regulated by hormones and other molecules that provide communication between organs [13]. Pheromones are used by bacteria and insects like ants to communicate with members of their community [14]. Unlike the systems used in telecommunication or computer engineering, it is feasible to integrate molecular communication into nanodevices and their power consumption is expected to be very low compared to traditional telecommunication technologies. However, there are still many open questions that need to be solved in the future; for example, which molecules are to be used to encode information?; how can these molecules be recognized by different nano-objects?; how is this recognition transformed into information propagation? Answering these issues is no trivial task.

In communication theory terms, communication can be defined as the process of establishing a connection between two points. At one point of the communication process, there is the sender, which/who receives a stimulus to send a message across. The sender transforms information into a code and transmits the message through a suitable medium. The receiver perceives the message and decodes it. Communication is considered effective if it finally results in a desired result, response or reaction.

Some groups have already reported stimulating advances by using biomolecules for information processing with the potential of being incorporated into inter-nanodevice communication. As in digital circuits, where signals are processed with AND, OR and NOT logic gates, Winfree and co-workers constructed logic gates using different DNA strands as inputs

and outputs [15]. Based on a mechanism of sequence recognition and strand displacement, one strand (or more) was able to recognize input strands and to release other output strands. Moreover, the output strand could serve as input for another logic gate or could produce an output fluorescent signal after displacement. Following these principles, complex networks have been constructed using DNA strand displacement cascades [16]. Enzymes have also been employed to mimic logic gates and enzymatic communication cascades [17]. Such ensembles rely on specific enzyme-substrate recognition, the generation of new products that can serve as inputs for other enzymes in the network, and the regulatory effects of cofactors and inhibitors. For instance, Katz et al. reported a network of three concatenated AND logic gates based on three enzymes (invertase, glucose oxidase and catalase) and three enzymatic reactions, which finally resulted in the formation of a colored product as an output signal [18]. Willner and co-workers constructed a hybrid system in which DNA scaffolds served to assemble enzymatic cascades [19]. Synthetic chemical systems [20] and gold nanoparticles [21] capable of transforming a combination of chemical signals into fluorescence and color changes have also been reported.

Interestingly, researchers have also recently started to explore how to program and modulate chemical communication between cells. Basu et al. reported the use of genetically modified 'sender' cells that secreted the chemical acyl-homoserine lactone, which induced 'receiver' cells to form ring-like patterns of differentiation [22]. Payne and co-workers reported having prepared gelatin-alginate beads to entrap 'sender cells', which synthesized and secreted a specific chemical that was taken up by E. Coli, inducing the synthesis of a fluorescent protein [23]. Others authors have reported using phospholipid vesicles that contained a DNA template, transcription-translation machinery and isopropyl β-D-1-thiogalactopyranoside (IPTG) to transform the presence of certain chemicals in communication with bacteria. In the presence of theophylline, the synthesis of a pore-forming protein in vesicles was activated, which led to the release of IPTG. In turn, this IPTG was detected by E. Coli that produced a fluorescent protein and closed the transduction loop [24]. Recently, the same group reported engineered vesicles capable of mediating communication between two different strains of bacteria. Signaling molecules secreted by the first bacterium induced the synthesis and release of a chemical from the vesicles, which induced the production of green fluorescent protein in the second bacterium [25].

However, communication between abiotic nanoparticles has practically not been explored. In this field, Martínez-Máñez and co-workers proposed a communicating system based on three different gated mesoporous silica nanoparticles that exchanged chemical

messengers [26]. A communication cascade was triggered by the enzyme pancreatin, which hydrolyzed the oligosaccharide cap of a first nanoparticle (NP-A) to result in the delivery of reductor (tris(2-carboxyethyl)phosphine, TCEP). TCEP cleaved a disulfide bridge uncapping a second nanoparticle (NP-B) and inducing the delivery of a surfactant (dodecyltrimethylammonium bromide), which finally disrupted the lipid bilayer of a third nanoparticle (NP-C) which, in turn, resulted in the delivery of a dye (safranin O). In this communication system, delivery from the third NP-C nanoparticle is governed by an input into NP-A and by a cascade communication between nanoparticles using two chemical messengers. In communication theory terms, this is a linear model of communication, and the message flows in a straight line from the sender (NP-A) to the receiver (NP-C) by using intermediate nanoparticles (NP-B) that works as both the receiver and sender.

More recently, we reported a communicating system based on enzyme-functionalized Janus gold-gated mesoporous silica nanoparticles that mimics an interactive model of communication in which the sender sends a message to the receiver, and the receiver then channels a message back to the original sender. [27] Janus nanoparticles consisted of mesoporous silica nanoparticles covalently anchored to a gold nanoparticle. In this case, a first nanoparticle (JNP-A) was functionalized with the enzyme β-galactosidase on the gold nanoparticle and the mesoporous face was loaded with a dye and capped with β-cyclodextrin (β-CD) attached to the silica surface through disulfide bonds. In a second nanoparticle (JNP-B) the mesoporous part was loaded with a reducing agent (N-acetyl-L-cysteine) and capped with a pH-responsive supramolecular nanovalve, whereas the gold side was functionalized with glucose oxidase. The communication process was triggered upon the addition of lactose. Lactose was hydrolyzed by β-galactosidase on JNP-A and the generated glucose (the first chemical messenger) diffused to JNP-B, where glucose oxidase transformed glucose into gluconic acid. This results in lowering the local pH, which produced the uncapping of the supramolecular nanovalve delivering the entrapped N-acetyl-L-cysteine (the second chemical messenger), which diffused as feedback toward JNP-A. N-acetyl-L-cysteine, induced the rupture of the disulfide linkages on the mesoporous face of JNP-B and the release of the entrapped dye. Cargo delivery from the first nanoparticle was observed only after biunivocal communication with the second nanoparticle. In this case communication was mediated by two enzymatic processes and the exchange of two chemical messengers. These examples rely on the use of mesoporous silica, which has interesting properties, such as a high loading capacity, chemical stability and the possibility of functionalization with molecular gates that control the release of a cargo when an external stimulus is applied. The gold part in the Janus

particles allows a single nanodevice to have two different surfaces. Notwithstanding, we believe that the properties of other materials, such as metallic or polymeric nanoparticles, could be used to develop different communication protocols.

Communication between nanodevices will allow nanoparticles to cooperate, share information and perform advanced tasks. New communication paradigms are expected to be developed in the near future and applications in a number of different areas are also expected. For instance, the design of nanoparticles capable of working cooperatively to enhance the delivery of drugs is envisioned. In this scenario, Bathia and coworkers have already provided an example of how tumor-targeted gold nanorods triggered a coagulation cascade, which increased the uptake of drug-loaded liposomes by the tumor and, therefore, enhanced treatment efficiency [28]. From another point of view, different nanoparticles can act as nano-containers capable of delivering a certain cargo on-command and of inducing the *in situ* synthesis of certain compounds of interest. In this field, Willner and co-workers have shown that certain chemicals loaded in mesoporous silica nanoparticles can be accurately delivered when selected stimuli are applied, and react between them to yield new molecules [29]. Another potential application could be the detection of low levels of target analytes by amplifying the signal through a cascade communication process with other nanoparticles. More advanced cooperative systems can also be envisioned in these fields (nanomedicine, *in situ* synthesis, sensing and others), in which circulating sensing nanoparticles collect information and transmit its information to static nanodevices that could emit an output signal or communicate to other actuating nanomachines. Although there is still a long way to go until these futuristic applications become a reality, and the described communication systems on the nanoscale are still far from complex, the design of new communication paradigms is envisioned to have a great impact in the chemical community.

In communication terms, on the nanoscale new advances in the knowledge of how the recognition of individual molecules (via chemical or biochemical reactions) can be used to encode information, and how this information can propagate, will require the collaboration of researchers from different fields. Moreover, the concept of creating communication between nanodevices embraces an enormous potential to prepare new and more advanced cooperative nanoscale systems whose response is governed by communication processes between individual nanoparticles. Inspired by how biological and humans communicate, the development of such systems will open up new directions in different areas and a number of new advances are envisioned in the near future.

Acknowledgements

References

[1]   R. P. Feynman, Caltech Eng. Sci. 23 (1960) 22-36.
[2]   J. Shi, A. R. Votruba, O. C. Farokhzad, R. Langer, Nano Letters 10 (2010), 3223-3230.
[3]   W. Lu, C. M. Lieber, Nat. Mater. 6 (2007) 841-850.
[4]   E. C. Dreaden, A. M. Alkilany, X. Huang, C. J. Murphy, M. A. El-Sayed, Chem. Soc. Rev. 41 (2012) 2740-277.
[5]   D. S. Markovic, D. Zivkovic, D. Cvetkovic, R. Popovic, Renew. Sust. Energ. Rev. 16 (2012) 2966-2972.
[6]   R. Tseng, J. Huang, J. Ouyang, R. Kaner, Y. Yang, Nano Lett. 5 (2005) 1077-1080.
[7]   I. Valov, E. Linn, S. Tappertzhofen, S. Schmelzer, J. van den Hurk, F. Lentz, R. Waser, Nat. Commun. 4 (2013). DOI: 10.1038/ncomms2784.
[8]   E. Aznar, M. Oroval, L. Pascual, J. R. Murguía, R. Martínez-Máñez, F. Sancenón, Chem. Rev. 116 (2016) 561-718.
[9]   T. Kline, W. Paxton, Angew. Chem. Int. Ed. 44 (2005) 744-746.
[10]   I. F. Akyildiz, F. Brunetti, C. Blázquez, Comput. Networks 52 (2008) 2260-2279.
[11]   K. M. Betke, C. A. Wells, H. E. Hamm, Prog. Neurobiol. 96 (2012) 304-321.
[12]   A. R. Saltiel, C. R. Kahn, Nature 414 (2001) 799-806.
[13]   K. G. Murphy, S. R. Bloom, Nature 444 (2006) 854-859.
[14]   R. Wirth, A. Muscholl, G. Wanner, G. Trends Microbiol. 4 (1996) 96-103.
[15]   G. Seelig, D. Soleveichik, D. Y. Zhang, E. Winfree, Science 314 (2006) 1585-1590.
[16]   L. Qian, E. Winfree, J. Bruck, Nature 475 (2011) 368–372.
[17]   E. Katz, V. Privman, Chem. Soc. Rev. 39 (2010) 1835-1837.
[18]   G. Strack, M. Ornatska, M. Pita, E. Katz, J. Am. Chem. Soc. 130 (2008) 4234-4235.
[19]   O. I. Wilner, Y. Weizmann, R. Gill, O. Lioubashevsky, R. Freeman, I. Willner, Nat. Nanotech. 4 (2009) 249-254.
[20]   A. P. de Silva, N. D. McClenaghan, Chem. Eur. J. 10 (2004) 574-586.
[21]   D. Liu, W. Chen, K. Sun, K. Deng, W. Zhang, Z. Wang, X. Jiang, Angew. Chem. Int. Ed. 50, (2011) 4103-4107.
[22]   S. Basu, Y. Gerchman, C. H. Collins, F. H. Arnold, R. Weiss, Nature 434 (2005) 1130-1135.
[23]   Y. Liu, H.-S. Wu, M. Chhuan, J. L. Terrel, C.-Y. Tsao, W. E. Bentley, G. F. Payne, ACS Biomater. Sci. Eng. 1 (2015) 320-328.
[24]   R. Lentini, S. Pérez Santero, F. Chizzolini, D. Cecchi, J. Fontana, M, Marchioretto, C. Del Bianco, J. L. Terrel, A. C. Spencer, L. Martini, M. Forlin, M. Assafalg, M. Dalla Serra, W. E. Bentley, Nat. Commun. 5 (2014). DOI: 10.1038/ncomms5012.
[25]   R. Lentini, N. Y. Martín M. Forlin, L. Belmonte, J. Fontana, M. Cornella, L. Martini, S. Tamburini, W. E. Bentley, O. Jousson, S. S. Mansy, ACS Cent. Sci. (2017) 117-123.
[26]   C. Giménez, E. Climent, E. Aznar, R. Martínez-Máñez, F. Sancenón, M. D. Marcos, P. Amorós, K. Rurack, Angew. Chem. Int. Ed. 53 (2014) 12629-12633.
[27]   A. Llopis-Lorente, P. Díez, A. Sánchez, M. D. Marcos, F. Sancenón, P. Martínez-Ruíz, R. Villalonga, R. Martínez-Mañez, Nat. Commun. 8 (2017). DOI: 10.1038/ncomms15511.

[28]   G. von Maltzahn, J.-H. Park, K. Y. Lin, N. Singh, C. Schwöppe, R. Mesters, W. E. Berdel, E. Ruoslahti, M. J. Sailor, S. N. Bhatia, Nat. Mat. 10 (2011) 545-552.

[29]   D. Balogh, M. A. Alemán-García, H. Bauke-Albada, I. Willner, Angew. Chem. Int. Ed. 54 (2015) 11652-11656.

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