let-7, by disrupting an inhibitory secondary structure within the pri-miRNA. This suggests that METTL1-dependent N7-methylation of guanosine plays a role in cell migration, by regulating miRNA structure and biogenesis [92].

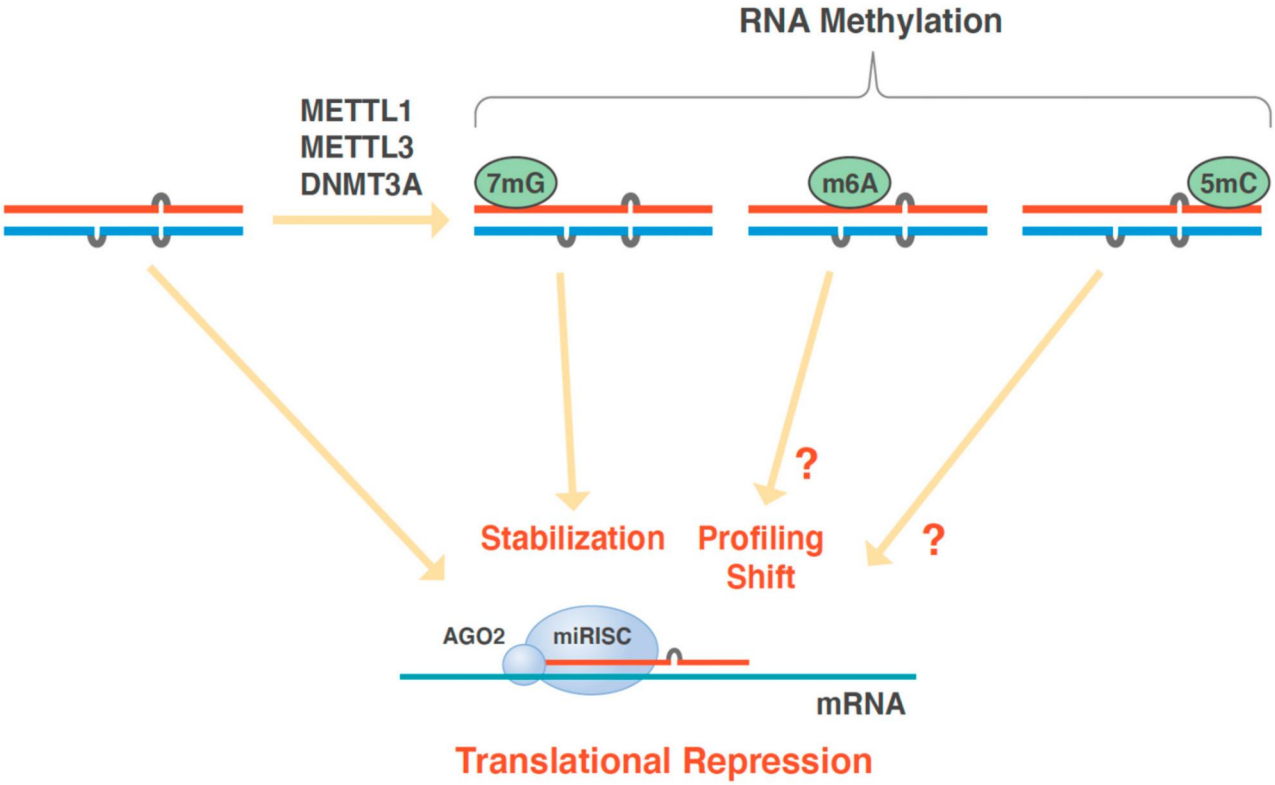

Figure 3. EpisomiR, a subtype of isomiR with different miRNA methylations. Although not fully understood, the methylation of miRNAs modulates miRNA silencing function and mRNA degradation. Recently developed state-of-the-art sequencing techniques, such as tunnel current sequencing and mass spectrometry analysis, enables the detection of m6A and 5mC modifications. 5mC, 5-methylcytosine; AGO2, argonaute RISC catalytic component 2; DNMT3A, DNA methyltransferase 3 alpha; m6A, N6-methyladenosine; m7G, 7-methylguanosine; METTL1, methyltransferase-like protein 1; METTL3, methyltransferase-like protein 3; miRISC, miRNA-induced silencing complex.

Identification of EpisomiR

To obtain information on RNA modifications of episomiR, several methods have been applied [99] (Table 1). RNA immunoprecipitation sequencing locates sites, where proteins bind to RNAs with m6A modifications. This technique might provide high-throughput information regarding the modifications in episomiRs, although a single-nucleotide resolution cannot be achieved. Additionally, capture mass spectrometry (capture MS) methods are useful, for studying methylation sites at the single-nucleotide level [90]. Given that the throughput of capture MS methods is limited, a recent study indicated that the usage of quantum sequencer might be complementary and beneficial for the direct detection of methylation sites, such as m6A and 5mC, in episomiRs [91]. This state-of-the-art technology is expected to enable the profiling of previously uncharacterized molecular targets, which will be indispensable for the precise diagnosis of diseases and the development of innovative therapeutic approaches. The technology can not only detect m6A, 5mC, and m7G modifications but also, if optimized, enable the detection of yet uncharacterized modifications. Furthermore, with the recent development of technologies, such as high-throughput sequencing, m6A, 5mC, and m7G modifications can be analyzed at a single-cell level, thereby expanding the knowledge of episomiR and its role in human diseases [90–94,100–102].

Table 1. Sequencing techniques for the investigation of episomiRs.

Technology	Target (RNA)	Single-Cell Level	Single Molecule Level	Throughput	Reference
Cap-MS	m6A, 5mC, and others (miR)	n.d.	possible	low	[90]
Tunnel current sequencing	m6A, 5mC, and others (miR)	n.d.	applicable	moderate or high	[91]
TRAC-seq	7mG (tRNA; the technology can be possibly applied to miR)	possible	possible	high	[94]
BoRed-seq	7mG (miR)	possible	possible	high	[92]
scDART-seq	m6A (mRNA, possible to miR)	applicable	possible	high	[101]
M6A-SAC-seq	m6A (mRNA, possible to miR)	applicable	applicable	high	[102]

BoRed-seq, borohydride reduction sequencing; Cap-MS, captured mass spectrometry; DART-seq, single-cell deamination adjacent to RNA modification targets; miR, microRNA; m6A-SAC-seq, m6A-selective allyl chemical labeling and sequencing; n.d., not yet determined; TRAC-seq, m7G site-specific tRNA reduction and cleavage sequencing.

Sequencing of miRNAs in Single Cells

Notably, recent studies have sequenced RNA modifications using little amounts of samples. A new technology, called "deamination adjacent to RNA modification targets" (DART-seq), was developed for transcriptome-wide m6A mapping, by utilizing a fusion protein consisting of the m6A-binding YTH domain tethered to the cytidine deaminase APOBEC1 to direct C-to-U editing at cytidine residues that invariably follow m6A sites [100,101]. Another study described m6A-SAC-seq, which consists of m6A-selective allyl chemical labeling and sequencing, as a method for quantitative, whole-transcriptome mapping of m6A at a single-nucleotide resolution [102]. However, sequencing miRNAs at a single-cell level requires further optimization. On the other hand, a study on tRNA demonstrated the crucial role of 7mG, an important modification in the cap site of mRNA, both in oncogenic transformation [94,103,104] and in the processing of miRNAs controlling the expression of the high mobility group AT-hook 2 (HMGA2) gene [92]. In particular, m7G promotes the processing of miRNA precursors, by antagonizing G-quadruplex structures [92,105]. These technologies, using chemical modifications, need to be further developed to enable the use of small sample amounts and single-cell resolution.

4. Conclusions

Since cancer is a genetic disease, the study of genomic alterations in human cancer has enabled the identification of the miRNAs in cancers [38,39]. Since these pioneering discoveries, the existence of miRNA variants, called isomiRs, which differ in length and sequences, have been revealed over two decades ago. Additionally, another subbranch of the isomiR family, called episomiR, has, now, emerged and comprises miRNA variants with different modifications (Table 2). Since the heterogeneity of tumors reflects the diversity of mechanisms involved in the occurrence and development of cancer, elucidating the precise miRNA alterations and compiling bioinformatics data from transcriptomic analyses is expected to contribute to the development of precision medicine against cancer (Figure 4).

Table 2. IsomiR-related genes and human diseases.

isomiR-Related Genes	Human Diseases	Reference
DICER1	pleuropulmonary blastoma familial tumor predisposition syndrome (G)	[106]
DROSHA	ovarian cancer (S)	[107]
TUT1	retinitis pigmentosa (U)	[108]

Table 2. *Cont.*

isomiR-Related Genes	Human Diseases	Reference
TUT4, TUT7	Perlman syndrome (U)	[109]
PARN	dyskeratosis congenita (G)	[110]
ADAR	dyschromatosis symmetrica hereditaria (G)	[111]
APOBEC	bladder cancer (U)	[112]
METTL3	acute myeloid leukemia (S)	[113]

G, germline mutations; S, somatic mutations; U, unknown.

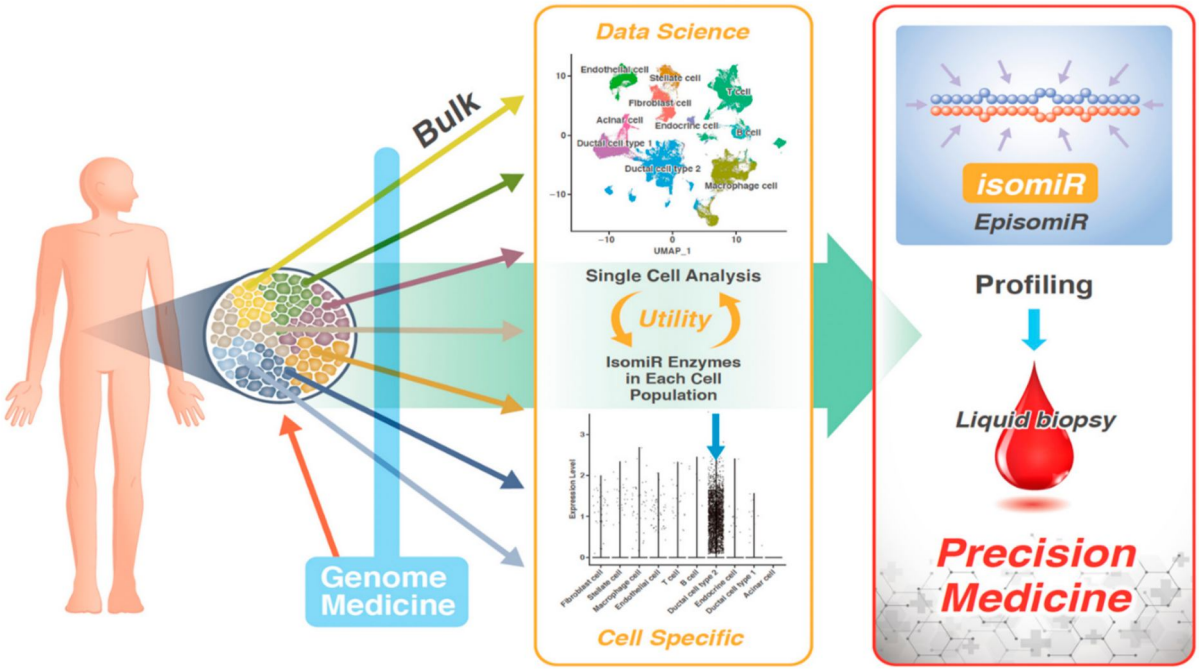

Figure 4. Outlook on high-precision medical care, achieved by the profiling of isomiR. A recent study, using single-cell sequencing of various tissues, has provided links with data from liquid biopsy, such as that of peripheral blood. Given that the expression of isomiR-generating enzymes varies, according to the cell populations present in tissues, the study of isomiR will enable the detection of cell-specific expression patterns. This will improve the diagnosis of diseases, in which unique expression patterns are observed due to genomic and epigenomic variabilities, and will enable the development of precision medicine based on liquid biopsy analyses.

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