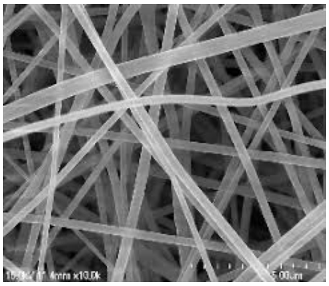

Sow's Ears, Silk Purses and Goats' Milk:
New Production Methods and Medical Applications for Silk

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Silk is a good example of a self-assembled natural material with attractive characteristics. Attempts are now being made to produce recombinant forms, through transgenic animals, that have potential in a number of medical technologies.

Regular readers of this column may remember that I prefaced the last article with a comment about the perilous state of the world and that, because I was enroute to Asia at the time, I was hoping that the SARS epidemic had peaked. That optimism turned out to be unfounded and travel plans for Beijing, Hong Kong and Singapore had to be changed. One result of this was an unplanned visit to Thailand, where amongst other good things, an abundance of silk and silk goods was in evidence. I had intended to write an article about the increasing interest in silk as a tissue engineering scaffold material. This change of travel plans gave me an opportunity to do this sooner than anticipated.

Biomimetic materials and molecular self-assembly

It has been known for a long time that silk is an exceptional material. Regarded for centuries as classic quality clothing and a decorative material, it is also known to have high strength, with a strength:weight ratio considerably in excess of the best engineering steels and synthetic engineering plastics. Silk, as everyone knows, can be produced by a number of species, including the spider. Spider silk has been the subject of most interest from a materials science point of view. Spiders can spin up to seven different forms of silk. The version used for the construction of their webs, usually referred to as dragline silk, is the focus of most attention. Silk is a protein that is synthesized in nature by a process that is referred to as self-assembly or "bottom-up" synthesis, and it is the nature of this process that has attracted so much attention from materials scientists. Molecular self-assembly, which mimics this natural process, is now being achieved in the laboratory and is expected to become one of the key procedures for the development of biomimetic materials.

It is worthwhile at this point to consider the essential differences between traditional engineering materials and self-assembled natural materials and their biomimetic analogues. We normally consider metals to be the most robust of all engineering materials, their properties being dependent on the strong metallic bonds. Although it is possible to create some ingenious microstructures with metals, they are essentially macroscopic materials and the uniform distribution of the metallic bonds means that they lack the elasticity and plasticity of natural materials. The same could be said of engineering ceramics, which are held together structurally by even stronger ionic bonds and, as a consequence, are usually even more rigid and brittle than metals. Interestingly, metallic structures are never encountered in biological tissues but some ceramics are. These are produced as nanocrystals within other matrices by self-assembly methods. Engineering plastics come much closer to the natural material paradigm, but even then they have profound differences because in the majority of cases they are also macroscopic materials without too much sophistication at the molecular interaction level.

It is interesting to note within this comparison that most engineering materials require a considerable input of energy for their synthesis, production and fabrication; this is typified by the massive temperature of steel blast furnaces and temperature-pressure combinations in polymer reaction vessels. Nature does not have that level of energy resource and has designed methods of material synthesis that do not need them. The bottom-up approach is one where atoms or molecules are added to each other, one at a time in an energy-efficient way. The critical factors here are a chemical complementarity between the atoms and the molecules and the reliance on weak interactions between the molecules. This gives elasticity and resilience, but also, where necessary, considerable strength through the molecular arrangements that maximizes the effect of these interactions.

Recombinant silk

Returning to the silk, if the dragline silk protein produced by the spider is dissolved, the solution can self-assemble into nanofibers, each of which has an extremely fine substructure. This substructure consists of nanocrystals within an amorphous matrix, the mechanical properties therefore being derived from a self-reinforcement of oriented protein strands. It is the arrangement of these components, induced by the self-assembly process with a minimum of energy expenditure and without any of the strong metallic or ionic bonds holding the structure together microscopically, that gives the resilient and tough structure. Not surprisingly, the military applications of these materials, for example, bullet-proof jackets, has catalyzed further studies of the materials because they have better properties than the best engineering materials such as Kevlar (DuPont <www.dupont.com/NASApp/dupontglobal/corp/index.jsp>).

It does not seem possible to naturally harvest dragline silk from spiders and so alternative methods to reproduce this type of material have been developed. Most notably this has involved the production of recombinant spider silk, not from spiders but from transgenic goats. The two spider genes that make the protein were identified more than 10 years ago, but attempts to splice these into bacteria have failed to produce silk of adequate quality. However, it was then found that it is possible to splice the spider genes into mammalian cells, for example, with cow or hamster cells. This led to attempts to splice the genes into the mammary cells of a breed of early lactating goats. These goats then effectively produced spider silk within their milk, which is extracted from the milk and woven into threads or other forms. A group of transgenic goats have been bred for this purpose. The material produced by this method has been patented and is called BioSteel.[1]

As implied above, nonmedical applications have received most attention, but there is some interest in medical technology. There is as yet little reliable data on the biocompatibility of the silk, but there is not likely to be too many problems here. Natural silk was used as a suture material for many years, but has lost its place on the surgeon's preferred list because of the availability of synthetic materials with more appropriate mechanical properties and resorption characteristics. The silk produced by this new method may well have superior properties and some microsurgical applications have been suggested. Ligament replacements are also being investigated.

Tissue engineering scaffolds

There are several problems yet to be solved with this recombinant silk as far as industrial applications are concerned, which include the cost of scale-up and the uncertainty over stability. Silk is essentially biodegradable, but degrades fairly slowly. Its properties are also heavily dependent on water content. When wet, its load carrying capacity is considerably reduced and it has a tendency to creep. It should be obvious that if a spider can produce a strong fiber quickly, the fiber is only meant to last a short while. Silk probably cannot be used in long-term applications under aggressive environmental conditions. The hope is that the properties may be tailored to suit the application. Tissue engineering may be one of those areas where this combination of properties will be of value. Scaffolds for tissue engineering constructs are usually required to be available in complex three-dimensional forms that are capable of controlling cell behavior through surface activity and are biodegradable without pro-inflammatory behavior. The evidence at this stage would suggest that the silk can be made with appropriate biodegradable characteristics and to avoid the significant inflammation seen with synthetic polyesters, and that the protein structure could be tailored to support cell behavior.

A significant level of investment has already been made in this specific area of biotechnology, and it is of considerable interest whether this form of biomimicry based on self-assembly can actually produce commercially viable and technologically advanced materials. As with all spiders' webs, a great deal is hanging on this particular thread.

Reference

1. Nexia Biotechnologies, www.nexiabiotech.com, accessed 5 May

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