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Editorial overview: Where are we with treating musculoskeletal disorders?

Isabel R Orriss & Vicky E MacRae

There are numerous pathological conditions that affect the musculoskeletal system and connective tissues; these range from common bone disorders typically associated with ageing (e.g. osteoporosis) through to rare inherited calcification diseases (e.g. pseudoxanthoma elasticum). Many of these conditions lead to disability and represent a significant financial burden to healthcare systems, an issue that will only worsen with the increasingly ageing population. Understanding the molecular mechanisms leading to the etiology of these disorders is essential for identifying and developing an effective treatment. In many cases, study of rare diseases has provided important insights into the complex biological processes which underpin normal musculoskeletal function. This special issue contains articles which expertly review our current knowledge on the causes of and therapeutic options available to treat conditions including cancer in bone [1,2], osteoporosis [2,3], osteoarthritis [4], connective tissue calcifying diseases [5,6] and bone pain [7]. Recent developments in our understanding of osteocyte biology [8] and the interactions between fat and bone [9], which may yield novel therapeutic targets in the future, are also reviewed.

The treatment of postmenopausal osteoporosis represents one of the success stories within the musculoskeletal field with several therapies being available. Most of these treatments (e.g. bisphosphonates, Denosumab) act by inhibiting osteoclast activity and reducing bone resorption, thereby increasing bone mineral density. At present the only bone anabolic agent currently available is the human parathyroid hormone (PTH) analogue teriparatide, which is not suitable for all patients. The bisphosphonates have recently come under scrutiny because they reportedly prevent bone remodelling leading to atypical femoral fractures. Given these potential limitations, the past few years have seen a considerable drive to identify new treatments to prevent bone loss, in particular bone anabolic agents. The review by *Harsløf and Langdahl* summarises these recent developments discussing a number of promising therapeutic agents including odanacatib (a cathepsin K inhibitor), Romosozumab (a monoclonal antibody against sclerostin) and abaloparatide (a PTHrP fragment) [3]. The option of combination therapy (i.e. an anti-resorptive along with a bone anabolic) as a therapeutic approach is also considered.

In stark contrast to osteoporosis, osteoarthritis currently lacks effective treatment. This degenerative joint disease is the most common form of arthritis and is characterised by loss of articular cartilage, subchondral bone thickening and osteophyte formation. Despite recent advances in knowledge, the underpinning molecular mechanisms are not fully understood. At present clinical management is largely palliative and with an aging population there is an ever growing need for treatments which prevent the onset and progression of this condition. The review by *Poulet and Staines* elegantly discusses the different tissues of the joint which have been targeted for therapeutic intervention with a particular focus on the subchondral bone and synovial membrane [4]. They also examine how it is becoming increasingly evident that osteoarthritis is a complex, multi-factorial disease and so any one treatment may not be appropriate for all patients. With the considerable amount of work taking place in this field, it is certainly one to watch for promising new developments.

Despite recent advances, cancer still remains a major cause of mortality. Bone can be affected by primary cancers (e.g. osteosarcoma) or, more commonly, the metastases associated with other tumours such as breast or prostate cancer. Availability and efficacy of treatments vary depending on the cancer involved but generally bone metastases are considered incurable. Consequently, there is a considerable amount of work being performed to identify new therapeutic targets for cancers in bone. This issue contains an elegant review by *Gooding and Edwards* focussing on multiple myeloma, which is a cancer of the plasma cells in the bone marrow [1]. In multiple myeloma, the cancer cells hijack the local microenvironment and disrupt bone homeostasis leading to significant bone loss. It is a relatively uncommon form of cancer but like secondary bone cancers there is currently no cure. The review also discusses some of the new avenues being explored in multiple myeloma research [1]; in particular it focuses on the interactions between the tumour cells and bone marrow niche and how this can be manipulated to treat multiple myeloma.

Autophagy is an essential process which involves the degradation and reuse of intracellular structures and macromolecules. Whilst specific regulators of autophagy are emerging as drugs or supplements for anti-cancer therapy, the effects of these compounds on the skeleton has yet to be elucidated. In this issue, *Chagin* [2] discusses the mTOR-autophagy pathway in relationship to epiphyseal chondrocytes, articular chondrocytes, osteoblasts, osteocytes and osteoclasts. Furthermore, the potential negative side effects of targeting either the mTOR pathway through anti-cancer treatment on bone growth and development are also highlighted.

Skeletal conditions are a common cause of chronic pain which can have a significant impact on quality of life. Bone pain is prevalent in a range of disorders including osteoporotic fractures, Paget's disease, osteoarthritis and bone metastasis. At present, there are very few therapies which can attenuate bone pain without unwanted side effects and, thus, there is a significant need for novel treatments. The past decade has seen an increase in the level of research into bone pain and as such the underlying mechanisms are beginning to emerge. *Frost et al* examine the latest developments in this field and discuss some of the exciting preclinical findings which could represent promising therapeutic targets (such as nerve growth factor) for treating bone pain [7].

It is widely accepted that bone homeostasis involves complex interactions between osteoblasts, osteoclasts and osteocytes. The importance of these interactions is considered in a number of the reviews in this special issue [4,6,8]. Osteocytes are increasingly being viewed as essential regulators of bone remodelling. The review by *Prideaux et al* summarises current knowledge regarding the role of osteocytes in bone formation, bone resorption and periacicular remodelling [8]. It also discusses the opportunities for therapeutics which specifically target osteocytes or osteocyte-derived factors (such as the anti-sclerostin antibody, romosozumab).

More recently, it has become apparent that bone cells also interact with other cell types and understanding these complex signalling pathways may help to identify novel pathways which can be exploited therapeutically. Bone remodelling is a highly active and regulated process that maintains skeletal structural integrity. This vital function is characterised by alternating phases of destruction by osteoclasts and formation by osteoblasts, and has a high energetic cost. To sustain energy balance, excess consumed calories are stored as glycogen, triglycerides and protein, allowing the body to continue to function in states of starvation and increased energy expenditure. Adipose tissue provides

the largest natural store of excess calories as triglycerides and plays an important role as an endocrine organ in energy homeostasis and beyond. *Suchacki, et al.* explore the novel role of bone marrow adipose tissue (MAT) as an endocrine organ and discuss the pharmacological agents that regulate MAT [9].

Whilst regulated mineralisation is essential for the normal functioning of the skeleton, soft tissue calcification usually results in severe pathological changes. There are many diseases which are characterised by abnormal calcium deposition in connective tissues. Some of these are widespread and the consequence of chronic disorders; for example vascular calcification is a common consequence of type 2 diabetes and chronic kidney disease. Others are rare inherited genetic diseases such as pseudoxanthoma elasticum (PXE) and generalised arterial calcification in infancy (GACI). At present there are only very limited pharmaceutical strategies to prevent or regress these disorders. The review by *Rashdan et al* discusses the molecular mechanisms underpinning these conditions and potential targets that could be used for therapeutic intervention [5]. It further highlights how the study of these rare disorders has yielded important information about the processes regulating biomineralisation.

Pyrophosphate, a simple and ubiquitous molecule, prevents unwanted calcification and acts as the body's natural "water softener". Since its role in inhibiting mineralisation was discovered in the 1960s, the importance of pyrophosphate within the body has tended to be overlooked. This issue contains a detailed review by *Orriss et al* highlighting the fundamental role of pyrophosphate in regulating bone mineralisation and preventing soft tissue calcification [6]. From a pharmacological perspective it is important to remember that the discovery of pyrophosphate paved the way for the development of the bisphosphonates. These drugs, which are chemically stable analogues of pyrophosphate, are an effective treatment for a range of conditions including osteoporosis and metastatic bone disease. New uses for bisphosphonates continue to be suggested; for example, as a treatment for conditions associated with unwanted calcification such as vascular calcification.

Taken together, the reviews in this special issue highlight the considerable pharmacological advances that there have been within the musculoskeletal field in the last 40 years. Whilst treatments for some conditions, such as osteoporosis, have been particularly successful, a vast number of diseases affecting the musculoskeletal system remain without effective treatment. Our increased understanding of the cellular and molecular mechanisms underpinning these conditions has identified a number of promising therapeutic targets. However, further work is still required to determine whether these pre-clinical findings can translate to effective treatments for these musculoskeletal and connective tissue diseases. This is particularly important given that many of these disorders are associated with ageing and, globally, the population is increasingly getting older.

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Editor Biographies

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