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Review Article

miRNA And Cancer : From Anticancer Drug Development To Cancer Diagnosis And Therapy-A Review Article

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ABSTRACT

miRNAs play an important function in development, differentiation, survival, proliferation, and cell metabolism. Various miRNAs are repeatedly transformed in pathological processes like cancers. Irregular expression of miRNA was seen broadly in cancer cells, which activates apoptosis. During the development and progression of tumors, miRNAs function as tumor suppressors or oncogenes. This review summarizes the various aspects of miRNA for the development of anticancer drugs. The role of various miRNA-based therapeutics in selected cancers and the activity of miRNA in the diagnosis of cancer is also discussed. This review scrutinizes the existing documentation in the literature related to the miRNAs and their role in cancer. English language articles were searched in various databases such as Pubmed, Science Direct, Scopus, Web of Sciences, and Google scholar. The keywords used for searching are "miRNAs", "miRNAs in cancer", "miRNAs and anticancer therapeutics", "miRNAs in diagnostics", and "miRNA and oncogenesis".

INTRODUCTION

microRNAs (also called ncRNAs, or endogenous noncoding RNAs) are constituents of non-coding RNAs that regulate gene expression and also control the immense array of biological processes by targeting mRNA (messenger RNA). Cells generally develop non-coding RNAs, called miRNAs, that possess their own promoted elements.miRNAs control gene expression by confining to mRNA of target genes.1,2 The miRNA duplex later allies with RISC (RNA-induced silencing complex and this procedure is arbitrated by the AGO (argonaute) family in the vicinity of different cofactors such as PACT.3,4 miRNAs are a subgroup of endogenously-originated single-stranded non-coding RNA molecules, detectable in various organisms, plants, algae, and viruses, that controls gene expression

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through union with effector complexes known and micro-ribonucleoprotein (miRNP) and sequence specific target sites (cognate mRNAs).5,6,7,8 miRNA illustrates one of the most appealing regions of current medical sciences because they carry the exceptional ability to modulate complicated regulatory systems of gene expression in different developmental as well as cellular processes like cell division, metabolism, protein secretion, cell proliferation and differentiation, apoptosis and viral infection.9-19 miRNAs are also identified in the extracellular fluid like serum,blood plasma, and urine.miRNAs are non-random and therefore have been confirmed to indicate the incidence of various events within the body.20,21 miRNAs is a clinically important biomarker, so further research is mandatory to ascertain its therapeutic relevance.22,23

Discovery of miRNAs

The first miRNA discovered is Lin-4 in 1993 by Victor Ambro's and Gary Ruvkun's laboratories.24In the C.elegans, heterochromic genes regulate the temporal development arrangement of all stages of larvae.Lin-4 is one of these genes which is discovered by the segregation of a null mutation that causes temporal development failure.25,26,27 The second miRNA discovered is Let-7, which is the heterochronic gene of C.elegans in 2000. Failure of let-7 activity results in the recurrence of larval cell fates, whereas an increase in let-7 activity results in aggressive expression of adult fates.28 In humans, it was identified at various expression levels in the greater part of the tissues, which includes the heart, lung, brain, trachea, spleen, thymus, kidney, stomach and small intestine.29,30Within human, Let-7 family consisting of 12miRNAs.Some members of let-7 family are mir-48,mir-84,and mir-241.31,32,33

Nomenclature of microRNAs

MicroRNAs are named by applying the prefix "miR" and by giving unique number labeling such as miR-1. Mature miRNAs that differ in one or two locations are given suffixes such as miR 10 a and miR 10b.34

microRNA – IN THE GENOME

There are various classes of small endogenous RNA molecules, such as ribosomal RNA (rRNA), small interfering RNA (siRNA), small transfer RNA (tRNA), small nucleolar RNA (snoRNA), and microRNA (miRNA).siRNA and miRNA are functionally and biochemically alike. These molecules are remarkable depending upon their various origins. siRNA is developed from long dsRNA (double-stranded RNA), whereas miRNA is developed from double-stranded RNA hairpin precursor.35,36,37 miRNA precursors are generally built in clusters employing various parts of the genome, most intermittently within introns of protein-coding genes and intergenic regions. These regions are called "junk DNA" as their function was not known. miRNA precursors are barely found inside the exons of transcripts as well as in antisense transcripts.38,39 miRNA transcriptional units differ with gene loci. Intronic miRNAs are positioned inside a host gene along with the primary transcript.40,41 Currently, the genomic analysis illustrates that primary miRNA precursors are long polycistronic transcripts. They are identical to mRNA as they have specific 7-methyl guanylate (m7G) caps, 5' and 3' boundaries, and poly(A) tails.42,43,44 The discovery of protein-coding intronic miRNA and intergenic miRNA linked with the work of Lee et al.45 This work demonstrated that most miRNAs are transcribed by RNA polymerase II (pol II).RNA polymerase II is a catalytic component of protein complexes liable for transcribing DNA into mRNA.It is also observed that miRNA can be transcribed by RNA polymerase III (pol III).46,47,48pol III categorically synthesizes small non-protein RNAs that are associated with

regulating growth and cell cycle.49,50,51 The synthesis of miRNA by pol II and pol III signifies that miRNA is an essential regulatory element arising from distinct loci within the human genome, which are associated with controlling gene expression necessary for normal cellular function.52,53,54

MECHANISMS OF miRNA-MEDIATED GENE REGULATION

Various studies demonstrated that miRNAs bind to definitive sequence at 3′ UTR at their target mRNAs to activate translational repression and mRNA decapping and deadenylation.55,56miRNA binding sites have also been identified in different mRNA regions encompass the 5′ UTR and coding sequence and promoter regions.57,58 The binding of miRNA to coding regions and 5′ UTR shows a silencing effect on gene expression. Interaction of miRNA with promoter region activates the transcription.59,60

MicroRNA-Mediated Gene Silencing via miRISC

The minimal miRNA-induced silencing complex is composed of AGO and a guide strand. The target particularity of the miRNA-induced silencing complex is because of its communication with integral sequences on target mRNA, which are known as miRNA response elements (MREs).61,62 The severity of miRNA response elements determines where there is miRNA-induced silencing complex inhibition or AGO2-dependent slicing of target mRNA. An adequate integral miRNA: MRE interaction encourages endonuclease activity of AGO2 and marks mRNA cleavage. On the other hand, this interaction destabilizes the linkage between AGO and the 3′ end of the miRNA which results in its degradation.63,64 The development of a silencing miRISC complex begins with enlisting the GW182 proteins family by miRISC.GW182 gives scaffold essential to enlist other effector proteins like poly(A)-deadenylase complexes PAN2-PAN3 and CCR4-NOT, following the interaction between miRNA: target mRNA.PAN2/3 activates the target mRNA poly(A)-deadenylation and is finished by the CCR4-NOT complex.65,66 Effective deadenylation is encouraged by the interaction between poly(A)-binding protein C (PAPBC) and tryptophan(W) repeats of GW182. Consequently, decapping takes place by DCP2 (decapping protein 2) and linked protein.67,68

MicroRNA-Mediated Translational Activation

Even though various studies are centered on how miRNAs inhibit gene expression, few studies have observed up-regulation of gene expression by miRNAs.To activate translation, in serum-starved cells, AGO2 and FXR1(Fragile-x-mental retardation related protein 1) were linked with AREs(AU-rich elements) at 3′ UTR.69,70 Various miRNAs were seen to be linked with AGO2 and FXR1 to trigger translation amid cell cycle arrest, but they prohibit translation in proliferating cells. Upregulation of gene expression by miRNAs was seen in quiescent cells like oocytes. Instead of GW182,miRNA-mediated translation activation contains FXR1 and AGO2.In such a way, it was it is indicating that miRNA-mediated upregulation of gene expression appears beneath definitive conditions.71,72

MicroRNA-Mediated Transcriptional and Post-transcriptional Gene Regulation Within the Nucleus

Human AGO2 commute amid the nucleus and cytoplasm employing interaction with TNRC6A containing export signal and nuclear localization. Nuclear localized miRISC is linked with euchromatin at gene loci along with an active transcription. Nuclear localized miRISC controls the post-transcriptional levels and transcriptional rates of mRNA.73,74 It is observed that within the nucleus, low molecular weight miRISC manages interaction with mRNAs.It results in the activation of nuclear mRNA degradation. Enhancement of

miRNA at actively transcribed genes advocates that post-transcriptionally miRISC interacts with target mRNA. The engagement of Drosha and AGO in mRNA splicing additionally encourages post-transcriptional miRISC-mRNA interactions. miRISC directly controls the transcription.75,76 According to the study done by Miao et al, they observed that nuclear mir522 interacts with DNA cruciform structure within the CYP2E1 promoter and suppresses its transcription.77,78

miRNAs and Their Role in Oncogenesis

About 60% of human gene expression is regulated by miRNAs.one miRNA molecule can adhere to various target mRNAs. Also, different miRNAs inhibit one mRNA molecule.79,80 Based on the miRNAs function in tumor development,miRNAs are classified into suppressor miRNAs (Table number 1) and oncogenic miRNAs (Table number 2).

Micro RNA	Type of Cancer
miR-34b/c	Lung cancer81,82
miR-126	Breast and Lung cancer83,84,85
miR-155	Breast cancer86
miR-375	Breast cancer87
miR-494	Lung cancer88
miR-551a	Gastric cancer89

Table number 1:Various Tumor suppressor miRNAs with their expression in cancer

Micro RNA	Type of Cancer
miR-21	Breast cancer90
miR-27a	Non Small cell lung cancer91
miR-30a/c	Renal cell carcinoma92
miR-181a/b	Breast and liver cancer93,94
miR-196a	Gastric cancer95
miR-421	Gastric cancer96

Table number 2 :Various oncogenic miRNAs with their expression in cancer

Lack of expression or decreased expression of suppressor miRNAs results in increased gene expression that is essential for tumor progression, in addition to transcription factors and anti-apoptotic proteins. In 2017, decreased expression of miR-15 and miR16 molecules was seen in CCL(chronic lymphocytic leukemia), which results in the prohibition of the apoptosis process and leads to uncontrollable leukemic cell proliferation.97 The procedure of DNA methylation plays a significant role in the regulation of suppressor miRNA expression in cancer cells. For example, hypermethylation of miRNA promoters (miR-342,miR-137,miR-9,miR-34,let-7) results in reduced expression and progress of colorectal cancer. Increased activity of methyltransferase 3A DNA (DNMT3A) is the result of decreased expression of miR-143 in colorectal cancer.98,99 Increased expression of selected miRNAs is more commonly seen in colorectal cancer cells because they are usually oncogenic in nature. Amplification of genes that encodes miRNA and further competent biogenesis results in increased miRNA expression.100 A number of miRNA molecules, participating in the initiation, progression as well as metastasis of breast cancer are recognized. Few studies have observed that there is overexpression of oncogenic molecules miR-221,miR-210, and miR-21 in triple-negative breast cancer, which is linked with smaller disease-free time and poor survival.101,102 Increased expression of miRNA results in the inhibition of many genes along with a suppressor effect. For example,oncomiR-1 prohibits the expression of the Rbl2 suppressor gene. By silencing CDK (cyclin-dependent kinases) inhibitors, oncogenic miRNAs such as miR-31,miR-24, and miR-21, increases proliferative potential of cells.103

miRNA AS AN IMPORTANT TARGET FOR THE DEVELOPMENT OF ANTICANCER DRUGS

The most essential subject matter in the development and research of new drugs is an analysis of drug targets. miRNA is an essential substance in the research of drug targets. miRNA has the peculiar feature of regulating numerous target genes and is present at the midway of multi-target regulatory network.104,105 Because of a complex and fine regulatory mechanism,

possesses by miRNA, the entire signal pathway becomes favorable drug therapeutic targets in cancer. Additionally, miRNA-based drugs targets the molecules that cannon be targeted by chemical drugs.106,107

Restoring miRNA by Small Molecules

The down-regulated expression of miRNA can be rejuvenated by a few small-scale molecular compounds like hypomethylating agents.5-azacytidine and Decitabine are two drugs used for the treatment of myelodysplastic and it is observed that they increase the expression of certain miRNAs.108Furthermore, enoxacin was also proven to boost the biosynthesis of different miRNAs.In the cell-cultured test, treatment by enoxacin leads to the upregulation of miRNA expression. Therefore, these examples proposed the possible role of restoring miRNA by small molecules for purpose of anticancer therapeutics.109,110

Restoring miRNA by Oligonucleotides

miRNA mimics are other more definitive procedures for miRNA restoration. miRNA are double-stranded RNA molecules that are chemically synthesized and by counterfeit of endogenous miRNAs, it regulated the miRNA function.111 It was found that target delivery of let-7 and miR-34a mimics by utilizing the lipid emulsions could necessarily prohibit the progression of cancer in the colon xenograft mouse model. The miR-26a inhibits the proliferation of cancer cells and reduces tumor volume by using adeno-associated virus carriers. Predominantly, the approach for restoring miRNA by liposome-formulated miR-34 mimic has been formed for clinical trials in patients having liver cancer.112,113

Inhibiting miRNA by Oligonucleotides

The most commonly used method to intercept the miRNA function is associated with Antisense oligonucleotide and miRNA sponges. Antisense oligonucleotides consist of locked nucleic acid and antagomirs.114 An increased expression of miR-21 was linked with the initiation and progression of cancer of melanoma. Using the B16F10 cell line, in vitro, a considerable reduction was observed in transfected cell quantity with LNA-anti-miR21. The transfected cells demonstrate observable apoptosis. Furthermore, treatment of anti-miR21 could prohibit the growth of tumors in xenograft mouse models.115 Antagomir is specifically labeled and chemically altered single-stranded small RNA. It is a competent blocker distinctively used to prohibit endogenous miRNA.116According to Arefeh Kardani et al, suppression of miR155 in cell lines of MCF-7 breast cancer was determined by the treatment of gold nanoparticles with antagomir-155.117In a study done by Chen et al, they observed that inhibition of miR194 by antagomir-194 substantially decreases the proliferation of MDA-MB-231 and MCF-7 breast cancer cells.118

Small Molecule Inhibitors of microRNA

A modern trend is an approach towards developing small molecule drugs in miRNA regulation. By free diffusion, small molecules cross the cell membrane and harmonize the miRNA function like a microRNA mimic.119Jiang's research group in 2010 stated that Trypaflavine (TPF) substantially downregulated the miR-21 expression. Additional research demonstrates that Trypaflavine could inhibit the development of RISC by limiting the assembly of Argonaute 2 (AGO2) and miR-21 protein, which results in the downregulation of miR-21 expression level.120 In their study, Davies et al observed that kanamycin A could prohibit the let-7 expression by confining to pre-let-7 and interrupting with Dicer.121 miR-122,a liver definitive miRNA ,grounds for almost 72% of total miRNA in adult liver.It is known as one of the earliest miRNAs with tissue specific expression.Presently,it is observed that miR-122 perform an essential role in governing

physiological functions of liver such as metabolism of fat.122,123

Various Strategies to use miRNAs Therapeutics

Regardless of the appreciable improvement in our knowledge of molecular carcinogenesis of human cancers and the considerable research on targeted and combined therapies, there is quite a need for the improvement of novel therapeutic tools.RNA molecules are now the midpoint of molecular oncology, with utilization for diagnosis and therapy. Sandwich RNAi Inhibition Strategy: This strategy is associated with the use of numerous agents to target one definitive molecular defect associated with cancer pathogenesis. This strategy is explained by targeting EphA2 (ovarian cancer oncogene), by employing an association of EphA2 targeting siRNAs and miR-520d-3p mimics. Dual targeting of EphA2 presented synergistic anti-tumor adaptability than either monotherapy only, both in vivo and in vitro. miRNA-siRNA therapy apparently decreases the level of EphA2 protein and prohibits invasion and migration. This therapy also suppresses the growth of the tumor.124,125 Multiplex RNAi inhibition strategy: In this strategy, numerous molecular defects combined in a multi-step passageway of precise cancer can be targeted. By using in vivo and in vitro modes, they demonstrate that siRNA-mediated suppression of KRAS along with RAAF or P13K conjunction could diminish KRAS-mutant colorectal cancer. These studies emphasize the relevancy and potential of RNAi-based therapeutic strategies in the treatment of cancers.126

Application of miRNA-Based Therapeutics in Selected Cancers

Breast Cancer

Human epidermal growth factor receptor 2 (HER-2) positive breast cancer grounds for 30% of cases linked with poor prognosis.In vivo studies of breast cancer in mice models determined that lentiviral delivery of miR-125a-5p decreases the growth of the tumor, angiogenesis, and metastasis by precisely targeting Histone deacetylase 4 (HDAC4).In their study, Hayward et al observed that transfection of miR-125a-5p brings down the HER-2 proto-oncogene in 21MT-1 breast cancer cells. This leads to lower proliferative and migratory potential because of MAPK and PI3K/AKT signaling inactivation.127,128 According to Deng et al, the dispensation of these formulations into mice improved the response to chemotherapy and reduces the migration of cancer cells as a result of Notch signaling inactivation by miE-34a.129In a related manner, the uptake of Adriamycin by MCF-7 cells was raised when delivered with anti-miR-21 in PEI graphene oxide carriers. As cancer cells persistently show alterations in multiple miRNAs, combinatory strategies have been carried out.130 In their studies, Panebianco et al observed that silica nanoparticles permit the distribution of miR-34a into mammary tumors and mammospheres. The potential of sphere formation and tumor growth was reduced by miR-34a/SiO2NPs complexes. The levels of various target genes of miR-34a such as Cyclin E2, NOTCH1, and c-Myc were substantially reduced which implies the biological activity of administering miR-34a.131,132

Lung Cancer

Lung cancer is the most common reason for cancer-related death worldwide depending upon population and stage. Liposomes are reported to be especially favorable for the delivery of drugs to the lungs.miR-34a is the most confirmable tumor suppressor miRNA, competent for causing initiation of apoptosis and cell cycle arrest. Downregulation of miR-34a is observed in different solid tumors like lung cancer, indicating that replacement therapy might be competent for restoring its physiological levels. Wiggins et al in their study observed that systemic delivery of synthetic miR-34a could actually inhibit the growth of tumors in Non-small cell lung cancer (NSCLC).however, no toxicity or immunogenicity

was seen.133,134 Kasinsi et al proposed a combinatory way to deliver miR-34 and let-7b by u.sing NOV340 liposomes in Non-small cell lung cancer (NSCLC). This method decreases tumor burden and encourages 40% increase in the survival rate of KrasG12D/+/Trp53flx/flx mutant mice.135 Another method shows that DOTMA-based cationic lipoplexes(Lps) strongly transported miR-29b to Non-small cell lung cancer A549 cells in culture and Non-small cell lung cancer xenograft mouse model. After multiple injections of miR-29b loaded lipoplexes, the treated mice show decreases tumor size when compared to negative controls. Wu et al in their study observed considerable reduction in miR-29b oncogenic targets DNA (cytosine-5-)-methyltransferase 3 beta (DNMT3B), Induced myeloid leukemia Cell differentiation protein (MCL1), and Cell division protein kinase 6 (CDK6).136

Adrenocortical Cancer

Adrenocortical cancer is a rare and extremely aggressive malignancy. It occurs in the cortex of the adrenal gland. Mitotant is the only drug for the treatment of this cancer that shows single-agent action located on its adrenolytic activity.137

The numerous molecular and genetic alterations stated in adrenocortical cancer consist of broad deregulations of miRNA expression. In most commonly deregulated miRNAs in adrenocortical cancer,miR-503,miR-483,miR-210, and miR-139-5p appeared to be upregulated, while miR-335 and miR-195 appeared to be down-regulated.138-143

Glioblastoma

Glioblastoma is a destructive malignancy. The application of RNA interference technology determines new awareness for glioblastoma (GBM) gene therapy. For example,mirR-21 has been identified as considerable oncomiR upregulated in glioblastoma. It leads to tumorigenesis by precisely targeting PTEN, hence inhibiting the expression of major apoptosis-enabling genes like p53 and caspases. Overexpression of miR-21 is also linked with drug resistance, consequently failure of chemotherapy occurs.144,145

Ovarian Cancer

A comprehensive study of The Cancer Genome Atlas (TCGA) data disclosed a broad panel of miRNA deregulations in three subtypes of ovarian cancer (endometrioid, serous, and clear cell carcinoma). The miR-200 family demonstrated to be of impressive prognostic value as it contains five tumor suppressor miRs.These are miR-429,miR-200a,miR-200b,miR-200c and miR-141.Upregulation of miR-200c shows a favorable prognosis in ovarian cancer. Its overexpression damages the invasive and migratory potential of SCOV3 cell lines and substantially raises their susceptibility to microtubule-targeting chemotherapeutics that as PTX (paclitaxel).146,147

Cervical Cancer

The most prevalent malignancy diagnosed in women is cervical cancer.HPV (human papilloma virus) is seen in 99% of all cases. Exact mechanisms are not assumed, but it appears that there is an association between the modified expression of miRNAs and the incident of cervical cancer.148,149,150 Some studies on cervical cancer have shown the upregulation of many circulating miRNAs. like miRNA-205,miRNA-203,miRNA-21,miRNA-20a,miRNA-485-5 along with upregulation of few tissue-specific miRNAs such as miR-149,miR-135b,miE-10a and miR-7. Some miRNAs were downregulated in cervical cancer such as miR-148b,miR-214,miR-195, and miR-138, indicating their function as tumor suppressors.151,152,153,154

microRNA in Cancer Diagnosis and Therapy

miRNAs are observed as potential markers of cancer. The use of miRNAs as predictive and prognostic biomarkers appears to be specifically clinically important. Such as, increased expression

of miR-21 has a strong link with a predilection to develop lung cancer155-156, pancreatic cancer157, breast cancer158, and colorectal cancer159. Expression of miRNA in chemo-resistant cancer cells may contradict from cells that are chemotherapy sensitive. For example, increased miR-21 expression corresponds with resistance to fluorouracil therapy because of decreased expression of MSH2 (repair protein).160,161 According to the various in vitro studies, it has been observed that increased expression of miR-224,miR-215,miR-140, and miR-20a develops the chemo-resistance to oxaliplatin, methotrexate, tenipozide, or fluorouracil in colorectal cancer cells.162,163,164,165. Selected serum/plasma circulating miRNAs may be well-used to differentiate numerous cancer patients from healthy people such as those with gastric, pancreatic, colorectal, lung, hepatocellular, and breast cancer, making them important for the earliest diagnosis. There are two tests that aid in the diagnosis of cancer depending upon miRNA profile. The ThyraMIR test evaluates the expression of 10 particular miRNAs.The miRNAs are miR-551b, , miR-375, miR-223-3p, miR-204-5p, miR-155-5p, miR-146b, miR-146b-5p, miR-138-1-3p, miR-31-5p miR-29b-1-5p).These miRNAs permit for recognition of the category of thyroid cancer.166-172 Another instance is the predictive diagnostic test,miRpredX-31-3p.It is used in those patients having colorectal cancer without any mutations in the K-RAS gene. Assessment of miR-31-3p expression is accomplished in histopathological sections from tumors of the colon. Decreased expression of miR-31-3-p concludes higher clinical effectiveness of anti-EGFR therapy against conventional chemotherapy.173,174 Observing the differences in the expression profiles of miRNAs could assist in the early recognition of cancer cells and aid as a predictive factor for treatment or diseases. Two therapeutic strategies have been developed using miRNAs that possibly inhibit the development of cancer.175,176 The first therapeutic strategy is called “replacement therapies” and the second is associated with the inhibition of oncogenic miRNAs. Replacement therapy acts by encouraging the expression of suppressor miRNAs.177,178,179 Prohibition of oncogenic miRNAs can be accomplished by the addition of synthetic DNA and RNA molecules that resembles on suppressive effects in cancer cells. Various types of inhibitory molecules are used such as miRNA masks, MTg-AMOs (Multiple-target anti-miRNA antisense oligodeoxyribo nucleotides), amiRNA (AntagomiRs), AMOs (Anti-miRNA oligonucleotides),miRNA sponges, LNA (Locked nucleic acid antisense oligonucleotides).180,181,182

CONCLUSION

A considerable total of miRNAs and their functions have been identified and more are predicted to be investigate in future. Most of the progressive conserved miRNAs is part of different gene families. Most of the miRNAs have different target genes, hence scientist will have to discover the link between the various members of miRNA gene family and various target genes. miRNA has wide application possibility in cancer treatment. Some miRNAs may be precisely related to cancer by regulating cell differentiation, proliferation and apoptosis, while others may be indirectly associated to cancer by aiming tumor suppressor genes and oncogenes. Research on miRNA role in incidence and improvement of malignant tumor develop into hot topic.

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