Nanotechnology Research: Applications in Nutritional Sciences[1,2]

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Abstract

The tantalizing potential of nanotechnology is to fabricate and combine nanoscale approaches and building blocks to make useful tools and, ultimately, interventions for medical science, including nutritional science, at the scale of ~1–100 nm. In the past few years, tools and techniques that facilitate studies and interventions in the nanoscale range have become widely available and have drawn widespread attention. Recently, investigators in the food and nutrition sciences have been applying the tools of nanotechnology in their research. The Experimental Biology 2009 symposium entitled "Nanotechnology Research: Applications in Nutritional Sciences" was organized to highlight emerging applications of nanotechnology to the food and nutrition sciences, as well as to suggest ways for further integration of these emerging technologies into nutrition research. Speakers focused on topics that included the problems and possibilities of introducing nanoparticles in clinical or nutrition settings, nanotechnology applications for increasing bioavailability of bioactive food components in new food products, nanotechnology opportunities in food science, as well as emerging safety and regulatory issues in this area, and the basic research applications such as the use of quantum dots to visualize cellular processes and protein-protein interactions. The session highlighted several emerging areas of potential utility in nutrition research. Nutrition scientists are encouraged to leverage ongoing efforts in nanomedicine through collaborations. These efforts could facilitate exploration of previously inaccessible cellular compartments and intracellular pathways and thus uncover strategies for new prevention and therapeutic modalities. J. Nutr. 140: 119–124, 2010.

Introduction

"Nanotechnology" is the creation of functional materials, devices, and systems through the manipulation of matter at a length scale of ~1–100 nm. At such a scale, novel properties and functions occur because of size (1). This emerging field is becoming important in enabling breakthroughs of new and effective tools in the medical sciences (e.g. nanomedicine), because it offers the possibility of examining biological processes in ways that were not previously possible. The medical use of nanotechnology includes the development of nanoparticles for diagnostic and screening purposes (i.e. early detection of cancer), development of artificial cellular proteins such as receptors, DNA and protein sequencing using nanopores and nanosprays, the manufacture of unique drug (and nutrient) delivery systems, as well as gene therapy and tissue engineering

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applications (2). Nanotechnology offers a range of tools capable of monitoring individual cells at the level of individual molecules. It enables researchers to investigate and monitor cellular and molecular function and to alter systems that are deregulated in disease. It is conceivable that nanomachines with the ability to circulate through the bloodstream, kill microbes, supply oxygen to hypoxic organs, or undo tissue damage could one day be delivered to the human body through medicines or even foods. There are challenges with the emergence of nanomedicine that include issues related to toxicity and the environmental impact of nanoscale materials. The social, ethical, legal, and cultural implications of nanotechnology must also be considered.

In nutrition research, nanotechnology applications may assist with obtaining accurate spatial information about the location of a nutrient or bioactive food component in a tissue, cell, or cellular component. Ultrasensitive detection of nutrients and metabolites, as well as increasing an understanding of nutrient and biomolecular interactions in specific tissues, has become possible. In theory, such new technologies have the potential to improve nutritional assessment and measures of bioavailability. They may help to identify and characterize molecular targets of nutrient activity and biomarkers of effect, exposure, and susceptibility and therefore may also inform "personalized" nutrition. Specific applications of nanotechnology to date in food and nutrition include: modifying taste, color, and texture of foods; detection of food pathogens and spoilage microorganisms; enhancing nutrition quality of foods; and novel vehicles for nutrient delivery, as well as serving as a tool to enable further elucidation of nutrient metabolism and physiology (3–5). For example, one food technology application involves creating coatings for foods and food packaging that serve as barriers to bacteria or that contain additional nutrients (6).

Nutritional products claiming to use nanotechnology are currently available in the market. It is important to recognize that the potential toxicity of nutrients can be affected by a change in particle size [see (7) for current updates]. Furthermore, little is known about the absorption and excretion of nanoparticles by experimental animals or in humans. Thus, there are challenges with the application of nanoscale compared with microscale materials. These include higher exposure per unit mass; small size:large surface area ratio; different routes of exposure due to smaller size (i.e. dermal penetration); different distribution to tissues by virtue of their different size or surface coating, chemistry, or particle charge; and novel properties of a nanoscale material that may alter absorption, digestion, metabolism, or excretion in the body.

To highlight nanotechnology applications and challenges for nutrition research and to encourage collaboration between various disciplines with the aim of advancing food and nutrition research, a symposium was convened at Experimental Biology 2009 on the topic "Nanotechnology Research: Applications in Nutritional Sciences." This session presented various nanotechnology approaches for use in food and nutrition research. It also identified several safety/regulatory issues in nanotechnology, foods, and health. Experts focused on topics that included "Nanotechnology approaches for medical and nutrition research," presented by Martin A. Philbert, University of Michigan School of Public Health. He provided an overview to set the stage about the application of nanotechnology in research, particularly focusing on how nanotechnology will be used to guide new prevention and therapeutic strategies for nutrition scientists. "Quantum dot technologies for visualizing live cell dynamic signaling and ultra-sensitive protein detection" was presented by Tania Q. Vu, Oregon Health and Sciences University. She discussed the use of quantum dots (QD)[15] to visualize cellular processes. The 3rd presentation, focused on nanotechnology applications for increasing bioavailability of bioactive food components in new food products, was presented by Dr. Qingrong Huang, Rutgers University (entitled "Bioavailability and delivery of dietary factors using nanotechnology"). "Food, nutrition and nanotechnology research: challenges and promises" was presented by Jozef Kokini, University of Illinois. He provided a compendium of nanotechnology opportunities for food science as well as safety and regulatory issues. A panel comprised of individuals from various federal agencies discussed and emphasized research opportunities and challenges in nanotechnology, foods, and health. The sections that follow provide a synopsis of each of these topics as well as recommendations for future applications of nanotechnology research in the nutritional sciences.

Nanotechnology approaches for medical and nutrition research

Dr. Martin Philbert discussed the challenges and opportunities of nanotechnology applications in clinical and nutrition settings. The very properties of nanostructured materials that make them so attractive could potentially lead to unforeseen health or environmental hazards (8). Some of these properties include high aspect ratio, bio-persistence, reactive surfaces and points that are capable of producing reactive oxygen species, composition and solubility. Coating the nanoparticle with biocompatible materials, however, has been shown to significantly reduce toxicity in some applications. Dr. Philbert also encouraged the design of products and processes in nanotechnology that reduce or eliminate the use and generation of hazardous substances. The translation of much of the current research in nanotechnology into clinical practice will rely on solving challenges that relate to the toxicity of nanoparticles.

Examples from this presentation highlight both the promises/possibilities and problems of nanomedicine. Probes encapsulated by biologically localized embedding (PEBBLE)[15] are submicron optical sensors that have been designed for minimally invasive analyte monitoring in viable, single cells (8). PEBBLE nanosensors are composed of matrices of cross-linked polyacrylamide, cross-linked poly(decyl methacrylate), or sol-gel silica, which have been fabricated as sensors for H^+, Ca^{2+}, K^+, Na^+, Mg^{2+}, Zn^{2+}, Cu^{2+}, Cl^-, and some nonionic species (9). A number of techniques have been used to deliver PEBBLE nanosensors into mouse oocytes, rat alveolar macrophages, rat C6-glioma, and human neuroblastoma cells (9). Using gene gun injection as a delivery method, a sol gel-based PEBBLE nanosensor for reliable, real-time measurement of subcellular molecular oxygen was inserted into rat C6 glioma cells. The cells responded to differing oxygen concentrations and provided real-time intracellular oxygen analysis. The PEBBLE contained an oxygen-sensitive fluorescent indicator, Ru(II)-Tris(4,7-diphenyl-1,10-phenanthroline) chloride ($[Ru(dpp)_3]^{2+}$), and an oxygen-insensitive fluorescent dye, Oregon Green 488-dextran, as a reference for the purpose of ratiometric intensity measurements (10). The small size and inert matrix of these sensors allow them to be inserted into living cells with minimal physical and chemical perturbations to their biological functions. Compared

[15] Abbreviations used: NGF, nerve growth factor; NIFA, National Institute for Food and Agriculture; PEBBLE, probes encapsulated by biologically localized embedding; QD, quantum dot; TrkA, tyrosine kinase A.

with using free dyes for intracellular measurements, the PEBBLE matrix protects the fluorescent dyes from interference by proteins in cells, enabling reliable in vivo chemical analysis. The matrix significantly reduces the toxicity of the indicator and reference dyes to the cells so that a wide variety of dyes can be used in optimal fashion. Hence, the sol gel-based PEBBLE sensors are extremely useful for real-time intracellular measurements such as oxygen levels. It is conceivable that PEBBLE technology can be utilized to monitor nutrient metabolism, the effects of reactive oxygen species generation, and ion distributions.

A nanoimaging example highlights the current challenge of brain tumor surgery to achieve complete resection without damaging normal structures near the tumor. Achieving maximal resection currently relies on the neurosurgeon's ability to judge the presence of residual tumor during surgery (11). The use of fluorescent and visible dyes has been proposed as a means of visualizing tumor margins intraoperatively. Such investigations have been hampered by difficulties in achieving tumor specificity, achieving adequate visual contrast, and identifying a dye useful for a wide range of tumors. Dye-loaded nanoparticles may be able to meet these challenges (11). Nanoparticle-based magnetic resonance contrast agents have been demonstrated to be useful to visualize portions of tumor in the brain that would be unclear with conventional imaging techniques. Nanoparticle-based contrast agents with a core of iron oxide crystals with or without a shell of organic material, such as polyethylene glycol, have been designed for such purposes (11).

Challenges related to nanoparticle clearance and toxicity need to be overcome before nanoparticles can be used clinically. Also, a greater understanding of the relationship between toxicity and particle size, geometry, pharmacokinetics, and surface coating is required before nanoparticles should be used in clinical practice.

QD technologies for visualizing live cell dynamic signaling and ultra-sensitive protein detection

Dr. Tania Vu demonstrated how nanotechnology can offer new capabilities that allow investigators to probe the function of key molecules using multiple modalities at the scale of single molecules in live cells. QD allow investigators to examine activities that cannot normally be resolved under a microscope with conventional dyes and florescent labels. When excited by laser light, the QD nano crystals emit photons and shine more brightly and longer in duration than any conventional label. Dr. Vu presented 2 main QD-based technologies that her laboratory has developed to investigate cellular function: *1*) QD imaging probes for imaging protein trafficking and endocytic events in live cells; and 2) ultrasensitive QD assays for studying protein expression and specific protein-protein interactions in limited cell samples. Dr. Vu described tracking a protein within rat cells that regulates the growth of nerve tissue with the use the peptide ligand β nerve growth factor (NGF) conjugated to QD surfaces (12). The βNGF-QD were found to retain bioactivity, activate tyrosine kinase A (TrkA) receptors, and initiated downstream cellular signaling cascades to promote neuronal differentiation in PC12 cells. This example of receptor-initiated activity of QD-immobilized ligands has wide-ranging implications for the development of molecular tools and therapeutics targeted at understanding and regulating cell function. It is possible that QD may soon be used to visualize drugs or nutrients as they move in cells and cellular compartments in living systems.

QD hybrid gel blotting, which allows the purification and analysis of the action of QD bioconjugate-protein complexes in live cells, was also discussed. This is an alternative approach to PAGE-based Western blotting and immunoprecipitation (13). Interestingly, the protein interactions that are identified can also be correlated with spatial location in cells. Dr. Vu initially employed this technique to investigate the association of ligand NGF with the TrkA receptor in PC12 cells (14). It was found that NGF-QD could be retrieved and separated from a mixture of cellular lysate, NGF-QD were colocalized with an anti-TrkA receptor antibody, indicating TrkA −NGF-QD ligation, and discrete NGF-QD were bound to TrkA receptor puncta on the cell membrane surface. This novel nano-based technique has several advantages as a method for: *1*) identifying specific QD-protein interactions in cells; *2*) correlating QD-protein interactions with their spatial location in live cells; *3*) studying the size and composition of QD bioconjugate probes/complexes; and *4*) directly isolating and visualizing proteins from complex mixtures, offering an improvement over traditional bead-based immunoprecipitation methods (13).

These QD-based technologies offer investigators a means to probe specific inter-molecular interactions with significantly improved sensitivity and to relate these interactions with high-resolution in real time in live cells at the scale of single molecules. Nutrition researchers can adopt these QD-based technologies to examine questions of interest in nutrient metabolism and physiology.

Bioavailability and delivery of dietary factors using nanotechnology

Dr. Qingrong Huang described how the disease prevention properties of dietary supplements such as polyphenols have attracted much attention in recent years. Their biological effects include antioxidative, anticancer, and other properties that may prevent chronic disease as suggested by evidence from in vitro, animal, and human studies. Sales of the dietary supplements are high and growing annually. Thus, the development of high quality, stable dietary supplements with good bioavailability could become important. Although the use of dietary supplements in capsules and tablets is abundant, their effect is frequently diminished or even lost, because many of these compounds present solubility challenges. The major challenges of dietary polyphenols include their poor water solubility and oral bioavailability. Thus, novel delivery systems are needed to address these problems.

Dr. Huang presented a series of experiments integrating food processing, formulation, and in vivo/in vitro test development for the design of novel polyphenol nanocapsules, specifically for the water insoluble compounds curcumin, extracted from the turmeric plant (*Curcuma longa*), and dibenzoylmethane, a β-diketone analogue of curcumin. For example, high-speed and high-pressure homogenized oil-in-water emulsions using medium-chain triacylglycerols as oil and Tween 20 as emulsifier, were successfully prepared to encapsulate curcumin (15). These curcumin nanoemulsions were evaluated for antiinflammatory activity using a mouse ear inflammation model. An enhanced antiinflammatory activity was demonstrated (43 and 85% inhibition effect of 12-O-tetradecanoylphorbol-13-acetate-induced edema of mouse ear for 618.6 and 79.5 nm 1% curcumin oil-in-water emulsions, respectively), but a negligible effect was found for 1% curcumin in 10% Tween 20 water solution (15). Dr. Huang highlighted other recent in vivo biological and pharmacological experiments, which included a skin carcinogenesis model, measures of a series of proinflammatory biomarkers, and products that have demonstrated greatly improved antiinflammation activity and oral bioavailability of nanoencapsulated curcumin and dibenzoylmethane.

A wide variety of encapsulation platforms, including nanostructured emulsions, water-in-oil-in-water or oil-in-water-in-oil double emulsions, solid lipid or biopolymer-based nanoparticles, and direct conjugation of phytochemicals to biopolymer side chains have been developed to encapsulate food constituents for enhanced delivery and bioavailability (6,16). With the aid of nanoencapsulation, in vivo absorption and circulation of bioactive food components appear to increase, which should assist in achieving the desired concentration and biological activity of these compounds. Although an increase in nutrient intake from an enhanced food supply may be beneficial, food and nutrition professionals may need to monitor overconsumption and potential signs of toxicity more closely. Additionally, micronutrient imbalances may become more prevalent and drug-nutrient interactions will also require careful observation (5). Thus, a greater understanding of the metabolic consequences of nutrients in novel food systems are required as nanotechnology applications expand in the food sciences.

Food, nutrition, and nanotechnology research: challenges and promises

Dr. Josef Kokini described the opportunities for nanotechnology applications to foods and agriculture, including nanomaterials in food packaging, food protein-based nanotubes to bind vitamins or enzymes, and rapid sampling of biological and chemical contaminants using nanocantilevers as detection tools for water and food safety. Nanotechnology has the potential to transform the entire food industry by changing the way food is produced, processed, packaged, transported, and consumed. Applications in food packaging are very promising, because they can improve the safety and quality of food products (17). The use of bionanocomposites for food packaging not only has the potential to protect the food and increase its shelf life but can also be considered more environmentally friendly, because such composites would reduce the requirement to use plastics as packaging materials, thus decreasing environmental pollution in addition to consuming less fossil fuel for their production (17). Zein, a prolamin and the major protein found in corn, has been an important material in science and industry because of its distinctive properties and molecular structure. Novel approaches are expected to yield new applications for zein in the foods and biodegradable plastics industry. After solvent treatment, zein can form a tubular structure meshwork that is inert and resistant to microbes (17). Zein nanoparticles have been synthesized and examined as edible carriers of flavor compounds, for nanoencapsulation of dietary supplements, as well as to improve the strength of plastic and bioactive food packaging. Importantly, controlling the uniformity and organization of zein films at the nanolevel is critical for its mechanical and tensile properties. Dr. Kokini et al. (18) tested different solvents and found that zein films that were generated in acetic acid were smoother and structurally more homogeneous than those produced using ethanol. Other investigators are examining the use of silicates to strengthen zein films.

Novel nanosensors are being tested to detect food pathogens. Array techniques with thousands of nanoparticles on a platform have been designed to fluoresce in different colors on contact with food pathogens. Furthermore, intelligent packaging with nanosensors is being considered that has the ability to react to the environment and perhaps interact with the food product with specific applications. One application might be to detect food spoilage.

The challenges for the application of nanotechnology in food and food science were also described. Because of their increased surface area, nanomaterials might have toxic effects in the body that are not apparent in bulk materials. Extensive use of nanoparticles in foods as additives is less likely in the near future because of possible safety concerns. Although nanomaterials from food packaging would not ordinarily be ingested or inhaled, the potential exists for unforeseen risk, such as release of airborne nanoparticles that might aggravate lung function or inadvertent consumption due to leakage of packaging materials into foods. The U.S. FDA requires that manufacturers demonstrate that food ingredients and food products are not harmful to health, but specific regulations about nanoparticles do not exist. Although there is a lack of regulation and knowledge of risk, still there are a number of food and nutrition products that claim to contain nanoscale additives, including iron in nutritional drink mixes, micelles that carry vitamins, minerals and phytochemicals in oil, and zinc oxide in breakfast cereals (17,19). Although more research is needed on the health consequences of nanoparticles, it is unclear what the full range of concerns are, because measurement of exposure to nanomaterials is neither well developed nor characterized. Therefore, an emerging challenge to benefiting from nanotechnology is having the foresight to develop and use it wisely. To this end, governmental agencies (via the National Nanotechnology Initiative) are working together to proactively research and evaluate the benefits and harms of nanotechnology.

Research opportunities and challenges in nanotechnology, foods, and health

A panel discussion entitled "Research Opportunities and Challenges in Nanotechnology, Foods and Health" followed the presentations and included federal government representatives from the Division of Nutrition Research Coordination, NIH (Dr. Crystal McDade-Ngutter), Telemedicine and Advanced Technology Research Center, U.S. Army Medical Research and Materiel Command (Dr. Charles Peterson), and the National Institute for Food and Agriculture (NIFA; formerly Cooperative State Research, Education, and Extension Service), USDA (Dr. Etta Saltos). Each panelist provided information about research opportunities in nanotechnology from their agencies that would be of interest to nutrition scientists as well as a perspective on the challenges of nanotechnology, foods, and health. The NIH has supported many initiatives on the topic of

TABLE 1 Examples of research areas in nutrition with nanotech enhancement potential

1) Discover novel nutrient properties
2) Quantify and characterize properties of nutrients and their metabolites
3) Assess nutritional status with special attention to target compartments and cells
4) Target delivery of nutrients to cells and compartments
5) Develop new devices and hybrid structures for pathway repair as well as prevent and cure nutrient deficiencies in a more quantitative and timely fashion
6) Explore epigenetic studies with emphasis on methylation and folate and one-carbon metabolism
7) Determine critical cell nutrient signaling pathways
8) Examine how nutrients/metabolites modulate cell signaling pathways
9) Determine the effect of cell nutrient signaling on overall cell function

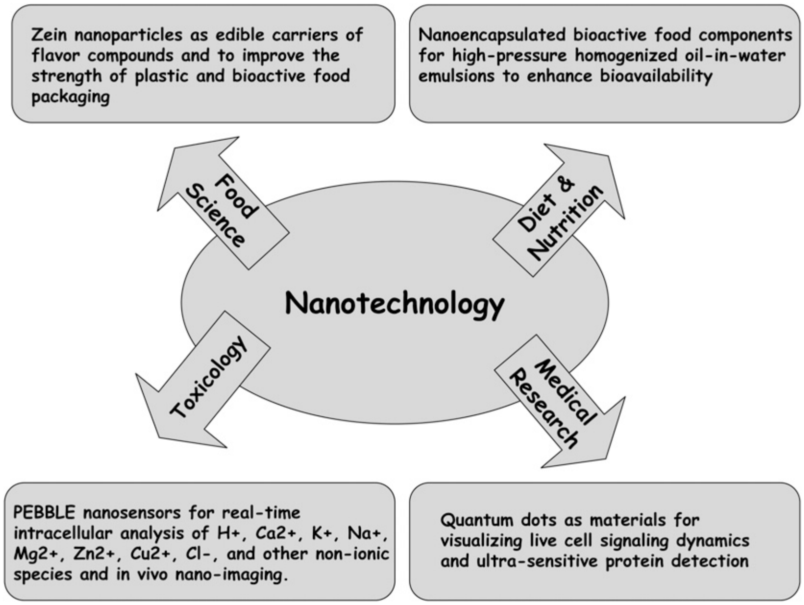

FIGURE 1 Examples of nanotechnology applications and their associated discipline highlighted during the symposium.

nanotechnology, such as the NIH Nanomedicine Roadmap Initiative (20) and the NCI Alliance for Nanotechnology in Cancer (21), but none that have been specifically targeted for nutrition research. More opportunities for nutrition scientists to interact and collaborate with nanotechnology experts were emphasized as a way forward for such NIH applications. Similarly, Telemedicine and Advanced Technology Research Center, U.S. Army Medical Research and Materiel Command supports a Nanotechnology and Biomaterials Portfolio that is focused on identifying novel developments in materials science and biomaterials that can improve drugs and devices for diagnosis and therapy of a broad range of medical conditions (22). NIFA, USDA in collaboration with food and agricultural scientists from land grant universities and the National Nanotechnology Initiative agencies developed the first strategic roadmap titled "Nanoscale Science and Engineering for Agriculture and Food Systems" (23). The resulting NIFA, USDA initiative "Nanoscale Science and Engineering for Agriculture and Food Systems" has been offered every other year with next cycle of new applications to be announced in fiscal year 2010 (24). The goal of this program is to provide knowledge, expertise, and highly qualified research and development in nanotechnology for food and agricultural systems. Examples of 2008 priorities included novel nanoscale processes, materials and systems with improved delivery efficacy, controlled release, modification of sensory attributes, and protection of micronutrients and functional ingredients suitable for food matrices as well as the assessment and analysis of perceptions and acceptance of nanotechnology and nano-based products by the general public, agriculture, and food stakeholders using appropriate social science tools.

During the discussion, several research areas in the nutritional sciences that would benefit from nanotechnology applications were highlighted (summarized in **Table 1**). Nutrition scientists may wish to leverage ongoing efforts and collaborate with experts in nanotechnology so that novel approaches can be developed to tackle many of these research questions. The panel discussion provided insight into the research opportunities and challenges concerning applications for nanotechnology so that nutrition and food scientists can be more informed and productive in their research endeavors.

Summary

Recent advances in biomedical and agricultural technology will likely assist in advancing our understanding of health and disease processes. The symposium "Nanotechnology Research: Applications in Nutritional Sciences" highlighted new and emerging technologies that are currently, or soon to be, available for nutritional sciences. Examples discussed included: *1*) nanoscale optical sensors, such as PEBBLE, for intracellular chemical sensing; *2*) QD technologies to visualize and quantify cellular protein interactions; *3*) nanoencapsulation of bioactive food components to improve their bioavailability; and *4*) intelligent food packaging that acts as a biosensor to monitor and detect spoilage or infection (**Fig. 1**).

Nutrition and food science research areas that might benefit from applying or understanding nanotechnology include research that aims to: *1*) identify sites of action (molecular targets) for bioactive food components; *2*) characterize biomarkers that reflect exposure, response, and susceptibility to foods and their components; *3*) identify new target delivery systems for optimizing health; and *4*) improve food composition. Because there is little information about the potential health risks of nanoparticles, more research on the toxicology of nanoparticles, both on a case-by-case basis and for general applicability, is also warranted. Nanotechnology has the potential to advance the science of nutrition by assisting in the discovery, development, and delivery of several intervention strategies to improve health and reduce the risk and complications of several diseases. This symposium was designed to enhance knowledge and understanding about technologies that may be utilized or are currently being employed and or/modified for nutrition and food science research. It is hoped that by highlighting these technologies the potential benefit of nanomaterials to revolutionize food and nutrition research is recognized.

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