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Review

Photoacoustic Molecular Imaging: From Multiscale Biomedical Applications Towards Early-Stage Theranostics

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Photoacoustic imaging (PAI) has ushered in a new era of observational biotechnology and has facilitated the exploration of fundamental biological mechanisms and clinical translational applications, which has attracted tremendous attention in recent years. By converting laser into ultrasound emission, PAI combines rich optical contrast, high ultrasonic spatial resolution, and deep penetration depth in a single modality. This evolutional technique enables multiscale and multicontrast visualization from cells to organs, anatomy to function, and molecules to metabolism with high sensitivity and specificity. The state-of-the-art developments and applications of PAI are described in this review. Future prospects for clinical use are also highlighted. Collectively, PAI holds great promise to drive biomedical applications towards early-stage theranostics.

Principles and Significance of PAI

By converting incident photons into ultrasound (US) waves, PAI ultrasonically overcomes the optical diffusion limit (Figure 1) [1,2]. Thus, PAI combines the rich contrast of optical imaging with the high resolution and deep penetration of US imaging. With the rapid development of laser technology and US detection, PAI has enabled scalable visualization at levels from organelles to organs and has attracted tremendous attention in the past few years [3]. This newly emerging, noninvasive, and nonionizing imaging technique can unveil different physiopathological processes and disease states in a wide range of biomedical applications [4].

By integrating fine optical focusing and advanced scanning techniques, PA microscopy (PAM) is capable of single-organelle and -cell imaging in real-time [5]. PAM is sensitive enough to capture subtle changes of disease microenvironments, including nutrition supply capillaries, drug pharmacokinetics, and local acidity [6,7]. Specifically, PAM can track functional cellular or subcellular activities such as cell entanglement after labeling with different dyes at unprecedented depth, which cannot be achieved by photo-activated localization microscopy (PALM), stochastic optical reconstruction microscopy (STORM), two-photon microscopy, or confocal microscopy. PA endoscopy (PAE) can provide structural and functional information of the esophagus and gastrointestinal tract [8]. In addition to direct images of internal structure, PA images have also been measured from tissue surfaces by a hand-held PA array transducer [9]. At the macroscopic level, PA computed tomography (PACT) allows brain, organ, and whole-body imaging from small animals to primates [10].

Trends

Improved interrogation of complex biological systems is possible through photoacoustic imaging.

The data generated from photoacoustic imaging has provided insights to design highly sensitive and specific imaging agents and biomarkers.

One important innovation in photoacoustic imaging has been to bridge relevant fields for early-stage theranostics.

Technical challenges and difficulties still remain, but the clinical outlook is promising.

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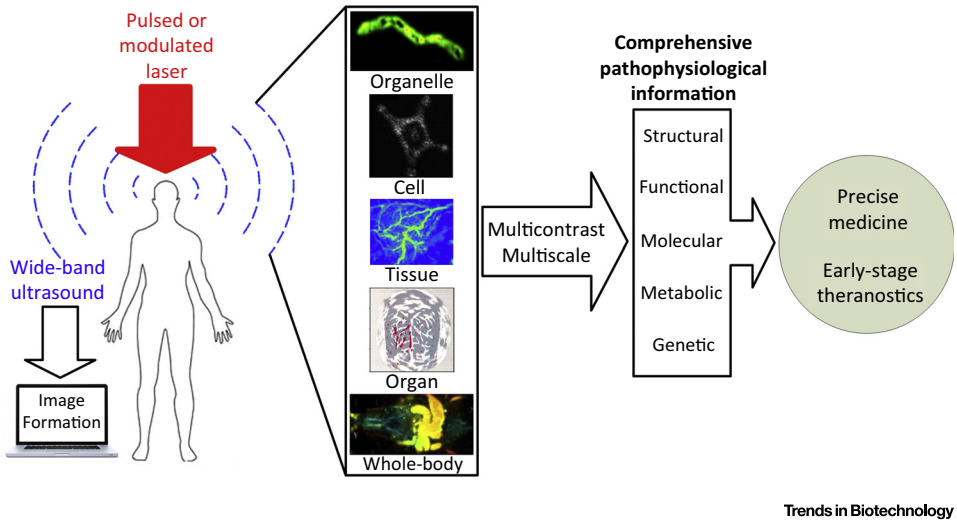

Figure 1. Photoacoustic Molecular Imaging for Multi-Scalable Biomedical Applications and Potential Trends Towards Early-Stage Theranostics [48,59,85–87].

Recently, PAI has received immense attention as a promising means for diagnostic and therapeutic monitoring purposes. In this review we will elucidate the recent advances in PAI in detail, followed by its potential applications for early-stage theranostics. The future development trends, clinical outlook, and potential limitations are also discussed. We hope this review will open up new visions to inspire a wider range of scientific discoveries for fundamental life science and clinical translation.

Specific Embodiments of PAI

Microscopic-Level PAM

PAM, which possesses ultrahigh sensitivity to light absorption, is a powerful technique that plays a unique role in imaging biological samples at multiple spatiotemporal scales. In this section we examine the advanced techniques and the state-of-the-art instrumental embodiments of PAM in biomedicine, and we summarize their enormous potential for clinical applications.

Mainstream PAM

By employing raster scanning of its acoustic or optical focus, PAM can form 3D images directly from acquired PA signals. Based on different focusing types, PAM can be implemented as either optical-resolution PAM (OR-PAM) or acoustic-resolution PAM (AR-PAM). In OR-PAM, the optical focus is tighter than the acoustic focus, which provides the system optically defined lateral resolution. Owing to high spatial resolution, OR-PAM has promoted technology advances to millisecond timescales and submicron length scales (Figure 2A). In AR-PAM, the acoustic focus is smaller than the optical focus. Because the acoustically defined lateral resolution is not affected by optical scattering, AR-PAM refers to a focused acoustic transducer that collects PA signals for imaging targets at depths beyond the diffusion limit (Figure 2B). In particular, the combination of newly developed functional contrast agents and advanced engineering mechanisms has pushed PAM to further uncover subtle changes of disease microenvironments. In addition, these advances have allowed PAM to monitor single organelles and cells such as melanosomes, mitochondria, circulating tumor cells (CTCs), and red blood cells (RBCs) in real-time. Jim *et al.* introduced a fast and cost-effective OR-PAM system that exploited a two-axis microelectromechanical system (MEMS) scanner to achieve a wide scanning region and high spatial resolution (Figure 2A). A PA image from a mouse ear showed that not only small capillaries but also individual RBCs were clearly captured [11].