Chapter 3

Time-Lapse Microscopy

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Abstract

Time-lapse microscopy is a powerful, versatile and constantly developing tool for real-time imaging of living cells. This review outlines the advances of time-lapse microscopy and refers to the most interesting reports, thus pointing at the fact that the modern biology and medicine are entering the thrilling and promising age of molecular cinematography.

Keywords: time-lapse, microscopy, real-time, imaging, cell

1. Introduction

Originally described as *time-lapse cinemicrography (microphotography)* [1], the modern *time-lapse microscopy* (TLM) emerged as a powerful and continuously improving tool for studying the cellular processes and cell-cell interactions with the applications ranging from fundamental aspects of molecular and cell biology to medical practice. The related *time-lapse photography* is more relevant to observing non-microscopic objects, such as plants and landscapes. TLM is the technique of capturing the sequence of microscopic images at regular intervals. TLM allows scientists to observe cellular dynamics and behavior of the population of living cells as well as of the single living cell within the population [2, 3]. Live cell imaging and the first non-sophisticated TLM techniques were pioneered at the very beginning of the twentieth century [4]. However, to be visible in the light microscope, the cells are to be subjected to fixation and staining, the processes that kill the cells. Introduction of phase-contrast microscopy in 1940s, development of fluorescent and multidimensional microscopy, flow cytometry and computational tools made live cell imaging a widespread approach and prompted scientists to consider TLM as an essential technique that carries an enormous promise for basic biological

science and medicine. For this review, we focused on mammalian cell cultures, although TLM can also be efficiently employed to study prokaryotic cells and unicellular microorganisms. In the absence of up-to-date comprehensive review on TLM advances, our aim was to familiarize the readers with the current advances of TLM methodology and provide for the reference guide to the most interesting reports where TLM has been utilized both for biological research and clinical purposes.

2. Time-lapse microscopy: from making movies to bedside

2.1. Versatility of TLM

In this part, we will briefly review some selected publications, which highlight the rapid development of TLM as a versatile discovery tool within the broad scope of modern biology and medicine. Importance of TLM as a new method in biological research was highlighted by Burton [5]. The progress of tissue culture methods, phase-contrast microscopy (see below) and real-time imaging by TLM enabled scientists to overcome the major limitation of traditional microscopy; preparation of very thin transparent samples, which required tissue fixation and did not make it possible to investigate living cells, let alone, and biological processes over time in the same sample. Early reports demonstrated the feasibility of TLM for comparative studies of cultured cells [6–8] and for monitoring living blood and lymph cells [1], cell division [9, 10] and reaction of cells to varying contents of electrolytes in perfusion chambers [11]. TLM was helpful to decode the process of multinucleation in the developing skeletal muscles [12] and to describe the variable cytotoxic response toward allografts [13, 14].

TLM is a suitable tool to monitor *cell motility and migration*, including quantitative assessment of migration, such as the number of migrating cells and the distance [15–20]. In multicellular organisms, the directed and coordinated cell migration (chemotaxis) occurs during embryonic development, tissue regeneration and inflammatory response [21], while cancer cells migrate into surrounding tissues and the vasculature. To monitor chemotaxis, TLM can be used together with the Dunn chamber [21–23]; Boyden chamber [24, 25]; Bridge chamber [26]; LOCOMOTIS, the motility tracking system [27] and other types of chambers for cell visualization and TLM applications [28–30]. TLM was employed to study embryonic stem cells [31]; hematopoietic progenitor cells [20, 32–34]; mesenchymal stem cells [35]; activated lymphocytes forming lymphocytes colonies [36]; primordial germ cells, a migratory cell population that will eventually give rise to the gametes [37–39]; the migration route of progenitor cells in cell cultures obtained from live chicken embryos [40, 41]; microglial cells [42–44]; olfactory cells from schizophrenia patients [45]; neurons [46]; chemokines that drive migration of megakaryocytes from the proliferative osteoblastic niche within the bone marrow to the capillary-rich vascular niche, which is an essential step for platelet production [47]; migration of osteoclasts toward bone surfaces [48]; motility of cultured endothelial cells to study remodeling of their intercellular junctions [49]; generation of a complete polarized epithelial monolayer by the epithelial cells of mammary gland [17]; movement of cancer cells that were cultured under hypoxic conditions [50] and treated with salinomycin [24]; individual cell

motility in fibroblastoid L929 cells [51]; human osteosarcoma MG-63 cells [52]; B35 neuroblastoma cells transiently expressing GFP and C6 glioma cells after staining with Hoechst 33258 [16] and motility of L5222 leukemia cells within the mesentery and migration of induced pluripotent cells during their early reprograming [53]. Of note, most studies are devoted to neural stem cells [18, 19, 54–63] due to growing clinical importance.

TLM allows investigators to visualize and characterize *cell-cell contacts* [46, 52, 64–71]. The most interesting reports are concerned with the contacts between the various types of stem/progenitor cells as well as the tumor-environment cell interactions: the importance of proper cell-cell contacts level for their correct positioning and cell polarity during organogenesis [39], glial-neuronal interactions [72–74], interactions between microglia and brain tumors [75], between astrocytes and neural progenitor cells [42], between mesenchymal stem cells and human myoblasts [76], dendritic cells [77], endothelial cells [78], cancer cells [79], extracellular matrix molecules [80], between erythroblastic islands in bone marrow [81], between neural progenitor cells [62, 82–84], between neural cells and hematopoietic stem cells that migrate to the central nervous system [85], hematopoietic stem cells and stromal cells [20], endothelial progenitor cells and cardiac myocytes [86], between induced pluripotent cells during the early reprogramming phase [53], vesicle traffic through intercellular bridges between prostate cancer cells [87] and synaptic contacts [88–94].

Cell division and *cell death* can be well investigated with TLM [50, 52, 95–97]. Division and growth of both labeled [96, 98–100] and non-labeled [101, 102] cells in culture [52, 95, 98, 103–105] and tissue slices [106], including monitoring of a single cell [95, 99, 107–112], can be observed and assessed with TLM. The fluorescent ubiquitination-based cell cycle indicator (FUCCI) system can effectively label individual G1, S/G2/M and G1/S-transition phase nuclei as red, green and yellow, respectively, to visualize the real-time cell cycle transitions in living mammalian cells [113–116]. Microinjection of complementary RNA to cyclin B1 was reported as a tool for TLM studying meiosis [117]. Real-time imaging was employed to monitor nuclear envelope breakdown, which is one of the major morphological changes during mitosis [118] and apoptosis [119]; nucleolar assembly after mitosis [120]; tracking of template DNA strands during mitosis [121, 122]; preferred mitotic orientation of daughter cells, which is important for their following self-organization and tissue formation [123, 124]; interkinetic nuclear migration toward the apical surface in epithelial cells [125, 126]; multinucleation of skeletal muscle cells [12]; asymmetric division of stem cells [127–129]; identification and characterization of cell division genes by combining RNA interference, time-lapse microscopy and computational image processing [130]; cytokinesis [131, 132]; cleavage furrow [133]; abscission by using TLM in combination with electron microscopy [134, 135] and mitotic synchronization in the cell population [136]. The observations related to *cellular senescence* and various forms of *cell death* include re-entry into the cell cycle [10, 124, 137–139] and variable frequency of divisions [140]; changes in mitotic and interphase duration [141–147]; short G1 phase, which is a distinctive feature of mouse embryonic stem cells [148]; delayed G2 phase [149]; *neosis*, the term used for karyokinesis via nuclear budding followed by asymmetric, intracellular cytokinesis [150]; secretion of exosomes with anti-apoptotic microRNAs [151]; apoptosis [119, 152–156]; phagocytosis of apoptotic cells [157]; necrosis [158]; autophagy [159]; mitotic catastrophe [52, 143] and phototoxicity [160].

TLM can also be used to study *intracellular dynamics* of subcellular organelles [161, 162], natural cellular proteins and reporters, introduced nanoparticles and even physiological effects of small inorganic molecules and gases. Time-lapse imaging was used to monitor and quantify movements and changes in mitochondria [163–165]; Golgi apparatus [166]; centrosomes and microtubules [167–170]; centromeres [171]; cellular membrane [172]; dendritic spines [173]; dynamics of interkinetic nuclear migration [174, 175]; intercellular uptake and distribution of nano-sized (less than 100 mkm) ceramic particles [176]; intracellular translocation of p65 and IkappaB-alpha proteins [177]; intracellular distribution of integrin beta1 and F-actin [178]; fluctuations in Notch signaling to maintain neural progenitors [179]; re-localization of PP1gamma, which is implicated in multiple cell cycle-related processes including regulation of chromosome segregation and cytokinesis [180]; movement of the replication origin region of the chromosome during the cell cycle in *Bacillus subtilis* [181]; dynamics of 53BP1 protein in DNA-damage response [182]; measuring gene dynamics with luciferase as a reporter [183]; colocalization of MAP kinases in mitochondria [184]; clustering of acetylcholine receptor on myotubes [185]; multiple chromosomal populations of topoisomerase II [186]; focal points for chromosome condensation and decondensation [187]; intracellular calcium dynamics [188, 189] and single-cell time-lapse imaging of intracellular O_2 [190].

Although TLM is mostly used with cultured mammalian cells and live cells in tissues, the significant number of reports indicates that TLM could be employed to observe and study prokaryotic cells and other unicellular and multicellular organisms as well as viruses. Here, we mention only few examples, such as time-lapse imaging of growth, cell-cell contacts and formation of spherical granules in *E. coli* [191–194]; time-lapse visualization of bacterial colony morphologies in the special bacterial chamber MOCHA [195]; screening and assessing effects of antibiotics, such as antibiotics-bacteria interactions [196–199] and studying yeasts [200–202] and viruses [203–207]. The smaller microorganisms, analogously to intracellular structures, usually require higher magnification and more sophisticated microscopic equipment.

2.2. TLM technical approaches

TLM monitoring of mammalian cells usually requires the inverted microscope, which is fully or partially enclosed by a cell incubator (environmental chamber), a partly sealed transparent box that maintains the temperature, humidity and even partial gas (carbon dioxide) pressure, protects cultured cells from the light and allows the investigator to manipulate with the microscope in order to choose the field of view and adjust other imaging parameters [208–210]. The TLM chambers and devices underwent significant improvements over the time, from the simple glass tissue chambers and manual capturing sequences of images to the automated high-resolution microscopes and sophisticated computerized equipment for long-term TLM observations [154, 162, 211–219]. The up-to-date portable live cell culture monitor (CytoSMART Technologies, Eindhoven, The Netherlands) works within the regular CO_2 incubator. The culture flask (T-flask, Petri dish, wells or any other transparent vessel) is positioned onto the lens of the device; the field of view is chosen by the investigator, and the cell growth and migration can be monitored and analyzed in the real-time mode by accessing the cloud [52].

The *phase-contrast* method of imaging is based on the ability of materials with a different refractive index to delay the passage of the light through the sample by different amounts, so that

they appear darker or brighter. This is the most common TLM technique that is used since 1950s [1, 6, 7, 11] for studying different types of cells and microorganisms both alone and in combination with electron microscopy [220–222]. The so-called differential interference contrast (DIC) microscopy (Nomarski microscopy) also produces high-contrast images of transparent non-stained biological objects, and it has been broadly used for TLM [223–226]. Fluorescent TLM dating back in 1950s TLM [9, 227] can be used nowadays with fluorescent proteins-reporters [207, 228–231], fluorescent nanoparticles [232, 233] and membrane dyes [160, 234, 235]. As the further proof of TLM flexibility, we present some reports where TLM is combined with other advanced microscopy techniques: multiplexed or multifield (recording of many fields simultaneously) TLM [236, 237], confocal TLM [156, 171, 207, 238–242], multi-photon TLM [58, 243–245], the so-called four-dimensional imaging (three-dimensional images over time) [242, 246], time-lapse bioluminescence analysis [247], Forster resonance energy transfer (FRET) microscopy [248], time-lapse optical coherence tomography [249–251], *in toto* imaging to image and track every single cell movement and division during the development of organs and tissues [241] and other innovative approaches [50, 252]. TLM can be used to monitor not only cultured cells (cell population and single cell [109] but also living cells in tissue slices up to a depth of 60 micrometers in brain slices, in regions where cell bodies remain largely uninjured by the tissue preparation and are visible in their natural environment [229, 253]. For real-time observation of corneal cells in a living mouse, a novel microscope system was designed, which consists of an upright fluorescence microscope for visualization of corneal cells, a mouse-holding unit for immobilization of the animal and the eye and a set of gimbals which permit observation of a wide area of corneal surface without refocusing [254].

TLM would not be possible without an *automated image analysis*, which is used to extract meaningful data from the bulk of images. Automated cell tracking faces problems associated with high cell density; cell mobility; cell division; multiple cell parameters such as object size, position or texture; cell lysis or overlap of cells [255]. A variety of algorithms, including *segmentation* (the process of partitioning a digital image into multiple sets of pixels or segments) algorithms, have been developed, and they are constantly improving. For most datasets, a *preprocessing* step is needed before information can be extracted. Irregular illumination and shading effects can be removed by using a *background subtraction method*. Other commonly used techniques include *contrast enhancement* and *noise filtering* [256]. In some cases, *registration* is needed to align subsequent image frames and compensate for unwanted movements. Global movements can be caused by movement of the specimen or imaging equipment, but local deformations in the specimen might also have to be corrected for. This is especially the case when considering TLM of living animals, which is heavily affected by breathing and heartbeat [257]. At higher magnifications, when studying intracellular dynamics, cell migration itself might also be considered an unwanted movement that has to be corrected [258]. *Object detection* is a set of techniques to separate objects of interest from the background. The objects of interest can be cells or intracellular particles [130, 259]. Basic segmentation techniques can be sufficient to detect individual cells, although more advanced techniques are still being developed to cope with increasingly complex data [260, 261]. Finally, several *analysis* techniques are available to quantify the different types of cell behavior over time, for example, *trajectory analysis* for assessing trajectory length and directional persistence [262]. By now, various algorithms are designed for quantifying and tracking cell migration [3] and

single cell motility [261, 263]; cell proliferation [264]; cell cycle and cell lineage analysis [107]; changes in mitotic and interphase duration [141]; cell-cell contacts [52]; studying specific cells and tissues [265] and specific intracellular processes such as transcription [99] or morphogenesis [266]; colocalization of cells and intracellular markers [184]; tracking cellular organelles [258]; highlighting the certain cell type within tissues or mixed cell cultures [267]; clustered, overlapping or dying cells [268]; *in toto* imaging of developing organisms, tissues and organs [241] and assessing development and selection of embryos for *in vitro* fertilization [269, 270].

2.3. TLM for assisted reproductive technology and its promise for clinical medicine

TLM is emerging as a promising clinical technique for selecting embryos for transplantation, although the discussion is still under way whether TLM may become an alternative to preimplantation genetic screening [271, 272]. The so-called morphokinetic analysis [273] by TLM is aimed to assess the number, development and quality (viability) of embryos by monitoring cleavage anomalies, multinucleation [274] or specific cell cycle kinetics [274, 275] and cleavage divisions [276], aneuploidy [277, 278], which is considered as a key causal factor of delays in embryonic development toward a blastocyte [278], and even chromosomal abnormalities [279]. Although more clinical research is required to finally prove that TLM can identify the best embryo for transfer and has an advantage over the conventional incubation of embryos [280], TLM is under consideration for patenting as a method for selecting embryos for implantation [281, 282]. TLM can also be used for sperm motility analysis [283].

One of the potential medical applications of TLM is the assessment of *ex vivo* engineered cells for cell therapy of degenerative and inherited disorders and other human pathologies like cancer [284–288]. TLM can also be used for diagnostics, for example, for detecting abnormalities in cell behavior in human dystrophic muscle cultures [289] or estimating tumor malignancy [290] in drug discovery [291], for testing gene therapeutic agents [292] and for evaluating side effects of antibiotics [293] and efficacy of chemotherapeutics [294, 295]. TLM is a valuable tool for understanding the pathogenesis of certain disorders, such as dysplastic erythroblast formation of erythroblasts from the patient with congenital dyserythropoietic anemia [296], thrombus formation [224], IgE-mediated mast cell degranulation and recovery [297], imaging of disease progression in deep brain areas using fluorescence microendoscopy [298], reprogramming in induced pluripotent cells [110] and other applications.

3. Conclusion

TLM is a powerful and versatile tool in modern biological research, with the immense potential for future clinical applications. One of the probably underexplored features of TLM is its promise to further characterize heterogeneity of cells within tissues [144], in particular, stem/progenitor cells and differentiating cells [299] as well as cancer cells [300]. Some of the above-mentioned methods are associated with unavoidable costs (expensive equipment, such as lenses, filters and sensors, and their damage due to high humidity

within the incubator), non-natural impacts on living cells by the high excitation energy of lasers and bleaching/degradation of the fluorochromes over time, which influences quantification of long-running processes. However, the growing number of reports about new improvements and advances in TLM techniques and TLM-related applications that provide valuable information, which is not imageable by other techniques, makes it possible to conclude that the era of microcinematography in biomedical research has just begun.

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Conflict of interest

None declared.

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