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Can nanosensors detect a nanopathology?

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Antonietta M Gatti
Nanodiagnostics Foundation, Italy

Correspondence: Gatti AM, Nanodiagnostics Foundation, Via E.Fermi 1/L, San Vito 41057, Italy, Email gatt@nanodiagnostics.it

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Introduction

Nanopathology is a word I invented in 2002 to connote a new European Project I proposed and coordinated, working (QOL-147-2002) with the University of Cambridge (UK), the University of Mainz (D), Fei Company (I) and Biomatech (F).[1,2] At that time, the word meant that Nanopathology is "the branch of learning that deals with how the organism reacts to the presence of micro- and nano-particles". That was a somewhat void concept, since, although we obviously knew that the organism reacts to the presence of those foreign bodies (and, in any case to the presence of anybody foreign to the organism), we did not know what "diseases" were actually related with this pathogenic agent. Some of my research, up to that moment conducted in an unsystematic way, made me suspect that the increasingly ubiquitous inorganic nanoparticles could trigger diseases as viruses, bacteria or parasites do. The first insights came when I dealt with a so-called cryptogenic granulomatosis and a case of leukemia that struck an Italian soldier who had served in a peace-keeping mission in the Balkans in 1998. In both cases I applied an innovative technique of Scanning Electron Microscopy (SEM). In the former instance, on the histological sections of the liver and the kidney, while in the second case I analysed the slide where the blood had been smeared. As a matter of fact, I analysed the same samples as those studied by the histopathologist who had issued the diagnosis.

In both cases, I found particles that were obviously foreign to the subject's body, whose presence and chemical composition needed a reasonable explanation. More in particular, in the first case, I found ceramic particles (Aluminium-silicate) smaller than 5 microns, while in the second I found submicronic metallic debris. At that time, my main research work was to identify biomaterials, i.e., materials the body does not reject or, in the best circumstances, accepts without putting in place adverse reactions. Among them, I studied the biocompatibility of materials to be used to make orthopaedic, vascular and heart prostheses. Inorganic bulk materials can be tolerated by the human body once in contact with body tissues, but, in the long run, they can be rejected or they can break, so they must be replaced, provided that is still possible. A well-known example is that of breast prostheses that after a certain time had to be replaced because of the painful body reaction due to the growth of a fibrotic capsule around the prosthesis.

At that time, I worked not only on the physical-chemical properties of the material to be implanted but also on biomimetic coatings to apply in order to suppress or mitigate the body reaction. However much a material can be improved, the fact remains that it can never be recognized as unconditionally acceptable by the human body. At that time, we all dealt with bulk materials, but very little could be said about dust and, more particularly, dust with a very small particle size (micro- and nano-particulate matter). One of the certainties we had from experience was that the very small wear fragments of the orthopedic prostheses induce granulomatosis.

Nanoparticles (NPs) were already being synthesized, and we spoke of buckyballs and quantum dots, but these materials were confined to high-tech laboratories. Some news had already reached the general public, if only because Prof. Richard Smalley of the Rice University was awarded with a Nobel Prize for his research on fullerene together with Professors Curl and Kroto.[3] Then, the discovery looked promising to solve a number of technological problems. But, when the October 28, 2005, Prof. Smalley died of leukaemia and lung cancer simultaneously, pathologies that he himself attributed to the materials with which he had conducted his experiments, I felt that the new studies undertaken with the EU project were going in the right direction (2002-05), as the fullerene dust he had inhaled without any efficient protection while creating these new nanosized materials could have been the trigger of some "bad biological reactions". In short, exactly what I was investigating.

My first EU project called Nanopathology (The role of NPs in material-induced pathologies) and the one that followed it, called DIPNA (Development of an integrated platform for nanoparticle analysis to verify their possible toxicity and the eco-toxicity),[4] a project of nanotoxicology with which we followed the particles through organs and tissues and simulated their access into cells, verified the impact that engineered and incidental nanoparticles could have on the human life.

In the years 2009-13, with another national Italian project of nano-eco-toxicology called INESE, sponsored by the Italian Institute of Toxicology (2009-13), we demonstrated also the impact of nanoparticles on vegetables and small animals (worms, zebra fish, sea urchins), finding similar adverse reactions, among which, embryo and foetal malformations.[5–7]

The projects showed the possibility to detect the nanoparticles not only when trapped in biological tissues, but also when dispersed in the body liquids, in addition to the blood on which we had already carried out many tests: seminal and cerebrospinal fluid, saliva and tears.[8,9] The possibility to use an X-ray Microprobe of an Energy Dispersive Spectroscope (EDS) equipping the Scanning Electron Microscope gives the possibility to analyse the chemical, elemental composition of the nanoparticles identified.

This type of data is particularly important, as it allows nanopathology experts to trace the source of the pollution responsible for the disease. This allows effective action, for example, by removing the subject from the polluting source. We found, especially in primary cancers, accumulations of nanoparticles in the interfacial zone between the cancer and the healthy tissue.[1,9] The analyses of more

than 3,000 cases of cancer affecting different parts of the body had us suppose that, if a nanosized entity enters the cell, it can interact with the mitochondria, impairing their function of "cellular respiration" and, while researching on the effects of Cerium oxide particles, we saw their deformation.[10] In most cases, we found debris containing metals like Iron, Chromium, Nickel (the three of them often alloyed as stainless steel), Aluminium, Tungsten, Titanium, Uranium, etc., and new types of unknown alloys.[11] We also came across ceramic materials like silica (SiO_2), zirconia (ZrO_2), and compounds like Barium sulphate and Calcium carbonate, while polymeric debris were hard to identify accurately with our equipment because their elemental composition is the same as the biological substrate. Nevertheless, we could detect polyvinyl-chloride, polysulphone and silicones.

At this point, it should be clarified that the body reacts to any foreign body, and this, at least largely, regardless of their composition. In short, it is in any case something that the body does not accept. Simplifying as much as possible, it is as if it were a bullet hitting the heart: what its chemical composition is indifferent. The reaction is particularly critical when the foreign body is not degradable, which is common when dealing with inorganic compositions such as, for example, metal alloys, often not listed in any materials manual, which are formed, for example, with the incineration of waste or with cases of explosions of weapons. When they do not enter a cell but stay in the extracellular territory, these foreign bodies remain forever wrapped in inflammatory tissue created by the body to isolate them, and chronic inflammation becomes the trigger for a variety of diseases. As for the dimensions, generally, the smaller they are, the greater the possibility of foreign bodies to penetrate the tissues. Obviously, to be able to penetrate cells, they must be small enough. As regards the shape, but only as regards what happens in the extracellular space, needle-like particles such as, for example, those of asbestos, manage to move and penetrate more easily than it is for particles with different shapes (e.g., spherical). Be that as it may, the path of the particle has an end, where it is wrapped in a granulation tissue or, in the case of nano-size, it can be hosted by a cell. NPs are not recognized by the cell membrane sensors, so they are internalized through a phagocitosis mechanism and can invade the intracellular matrix. It is a known fact that the cell's own defense mechanisms are weakened or canceled in the presence of NPs.[12–14]

We have also observed that during mitosis, when the nuclear membrane disappears, there is the possibility to have a direct contact of the NPs with the DNA. That can involve a damage that can be heritable.[15,16] This mechanism of free entrance is what occurs with the introduction of new vaccines that use as a sort of Trojan horse nanoliposomes that, once inside the cytoplasm, release the spike protein.

Probably, the main problem with nanopathologies is that medical doctors cannot diagnose them, since, generally, medical school programs do not include this type of subject. They know that some foreign bodies, if inhaled, can induce diseases like pneumoconioses or problems caused by the urban pollution, and the WHO estimated that every year 7Million people/year die a premature death due to environmental pollution.[17] But the subject is much more complex and articulated, and, without adequate knowledge, it is inevitably difficult to implement suitable therapies.

A diagnostics problem is the lack of specific sensors. When the pathology is already expressed and the doctor removes part of the tissue affected, it is possible to prepare the sample for the FEGESEM investigation. In the case of leukaemia, a similar analysis can be performed on a blood sample,[18,19] but in other cases, especially those involving deep internal tissues, there is no possibility. As mentioned, micro- and NPs, no matter how entered in the body, can be carried by the bloody stream but, sooner or later, they are trapped in a tissue behaving like a sort of mechanical filter, and they can go directly inside the cells. This behaviour is driven by a probabilistic mechanism of entry, but the small size, the morphology, the surface electrical charge or the chemical composition can favour the process. At that stage, there is no more possibility to detect or get rid of them. Years ago, we verified the possibility to detect NPs by observing them through the eye, when they are still present in the blood circulation.

At experimental level, we developed a Diffuse Correlation Spectroscope that, through a laser ray, checked the state of the ocular fundus and its blood vessels of a rabbit that had been injected with NPs. The preliminary results were encouraging, but the project was not financed, we could not find any investor, and the project was abandoned.[20] The conclusion is that, once the NPs have been captured and are hosted inside the cells, there is no actual possibility to locate them. With the necessary technical and economic means, nano-sensors can be designed to detect them in the blood circulation. Of course, detecting foreign bodies does not mean diagnosing a nanopathology but simply identifying something that may be the origin of the disease. Perhaps, in the future, it will be possible to have molecular sensors with, for instance, bioluminescent, fluorescent or piezoelectric properties, capable of detecting particles inside cells. But we must be certain that the molecules used as sensors do not interact in any adverse way with the cells and do not even constitute the trigger of pathological situations. In short, we must use all the necessary prudence. What we can do today is to use the electron microscopy technique briefly described above, looking at explanted tissue and body fluids. While waiting for more refined technology, this allows in many cases to distance the patient from the source of the pathology and to build up an important database for the knowledge of nanopathologies.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest exists.

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