投稿 ▶総説

核酸医薬の組織分布評価に用いられる手法の分類と特徴

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（受付：令和7年4月2日，受理：令和7年9月16日）

Classification and Characteristics of Evaluation Methods for Tissue Distribution of Oligonucleotide Therapeutics

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Summary

This review provides a comprehensive survey of analytical methods for evaluating the tissue distribution of approved antisense oligonucleotides and small interfering RNAs, as well as developmental products still in preclinical and clinical trial stages (hereafter referred to as developmental products), based on original research articles, reviews and regulatory application documents from the US, EU and Japan.

The analytical methods employed for evaluation can be classified into imaging-based and non-imaging-based methods. These can be further subdivided based on the detection strategy: whether they utilize direct labeling for detection, employ detection reagents without direct labeling, or detect directly without the use of detection reagents. The imaging-based methods utilized for approved drugs were limited to quantitative whole-body autoradiography and microautoradiography using radiolabeled substances. In contrast, non-imaging-based methods encompassed various quantitative analytical methods, including liquid chromatography (LC) and capillary gel electrophoresis (CGE) coupled with detectors such as ultraviolet, fluorescence and mass spectrometric detection, as well as ligand-binding assays (LBAs) including enzyme-linked immunosorbent assays and electrochemiluminescence. These methods are described and stipulated in bioanalysis guidelines in the US, EU and Japan, enabling an objective demonstration of method validity. For developmental products, the imaging-based methods included radio-imaging, fluorescence imaging, immunohistochemical staining, in situ hybridization and mass spectrometric imaging, in addition to the methods adopted for approved oligonucleotide therapeutics. Non-imaging-based methods encompassed LBAs and analytical separation methods via LC or CGE, in addition to quantitative polymerase chain reaction. While approved oligonucleotide therapeutics typically adhered to stringent analytical method guidelines, employing a limited range of imaging-based methods, developmental products utilized a broader selection of both imaging and non-imaging-based methods tailored to specific objectives.

In case studies utilizing the evaluation methods for tissue distribution, research was undertaken to assess the

relationship between tissue distribution in target tissues and pharmacological activity or toxicity, as well as the changes in overall distribution characteristics due to different drug delivery systems. The selection of evaluation methods was determined based on considerations such as whether the distribution assessment focused on the whole body or specific tissues, the desired locations within the tissues, and whether sufficient information could be obtained from a sensitivity viewpoint.

This review of analytical methods available for evaluation of the tissue distribution of oligonucleotide therapeutics is expected to promote an understanding of the characteristics and limitations of the analytical methods and to assist in the selection of appropriate evaluation methods aligned with particular study objectives.

Key words

Tissue distribution, Analytical method, Antisense oligonucleotide, Small interfering RNA, Oligonucleotides in preclinical and clinical processes