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Refine, reduce, replace: Imaging of fibrosis and arthritis in animal models

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A B S T R A C T

Non-invasive imaging has great potential to contribute to the 'Three R's' principles for more ethical use of experimental animals. It enables repetitive monitoring of disease progression and measurement of quantitative biomarkers that report on disease progression and therapy efficacy in the same animal, thereby reducing manifold the number of animals needed for in vivo studies whilst advancing our knowledge into the pathophysiology of these diseases.

This article reviews applications of non-invasive imaging in the field of fibrosis and arthritis research. It provides evidence for the viability of this approach not only for ethical reasons (reducing numbers and suffering in research animals, according to the 3R principles) but also for accelerating experimental output and making it more translational. The emphasis is on promising developments which will help improving throughput by reducing experiment length and size as well as human resources for data analysis, therefore encouraging a wider spreading of novel imaging technologies.

Introduction

Studies on human conditions involving a complex interplay of environmental and host factors such as in the Rheumatology field cannot but rely on animal models with a genetic or induced disease that is similar to the human disorder. Therefore, simply avoiding animal testing is not always feasible in order

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to achieve the same scientific aims. Considering the guiding principles of the 'Three R's' for more ethical use of animals in laboratory practice that were first described by Russell and Burch in 1959, there is more to it than simply feeling encouraged to avoid animal experimentation by 'replacement' [1]. 'Reduction' using tools that enable researchers to obtain more information from fewer animals and 'Refinement' using methods that avoid, alleviate, or minimize any potential suffering, pain, or distress of the animals are at least as important [1]. Small animal models that mimic important aspects of rheumatic disease, such as fibrosis and arthritis, are widely used for target discovery and drug development in the field.

Semi-quantitative assessment by histological analysis of isolated organs *post mortem* is the current gold standard, but requires many animals to be killed at several time points during the study. While these ex vivo analyses on tissue samples can provide the most detailed cellular and molecular analysis of the disease, they are intrinsically unable to follow the kinetics of disease and host response processes which are, by definition, dynamic in space and time. Ex vivo analyses also carry the ethical burden of requiring the use of many animals to overcome the statistical issues inherent to high inter-animal variation that would otherwise reduce the power of experiments.

Two-dimensional (2D) sampling is too limited for processes that are not evenly distributed throughout an entire organ such as the pulmonary lobes in lung fibrosis. Isolation of the lung for ex vivo assessments also suffers from some specific issues such as distortion of lung structure during fixation, thus resulting in potential artefacts and biased alveolar properties. Because non-invasive pulmonary function measurements have limitations regarding sensitivity, specificity and available readout [2–4], current developments in nondestructive imaging, with the ability to assess the disease in situ, hold great promise in this regard. Similarly, the volumetric reconstruction of the joint morphology obtained with non-destructive imaging offers a superior localisation of arthritic lesions, increased precision in the assessment of the severity and the possibility of modelling joint mechanics.

However, the spatial localisation of morphological and molecular alterations achieved through non-destructive/in situ imaging becomes truly informative when such changes can be determined longitudinally in the same individual, which provides the otherwise missing knowledge about their temporal progression and interaction. There is therefore a strong requirement for tools that enable the repeated measurement of dynamic processes in the same animal in vivo and that are therefore non-invasive.

Home Office statistics on the use of research animals in the UK show that mice are by far the most frequently used species and the number of mice used between 2004 and 2014 has increased, while for larger rodents such as rats, this trend was opposite [5]. Due to the amenability of mice to genetic modifications, which allows to testing specific molecular hypothesis in vivo, their use in experimental labs is predicted to further increase in future years. This suggests that, in order to achieve a significant reduction in the use of experimental animals, non-invasive imaging technologies will have to be optimised for the mouse.

The aim of this review is to describe the available non-invasive imaging technologies for the assessment of arthritis and fibrosis in small rodent models of these pathologies, with a focus on new promising developments in this area and on the impact of present and future imaging technologies on the 3Rs principles.

Animal models

Animal models used in the field of systemic rheumatic diseases always highlight certain aspects of rheumatology or systemic syndromes and will, as such, focus on an important manifestation of the disease. There is no true experimental model that exactly reproduces human disease. Animal models are induced to reproduce the pathological conditions of the patients as faithfully as possible, but, as the aetiology of many rheumatic conditions is still unclear, one has to rely on the induction of certain known aspects of a disease. Despite their imperfections, animal models are indispensable for research and many insights we know today that we have gained through help from our little friends.