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Magnetic resonance imaging of cells in experimental disease models

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1. Introduction

1.1. A brief history of cellular imaging

The illustrious history of cellular imaging began in 1595 when spectacle makers Hans Lippershey and Hans Janssen in Middelburg, The Netherlands, developed a prototype microscope with lenses capable of threefold magnification. Using this revolutionary apparatus, Robert Hooke coined the word "cell" in 1665 upon witnessing the structure of non-living plant tissue (cork) that, to him, resembled monks' chambers called "cellula". Nearly a decade later, in 1674, Anton Van Leeuwenhoek became the first to describe live algae, bacteria, spermatozoa, and even blood flow in capillaries using a device equipped with hand ground lenses that were capable of greater than 200-fold magnification. Almost two centuries would pass before the seminal observations of Hooke, Leeuwenhoek, and contemporaries in botany were expanded to include animal cells by Theodor Schwann and Matthias Schleiden and cell division by Rudolf Virchow; ultimately giving rise to the universal Cell Theory stating that cells are the basic unit of life [1].

1.2. Non-invasive cellular imaging in the 21st century

Presently, a microscope can be found in nearly every biomedical laboratory and innumerable images of cells are published each month in research journals. Along with the omnipresent microscope, technological developments in histology, immunohistochemistry, mammalian cell culture, and molecular biology over the past century have provided enormous contributions to our understanding of cell development, physiology, and pathology. Analyses of cultured cells and postmortem tissue rapidly encouraged deeper enquiries into cell physiology *in situ* and the pathogenesis of disease. This flourishing interest in live cellular processes stimulated the development of multi-photon confocal microscopy and highly sensitive charge coupled devices for bioluminescent imaging (BLI) as well as the adaptation of non-invasive medical imaging devices, including ultrasound, magnetic resonance (MR), computerized tomography (CT), positron emission tomography (PET), and single photon emission computerized tomography (SPECT) scanners for imaging studies in animals and humans. Much like the dawn of the microscope, the advances in biomedical imaging achieved in recent decades have generated new possibilities for non-invasive detection of the progression of pathology at the cellular level and methods for monitoring the efficacy of cell therapy in animal models of disease.

The forté of non-invasive imaging is that cells and tissues within living animals can be visualized at regular time intervals without disturbing their anatomical context. Even more remarkable is the fact that this feat can generally be performed within 10–20 min; including the total time required to initialize the scanner, position the subject, apply contrast if necessary, and acquire an image. Though non-invasive imaging devices bear significant instrument costs and require dedicated facilities, support staff, and skilled operator training, they are nevertheless increasingly commonplace as shared resources in biomedical institutions. In this review, we discuss recent advances in non-invasive cell detection that have significantly expanded the researcher's repertoire for monitoring the basic unit of life in its native or diseased context. In order to emphasize novelty, we chose to limit our discussion to major developments reported within the past five years.

2. Imaging modalities for non-invasive cellular detection

2.1. Multi-photon confocal microscopy as a starting point for non-invasive cellular imaging

Each imaging modality has well known relative advantages and disadvantages associated with detection method and imaging probe characteristics. For anatomical purposes, X-ray, ultrasound, CT, and MRI each provide excellent detail and are widely used for direct detection of gross tissue anomalies. Delving beyond anatomical features, however, often requires indirect means to reveal the biodistribution of specific cell populations and expose the cellular processes that underlie disease. Classically, cell labeling is achieved by either introduction of enzymatic or fluorescent molecules into a well defined cell population, binding of enzyme- or fluorophore-conjugated antibodies directed against cell-specific protein markers, or detection of the expression non-mammalian proteins from either constitutive or cell-specific promoters. Though potentially immunogenic in humans, the expression of non-mammalian proteins is well tolerated in mice, as indicated by the widespread usage of this cell labeling method in transgenic animals. For example, transgenic mice designed to express genes encoding non-mammalian proteins such as green fluorescent protein (GFP, *Aequorea victoria*) and red fluorescent protein (RFP, *Discosoma* sp.) are increasingly applied in organotypic cultures and *in vivo* to discern cellular responses to experimental manipulation and to probe cell–cell connectivity in highly complex systems such as the nervous system [2–5]. In particular, multi-photon confocal microscopy has been used to reveal dynamic changes in the posi-