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Recent developments and future research in the Bone and Joint Decade 2000–2010

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Musculoskeletal disorders encompass a broad spectrum of conditions of multifactorial origin and very different clinical appearance. Connective tissues are primarily affected in osteoporosis and joint diseases such as osteoarthritis and rheumatoid arthritis, which cause severe long-term pain and physical disability and give rise to heavy costs to society.

Many of the major connective tissue diseases involve inflammatory mechanisms. Rheumatoid arthritis, psoriasis, and systemic lupus erythematosus are among the last-remaining widespread diseases for which the scientific community has insufficient knowledge of pathogenesis or treatments that can prevent or reverse the disease course. Mechanisms and pathways leading to destructive inflammation may to a large extent be shared among these diseases and may also operate in other conditions such as osteoarthritis, vasculitis, arteriosclerosis, and osteoporosis. This is clearly demonstrated in genetic studies of animal models in which many genes have been shown to be associated with a wide spectrum of inflammatory diseases, and many diseases include components of spreading the inflammation to various other organs. One prominent example is rheumatoid arthritis, in which vasculitis and increased arteriosclerosis morbidity occur. It is also important to take into account that the mere occurrence of widespread inflammatory diseases in humans is likely to be caused not only by rapidly changing environmental factors but also by natural selection for protection against infectious diseases. In addition, there is often a connection between infections, especially chronic infections, and inflammatory diseases.

Most inflammatory diseases affect connective tissues, either by inducing catabolic events or by triggering repair attempts; both will lead to altered function and may develop further to fibrosis.

Key features of connective tissues are to take up and distribute load and to provide a barrier and protective function, as well as to retain shape. The component of tissue destruction may be initiated by factors such as mechanical overload that brings the normally very dynamic turnover out of balance. This turnover is aimed at replacing fatigued tissue, for example, with new and mechanically more stable tissue. Many factors govern the basis for this remodelling in connective tissues. Exaggerated load will lead to damage and a higher risk for initiation of a pathological process. In addition, inflammation is a condition that will affect the metabolism in connective tissue cells and usually hamper their ability to repair. This is likely to increase the sensitivity to mechanical load and may perhaps drive the process into a pathological condition. Interestingly, components released from connective tissues as a result of a pathological process appear to have the capability to modulate the inflammatory response and in some cases also to trigger autoimmune reactions. It is thus becoming apparent that the reactions in connective tissues leading to tissue damage are extensively influenced by environmental factors, including vascular and nerve ingrowth and local inflammation.

The gap between biology and clinical research

The wide gap between clinical approaches and more basic approaches to understanding the disease mechanisms has been difficult to overcome. The clinically oriented approach had its golden age decades ago, when empirical observations could lead to major breakthroughs and built the basis of today's clinical practice. It has, however, shown clear limitations in solving the pathways of disease: some of the treatments given today still have no rational explanation or produce side-effects because of unspecific targeting. The molecular approach has recently been successful in providing tools such as the genome sequence, specific molecular structure and tissue composition but has not yet been significantly explored in understanding disease processes. This gap between biology and everyday clinical work is very apparent in chronic diseases such as osteoarthritis, rheumatoid arthritis and osteoporosis. The difficulties of recruiting physicians to both basic and patient-oriented research are well known and have recently resulted in a change of funding priorities that support bridging projects. We are now facing a unique opportunity where we can see how the biology that is being unravelled in basic science can and will be applied in clinical treatment.

Closing the gap

The most important aim should be to strengthen evidence-based medicine by closing the gap between clinical disease-oriented research and basic molecular research. Fig. 1 shows an example of how the findings of molecular research could be applied to clinical treatment. Recent advances in genomics, proteomics, high-resolution imaging and tissue engineering provide new opportunities. Diseases affecting connective tissues involve many complex biological pathways, often including molecular interactions between inflammatory cells and constituents derived from connective tissue. Over the years, considerable efforts have been directed towards identifying genes and gene regions controlling

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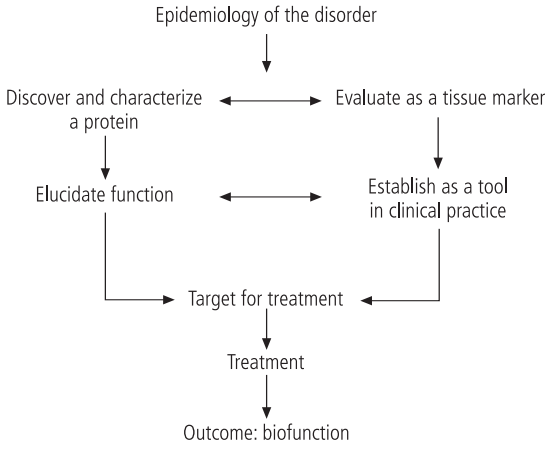
Fig. 1. **Pathway from molecular research to treatment**



connective tissue and inflammatory diseases as well as on identifying and characterizing individual molecules. A number of key molecules in cartilage and bone have already been identified. More recently, efforts have been focused on the functioning of molecules that form the tissues, and information is being gathered about the important events in assembly of the structures that provide their properties. These structures are fibrous networks, with collagens as major constituents forming a core and associated molecules providing connections between the fibrils to improve and extend the mechanical properties. The fibrils have different properties in different tissues and different compartments of a given tissue. These properties are governed by a number of collagen-binding proteins: we are finding some that have primary roles in catalysing and accelerating the process and others that have primary roles in its modulation.

Connective tissue structure at the molecular level

Another major functional unit in most connective tissues is a network of highly negatively charged proteoglycans, creating a fixed charge density that immobilizes water and regulates compressivity as well as providing a barrier that regulates diffusion and water flow. In addition, these molecules are assembled in the matrix in processes apparently catalysed and regulated by a variety of factors. In creating such a complex system, it is of key importance that production of the various components is well coordinated. This is accomplished by sensors at the cell surface in the form of receptors, for example integrins and specialized proteoglycans. These receptors provide intracellular signalling similar to that of another set of regulating components in the form of growth factors, such as transforming growth factor b (TGF-b), fibroblast growth factor (FGF), bone morphogenetic proteins (BMPs) and many others. Such factors include a variety of cytokines both with inhibitory and stimulatory effects. This latter group constitutes one of the mechanisms for effects on connective tissue by inflammation. Yet another stimulus to the cells is mechanical load. This has dual effects in providing positive stimuli to the cells in remodelling and responding to novel requirements, but also apparently in maintaining proper homeostasis. Signals induced by load are similar to those induced by other stimuli such as integrins and growth factors, and there is extensive crosstalk between pathways.

Ongoing developments that will lead to a deeper biomechanical and biological understanding of molecular and cellular events in connective tissues, particularly bone, cartilage and tendon, include programmes using material testing, high-resolution imaging such as microcomputer tomography, position emission tomography, stereophotogrammetry and finite element modelling in studies of tissue integration as well as dynamic loading of cells.

Mechanisms of skeletal tissue damage

As a result of increased understanding of the roles of individual matrix molecules, it is now becoming increasingly apparent that one of the mechanisms leading to tissue destruction is inefficient repair in disease as a result of lack of coordinated production of the various components that are needed for adequate and optimal repair. Other mechanisms in disease include degradation and loss of function of matrix constituents by proteolytic fragmentation. These proteases are often released by the cells in the tissue as a result of various forms of stimuli. They are released in a proform, which is activated by a number of mechanisms that in most cases are not clearly defined. As a safeguard, the cells will also produce specific inhibitors of these proteinases.

In progressive musculoskeletal disease, a key element is increased proteolytic activity leading to fragmentation of constituents of the various networks with the result of tissue failure, given that the repair is not sufficient. We are thus starting to see a situation where the responsiveness of the cells is governed by a number of factors, some produced centrally (such as growth hormone) setting a sensitivity level and others produced locally and affecting responses. In many cases, the response leading to this normal dynamic turnover is driven by fatigue and altered load. At the same time, excessive load leading to extensive fatigue or perhaps cell damage will induce pathological processes that, as a result of the continued exposure to the strenuous environment, will become chronic. One problem in evaluating what happens in the tissues is an almost total lack of procedures to monitor such events in the intact living organism. Current diagnostic protocols thus discover tissue damage when the process is far advanced. Nevertheless, there has been a development of novel procedures making use of the fact that constituents of a particular connective tissue become fragmented and released to its surroundings and eventually to the circulation as a result of the tissue-damaging process. This molecular marker technology has the potential to identify early events that will eventually lead to severe tissue damage. The combination of this molecular approach with attempts in the clinical routine to initiate and modulate tissue repair by physiotherapy, for example, or by surgical intervention altering the load is, of course, opening possibilities for entirely new biological treatment.

Connective tissue and inflammation

An important component of many diseases affecting connective tissue is inflammation, with immune-mediated mechanisms often regulating the inflammatory cascades. It is becoming apparent that this activity may be modulated — or at least partly driven — by components released from

connective tissues by fragmentation. A well-functioning interface between connective tissue research and research on inflammation is therefore extremely important in understanding how the different processes affect one another.

Although different connective tissues appear very dissimilar from a gross morphological standpoint, at the molecular level there are many shared components, and findings from studies of one system have major implications for studies of other tissues. External factors such as stress elicit modulation, which is very similar between different tissues. For example, up-regulation of particular molecules appears to be similar in cartilage, tendon, blood vessel wall and the spine.

Molecular interactions in inflammation and connective tissue diseases should be investigated not only in human studies but also using animal models and technology. Approaches by proteomics will be efficient in characterizing gene products and their roles in controlling diseases in animal models as well as in developing the tools and targets for disease affecting connective tissues in humans. With transgenic technologies, a particular gene can be inactivated or mutated and the consequences can be studied. The animal models can be "humanized" by inserting the critical human genes. Studies of patients will provide additional information against the background of alterations observed in various animal models.

Future research

To help close the gap between clinical disease-oriented research and basic molecular research, we suggest that research concerning musculoskeletal disorders during the Bone and Joint Decade 2000–2010 should include work in the following directions:

- encourage interactions between different research areas, which will provide openings for the development of new procedures to influence the progression and treatment of disease;
- assess the burden of diseases and risk factors, in order to optimize disease prevention and treatment outcomes;
- identify pathogenic molecular interactions in a relevant context — using animal models and genomic, transcriptomic and proteomic technology platforms;
- identify disease-regulating genes and modify their expression;
- develop an understanding of the roles of proteins in tissue formation, function and cell behaviour;
- develop an understanding of cellular mechano-transduction and its role in patient treatment;
- develop new targeted therapy based on an understanding of molecular mechanisms in tissue turnover;
- develop new procedures for diagnosis and disease monitoring;
- optimize the interaction with the biological system in biomaterial applications; and
- develop tissue-engineered repair systems.

Development of disease-modifying therapy must be based on an understanding of the complex underlying biological processes, and this requires a wide range of competence that cannot easily be gathered into one research group or clinical discipline. Initiatives promoting collaborative efforts are therefore paramount. ■

Conflicts of interest: none declared.