The Use of Nanotechnology in the Treatment of Epidermolysis Bullosa

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PASS WITH MERIT

RESEARCH PAPER
BASED ON
PATHOLOGY LECTURES
AT MEDLINK 2010

ABSTRACT

Nanotechnology is a fast developing area of medicine which has potential applications in diagnosis and treatment of disease. Epidermolysis bullosa is a hereditary disease, which affects the junction joining the epidermal and dermal layers of skin. The disease causes a weakness in the skin making it extremely fragile so that it blisters and tears in normal activities, such as walking or writing. It is a painful and disabling disease, and in the most severe cases can be fatal. Nanotechnology could offer an improvement in the quality of life for sufferers, with a development in dressings, delivery of missing proteins, and eventually gene therapy.

INTRODUCTION

The term nanotechnology comes from the Greek word "nano" meaning "dwarf" and is simply technology which measures 100 nanometers and smaller, with a nanometre being 1 billionth of a metre. To put this in perspective, on average a virus is 100nm in length and a bacterium is 1000nm. It is a relatively new branch of engineering with its origins dating back to the 1950s when physicist Richard Feynman proposed the idea of making tiny machines. Then in the 1970s, K. Eric Drexler designed molecular nanomachines consisting of pulleys, gears, and screws that could self assemble. There are fundamentally two different ways of approaching nanotechnology which are termed "top-down" and "bottom-up". In the "top-down" approach, scientists try to make something smaller and smaller until it is nanosized. An example of this would be making silver particles nanosized to increase their reactivity. The "bottom-up" approach is where the nanotechnology is built up from the atomic level. The most famous example of this is the buckyminsterfullerene or the buckyball. This is a sphere shaped structure made up of 60 carbon atoms which is capable of encapsulating another molecule. Carbon can also be engineered into nanotubes, which are single layered tubes that are incredibly strong and can also conduct electricity.

At the nanoscale, all chemical forces work differently. As particles decrease in size, their surface-volume ratio alters dramatically. This means the reactivity of substances increases as they are made into nano particles. The uses of nanotechnology in medicine includes advances in drug delivery, increased efficiency of known ingredients and diagnostics. The cosmetic industry has a keen interest in nanotechnology, especially the area of nanodermatology. Furthermore, nanotechnology is beginning to be used in the treatment of severe skin diseases for example, photodynamic therapy is used for the treatment of skin cancer. Epidermolysis bullosa is a lifelong disease, disabling sufferers either completely or partially, and causes them to be in significant pain. This paper will look at potential applications of nanotechnology for the care and treatment of sufferers.

DISCUSSION

There are many different applications of nanotechnology in medicine, and more and more uses are being discovered every year. Below I will describe three key areas of development already underway.

Drug Delivery

Chemotherapy, a treatment for cancer, is very harmful to patients because the powerful drugs used kill healthy normal cells as well as cancer cells. One application of nanotechnology in medicine currently being developed involves employing nanoparticles to deliver drugs, heat, light or other substances to specific types of cells (such as cancer cells). Particles are engineered so that they are attracted to diseased cells, and this allows direct treatment of those cells. This technique reduces damage to healthy cells in the body.

An example which has already been used successfully in animal trials is a new method to deliver a chemotherapy drug in prostatic cancer. The researchers first engineered a nanoparticle made of the polymer poly(d,l-lactic-*co*-glycolic acid) and poly(ethylene glycol) which dissolves once inside a cell. They then encapsulated the chemotherapy drug docetaxel in this polymer and attached receptor proteins capable of specifically binding to prostate cancer cells. Once inside the cell, the nanoparticle dissolves releasing the destructive chemotherapy drug.

Another technique used is for a molecule engineered by scientists to encapsulate a drug molecule so it can easily enter the body through the digestive system allowing it to be taken orally rather than having to be injected. Without the help of nanotechnology the treatment would have to be carried out by someone trained in how to give an injection which would therefore use more resources. If the drug was put into a tablet, without being encapsulated in a nanoparticle, it would simply be broken down by the strong acidic conditions of the stomach so would be useless. Instead, the use of a carrier nanoparticle enables the drug be absorbed directly into the blood stream. With the help of nanotechnology, more treatments are becoming available for patients that are quicker and easier to use.

Increased Drug Effectiveness

Silver and silver salts have been used for years for their antiseptic and antibacterial qualities. Silver impregnated dressings have been used for dressings. Nanotechnology has been utilized to make a new dressing containing nanosized particles of silver which measure from 5-50 nm, and this makes them more effective at killing bacteria, viruses and fungi because they have a larger surface area to volume ratio and so are in contact with the foreign microbes more.

As particles shrink in size, they interact with light differently. If they are smaller than the wavelength of visible light, they can even become transparent. This is a big advantage in making creams more cosmetically acceptable. One key area where this is very useful is sunscreen. Sunscreens made from titanium microparticles can effectively block UVA and UVB light however most also reflect visible light, producing a white sheen on the skin. Nanosized titanium particles still reflect the harmful UVA and UVB, but do not reflect visible light meaning they appear transparent. The use of nanoparticles also means they can be suspended in water-based solutes or lighter oils. These lighter creams are better tolerated on the skin, especially in hot weather as the water evaporates cooling the surface. While traditional titanium dioxide sunscreens are prepared in heavy molecular weight oils which do not evaporate. These are more uncomfortable in hot weather and can even prevent effective sweating.

Diagnostics

Biosensors are chemical sensors used in the diagnosis of disease. The use of nanotechnology in diagnostics is proving very beneficial, with diagnoses being made in the earlier stages of disease. They also allow the use of less invasive techniques. Biosensors rely on biochemical reactions and can sense changes in many different things such as pH, temperature or light. They consist of a biological part which binds to receptors in cells and a physical element that allows the reaction to be observed. One application already in use is for the diagnosis of cancer. Nanoparticles of gold with diameters between 15 to 60nm have very interesting properties. When an infrared light is passed over the gold nanoparticles, they heat up, meaning there is a change in pressure around them. This then causes ultrasound to be given out, and this sound can be picked up and would indicate the location of the nanoparticle. The particles are attached to antibodies that can locate and bind to cancer cells and can then be used to locate the cells very precisely.

Safety Issues

Prince Charles' concern about the safety of nanotechnology sparked a debate in the British national press in 2004. His concerns may have been over exaggerated, however it is important to realise that because making a chemical into a nanoparticle affects its reactivity, this can also affect its safety. In an experiment, two groups of rats were exposed to polytetrafluoroethylene (PTFE or Teflon®) particles of different sizes. The first group were exposed to 130nm diameter particles, and these rats remained healthy even after a long exposure. The second group were exposed to 20nm particles, and died shortly after. This shows the importance of considering the safety of nanoparticles of different sizes, especially when this type of technology is relatively new.

The use of nanoparticles of titanium dioxide has been seen to be very effective. However, there have been reports that they can cause beta-amyloid fibrillation which possibly leads to Alzheimer's disease. Investigations by the Australian government's Therapeutic Goods Administration have concluded that the nanoparticles could catalyze the generation of free radicals. Obviously if these highly reactive species got into the body they could cause significant damage, however, in healthy skin the nanoparticles are absorbed into the top layer of skin and don't penetrate further meaning there are no harmful effects. Further testing revealed that even under prolonged exposure there were still no nanoparticles present in lower levels of skin. It is thought that nanoparticles may also be able to penetrate in broken or UV-damaged skin.

Ethical Issues

Although high profile figures have expressed their concern about the development of nanotechnology, I do not believe there are any ethical dilemmas with the technology currently being used. However, nanotechnology has the potential to develop greatly, and if the original vision of self-replicating "nanobots" is ever realised, then there could be claims that mankind had created new life. My personal opinion is that the development of a self-replicating nanomachine is not the same as creating a new species.

Furthermore, as new technologies are created, their testing needs to be thorough. A balance needs to be struck between getting a treatment to a patient quickly, and keeping them and trial participants safe. In addition ethical issues can arise with the process of gene therapy. Some may believe this is tampering with the building blocks that make us unique and should not be permitted.

Epidermolysis Bullosa

Epidermolysis Bullosa (EB) is a very rare genetic condition in which the skin and internal body linings blister at the slightest knock or rub, causing painful, open wounds. EB affects 1 in 17000 people and there are thought to be 5000 people with the condition in the UK. Normal skin is made up of the epidermis and dermis which are joined by a complex structure called the dermoepidermal junction. The dermoepidermal junction is made up of over 50 proteins. When any of these proteins are absent or abnormal EB arises. Luckily, the disease isn't contagious but it is hereditary, with the more severe types generally being autosomal recessive.

The disease is usually passed on from parents who do not realise that they have one abnormal gene, as its characteristics are not shown. This means that if both parents have the mutated gene their children have a 1 in 4 chance of having the disease. Although most severe forms of EB are autosomal recessive, some are autosomal dominant. Figure 1 below shows how the autosomal recessive gene is inherited.

At its mildest, the condition is confined to the hands and feet making holding things and walking extremely painful. In more severe forms all the body is affected and the wounds heal very slowly, causing the skin to scar and sufferers to be physically disabled. Repeated injury on the hands leads to loss of finger nails and deformity, with the fingers losing their definition and eventually becoming webbed. Figure 2 shows how EB can affect the hands of an infant. Furthermore, the blistering can affect inner body linings such as the mouth and the oesophagus. This means eating is very painful so leads to malnutrition, which reduces the body's resistance to infection. People with the more severe types of EB also have an exceptionally high risk of developing skin

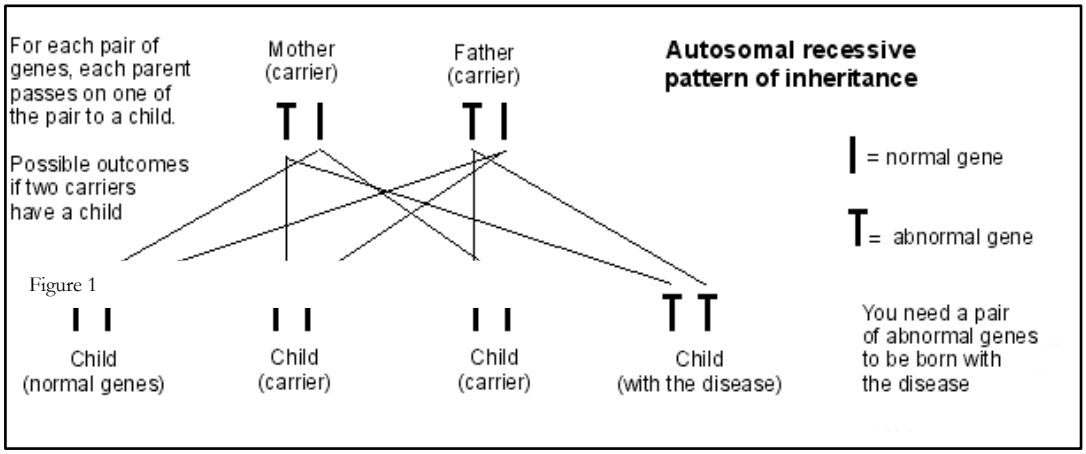

Figure 1

cancers, shortening their lives by approximately 30-40 years. In its most severe form, the condition is fatal in infancy.

The most common types of EB are caused in mutations in the KRT5 and KRT14 genes. These genes provide the instructions for making the proteins keratin 5 and keratin 14. These tough, fibrous proteins work together to provide strength to the outer layer of the skin (the epidermis). Mutations in either the KRT5 or KRT14 gene cause cells in the epidermis to become fragile and easily damaged. As a result, the skin is less resistant to friction and minor trauma, thus it blisters easily. In rare cases of EB, there are mutations in the PLEC gene, not the KRT5 and KRT14. The PLEC gene makes the protein plectin which helps attach the epidermis to the underlying layer of skin.

Figure 2

Research into the genetic basis of disease has transformed our understanding of many types of disease. In this case, the identification of the specific gene mutation that causes a particular type of EB has increased our understanding of the specific proteins involved. Although this is a big step forward in finding what causes the disease, a cure is yet to be found. One of the main barriers which is stopping this is the delivery of the correct gene or proteins to the skin.

Although there is no known cure for EB, healthcare teams do their best to make sure patients are as comfortable as they can be with careful bandaging. This is a massive burden for the patient, as the process is very time consuming and painful. Old dressings have to be soaked off, then blisters have to be popped and dead or loose skin removed before new dressings can be applied. This takes several hours in severe cases, and is repeated every few days, depending on what makes the sufferer more comfortable. Clearly, an improvement in dressings would be worth having and would improve the quality of life for those with the disease. In addition to bandaging, drugs are used if the patient has trouble eating to loosen the oesophagus. People with EB also have to have special dentists who are experienced with dealing with the disease because of the fragility of the epidermis in the mouth.

Uses of Nanotechnology Already in Development

Scientists are developing a new type of dressing which incorporates nanotechnology to stop infection. The dressing will release antibiotics when nanocapsules in the dressing are triggered by the presence of unfriendly bacteria. When the dressing releases the antibiotic, the dressing will change colour, alerting healthcare workers that there is an infection. This means that the dressing will be able to target and begin treatment before the infection actually overtakes the wound, and it will mean that patients do not have to wait for cultures to tell their healthcare team that an infection is present. The treatment process will be speeded up greatly. Furthermore, it would mean there would be no unnecessary dressing changes as the dressing would change colour if there was infection.

Possible Future Developments

One developing treatment is that of gene therapy. Scientists are working on ways of transporting the correct proteins, or the correct gene to make the proteins, to the areas where there are mutations. This would effectively be a cure for EB. Nanotechnology could be the missing piece of the puzzle for the transportation of the correct gene. Nanocapsules are already being tested to see if they can safely transport chemotherapy drugs to cancer cells. In theory, the same technology could also be used for the treatment of EB. The development of liposomes which have the ability to encapsulate plasmid DNA is already underway. This technology is already being proposed for the use with another rare skin condition, called lamella icthyosis. One problem that could arise would be getting the nanomolecules to the correct cells. However this could be achieved by using needle less delivery. The particles could be sprayed at a high velocity through a small hole in the device, creating a very fine stream with particles small enough to penetrate the skin. This would put the particles exactly where they are needed, as the mutation occurs in genes in the dermoepidermal junction.

Currently, nanotechnology is being used to great effect in sports clothing. New swim suits have been developed that can squeeze the swimmers body in specific areas to make them more streamlined and to reduce muscle fatigue. Nanocomposite fibres are used to create this effect, because they can be woven to the correct density and tension required in certain areas. This technology could be transferred for further development in bandaging, where the bandage could compress certain areas at varying strengths meaning it would be held tightly again the fragile skin of EB sufferers.

A natural phenomenon that involves nanotechnology is how geckos stick themselves to walls and ceilings. This works because their feet are covered in tiny hairs, which are in turn covered in even smaller hairs. These hairs offer such a large surface area that they can use Van de Waal's force to hold them to the ceiling. The hairs also have another interesting characteristic: when moved to a certain angle, they slip straight off the surface. This technology could be transferred to a use for fixing bandages in place to patients and would also mean that when the bandages were removed, they wouldn't pull off against the skin, which could potentially cause more harm. This nanotechnology could improve the quality of life for sufferers.

CONCLUSION

In conclusion, it is clear that nanotechnology is one of the most exciting areas of developing technology today. Nanotechnology has enormous potential to offer solutions to many medical challenges; such as the early diagnosis of cancer and more effective, less toxic chemotherapy.

The development of nanodermatology has mainly been driven by the billion dollar cosmetics industry, with their large amounts of funding for research. Advances in sunscreens are an example of nanotechnology being used in a highly beneficial way to manufacture more effective and cosmetically acceptable products. Although many new products and treatments involving nanotechnology are very expensive, in the future, they should become more readily available and will be able to be used in the treatment of rare disorders such as epidermolysis bullosa.

In EB, nanotechnology could be used to improve the quality of life for sufferers, in terms of clothing and dressings as this technology is available in other settings. Furthermore, the technology will be able to potentially cure the disease in the future through gene therapy. It is marvelous that a technology is finally becoming available to deliver treatments such as gene therapy, which have been sought after for so long.

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