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Review Article

Enzymatic Catalytic Attributions to lncRNAs: A Narrative Review of Mechanisms, Metabolic Regulation and Therapeutic Implications

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Abstract

Long noncoding RNAs (lncRNAs) have traditionally been viewed as transcriptional regulators or molecular scaffolds with limited functional capacity beyond the regulation of gene expression. However, increasing evidence has demonstrated that lncRNAs can directly and indirectly modulate enzymatic activity through diverse mechanisms, including allosteric regulation, molecular scaffolding, substrate channeling, enzyme stabilization, and regulation of post-translational modifications. This narrative review summarizes current understanding of lncRNA-mediated regulation of metabolic enzymes and protein modification pathways, with particular emphasis on cancer metabolism. We examine reported interactions between lncRNAs and metabolic enzymes including ENO1, PKM2, LDHA, IDH1, and ACLY, as well as their involvement in phosphorylation, ubiquitination, and SUMOylation pathways. The review also discusses emerging evidence concerning ribosome-associated lncRNAs, RNA stability, nonsense-mediated decay, and the possibility that some functions attributed to lncRNAs may be mediated by encoded micropeptides. Although lncRNAs can substantially influence enzymatic activity and metabolic flux, current evidence does not establish that human lncRNAs generally function as independent catalysts of chemical reactions. Distinguishing direct RNA-mediated regulation from indirect effects and peptide-mediated functions remains an important challenge. Finally, we discuss the therapeutic potential of targeting lncRNA-enzyme interactions and identify key questions regarding interaction specificity, spatiotemporal regulation, evolutionary conservation, and the development of RNA-based therapeutic strategies.

Introduction

The central dogma of molecular biology, which describes the transfer of genetic information from DNA to RNA to protein, has been expanded by the recognition of extensive regulatory functions performed by noncoding RNAs. Among these transcripts, long noncoding RNAs (lncRNAs), generally defined as RNA molecules longer than 200 nucleotides with limited protein-coding potential, have emerged as important regulators of gene expression and cellular processes.

Initially regarded largely as transcriptional noise or passive scaffolds for protein complexes, lncRNAs are now recognized to participate in diverse regulatory mechanisms through interactions with DNA, RNA, and proteins. An increasing body of evidence indicates that lncRNAs can influence enzymatic processes by interacting directly with metabolic enzymes and proteins involved in post-translational modification. These interactions may alter enzyme conformation, stability, localization, oligomerization, substrate accessibility, or recruitment to regulatory complexes. In addition, lncRNAs can function as molecular scaffolds that bring enzymes and their substrates or interacting partners into proximity, thereby influencing metabolic flux and signaling pathways. Such mechanisms have been increasingly investigated in cancer, where altered metabolism and dysregulated protein modification are important features of tumor development and progression. It is important, however, to distinguish between lncRNA-mediated regulation of enzymatic activity and true RNA catalysis. While some RNAs are established catalysts, particularly ribozymes, current evidence does not demonstrate that human lncRNAs generally catalyze chemical reactions independently of protein partners. Rather, the available evidence primarily supports regulatory functions in which lncRNAs influence the activity, stability, localization, or interactions of protein enzymes. This distinction is particularly important when interpreting studies describing lncRNAs as catalytic regulators or components of cellular catalytic networks.

Several mechanisms have been proposed to explain lncRNA-mediated regulation of enzymes. These include direct binding and allosteric effects, molecular scaffolding and substrate channeling, regulation of protein stability through ubiquitination pathways, and recruitment or modulation of enzymes involved in post-translational modifications. Metabolic lncRNAs have received particular attention because their interactions with glycolytic and other metabolic enzymes can influence glucose utilization, lactate production, redox balance, and cellular adaptation to metabolic stress. This review examines recent evidence concerning lncRNA-mediated regulation of enzymatic pathways, with particular emphasis on cancer metabolism and protein modification pathways. We discuss reported interactions involving metabolic enzymes such as ENO1, PKM2, LDHA, IDH1, and ACLY, as well as lncRNA involvement in phosphorylation, ubiquitination, and SUMOylation. We also consider ribosome-associated lncRNAs, RNA stability, nonsense-mediated decay, and the possibility that some functions attributed to lncRNAs may instead involve encoded micropeptides. Finally, we discuss therapeutic implications and the major unanswered questions surrounding the specificity, biological significance, and translational potential of lncRNA-enzyme interactions [1-3].

Conceptual Framework: LncRNAs as Catalytic Regulators

Redefining Catalytic Function in RNA Biology

Traditional definitions of biological catalysis have centered on protein enzymes and ribozymes. However, lncRNAs exhibit several properties that warrant reconsideration of their catalytic potential. First, lncRNAs possess complex secondary and tertiary structures, including stem-loops, pseudoknots, and G-quadruplexes, that create specific binding interfaces for protein partners. Second, lncRNAs demonstrate conformational flexibility, enabling induced-fit interactions with enzymes. Third, lncRNAs can position multiple enzymes in close proximity, effectively increasing local substrate concentrations and reaction rates (figure-1). Shin and colleagues have proposed that lncRNAs function as “fine-tuning regulators” of enzymatic reactions, optimizing rather than simply activating or inhibiting catalytic processes. This nuanced perspective distinguishes lncRNA-mediated regulation from classical allostery or competitive inhibition [4,5].

Mechanisms of LncRNA-Enzyme Interaction

Current evidence supports at least four distinct mechanisms by which lncRNAs modulate enzymatic activity:

Direct binding with allosteric effects: LncRNAs bind directly to enzyme surfaces, inducing conformational changes that alter catalytic efficiency. For example, lncRNA-6195 binds enolase 1 (ENO1) at amino acid residues 237–405, reducing its enzymatic activity without affecting protein stability.

Substrate channeling and scaffolding: LncRNAs serve as physical platforms that co-localize multiple enzymes within metabolic pathways. NEAT1_1 simultaneously binds PGK1, PGAM1, and ENO1, facilitating substrate transfer between sequential glycolytic enzymes.

Post-translational modification enhancement: LncRNAs recruit kinases, ubiquitin ligases, or SUMOylation enzymes to specific targets, increasing modification efficiency. The lncRNA HULC enhances phosphorylation of LDHA and PKM2, thereby activating glycolytic flux.

Metabolite-mediated regulation: Some lncRNAs respond to metabolic cues and adjust enzyme activity accordingly. gLINC is transcriptionally induced by c-Myc under serine/glycine starvation, promoting glycolytic enzyme assembly and ATP production [6].

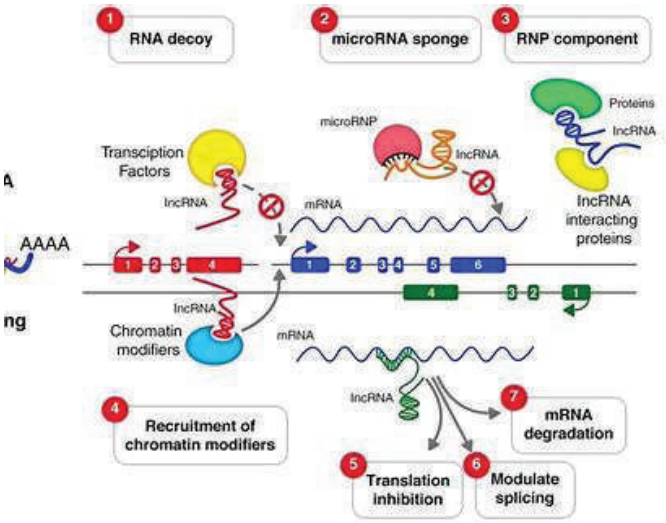


Figure 1: Basic mechanisms of action of lncRNA.

LncRNAs in Metabolic Enzyme Regulation

Glycolytic Pathway Modulation

The Warburg effect enhanced aerobic glycolysis in cancer cells represents one of the best- characterized contexts for lncRNA-mediated metabolic regulation. Recent studies have identified multiple lncRNAs that directly interact with glycolytic enzymes to modulate reaction rates and metabolic flux.

ENO1 regulation by lncRNA-6195: Enolase 1 catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate, a critical step in glycolysis. Yu and colleagues demonstrated that lncRNA-6195 forms a complex with ENO1 in hepatocellular carcinoma (HCC) cells, reducing enzymatic activity by approximately 40%. Mechanistically, nucleotides 101–529 of lncRNA-6195 bind the 237–405 amino acid region of ENO1, inducing conformational changes that impair substrate binding. Overexpression of lncRNA-6195 decreases phosphoenolpyruvate levels and shifts cellular metabolism toward oxidative phosphorylation, suppressing HCC proliferation in vitro and in xenograft models.

NEAT1_1 as a glycolytic scaffold: The nuclear paraspeckle assembly transcript 1 (NEAT1) generates two isoforms, with the shorter NEAT1_1 localizing to the cytoplasm where it promotes aerobic glycolysis in breast cancer. Using fluorescence polarization assays and cross-linking immunoprecipitation, Park and colleagues demonstrated that NEAT1_1 simultaneously binds PGK1, PGAM1, and ENO1. This scaffolding function accelerates substrate channeling, increasing glucose consumption and lactate production. Notably, NEAT1 knockout mice crossed with MMTV-PyVT transgenic animals showed reduced mammary tumor weight and size compared to wild-type controls, establishing in vivo relevance.

gLINC coordinates multiple glycolytic enzymes: The c-Myc-responsive lncRNA gLINC (glycolysis-associated lncRNA) represents a paradigm for coordinated metabolic regulation. Under serine and glycine starvation conditions, gLINC binds PGK1, PGAM1, ENO1, PKM2, and LDHA simultaneously, as demonstrated by RNA affinity pull-down and RIP assays. This multi-enzyme scaffolding enhances glycolytic flux and accelerates ATP production, sustaining tumor cell viability under nutrient stress. gLINC depletion reduces complex assembly and decreases proliferation in HCC, colorectal cancer, and cervical cancer models.

WFDC21P disrupts enzyme oligomerization: An elegant mechanism is exhibited by WFDC21P, which binds both PFKP (phosphofructokinase, platelet type) and PKM2 in HCC cells. PFKP functions as a tetramer, and WFDC21P binding disrupts tetramer formation, reducing enzymatic activity. Concurrently, WFDC21P inhibits PKM2 nuclear translocation, preventing its non-metabolic functions in gene regulation. This dual mechanism suppresses HCC proliferation and metastasis, demonstrating how lncRNAs can simultaneously regulate metabolic and non-metabolic enzyme functions [7,8].

Tricarboxylic Acid Cycle Regulation

While glycolysis has received substantial attention, emerging evidence indicates that lncRNAs also modulate tricarboxylic acid (TCA) cycle enzymes.

TINCR protects ACLY from ubiquitination: Terminal differentiation-induced ncRNA (TINCR) binds ATP-citrate lyase (ACLY) in nasopharyngeal cancer cells, protecting it from ubiquitin-mediated degradation. ACLY generates acetyl-CoA from citrate, providing substrates for fatty acid synthesis and histone acetylation. TINCR binding, mapped to the ACLY C-terminus through RNA-EMSA, stabilizes the enzyme and maintains acetyl-CoA pools, promoting cell proliferation, migration, and invasion [9,10].

IDH1-AS1 enhances isocitrate dehydrogenase activity: The antisense lncRNA IDH1-AS1 binds IDH1 (isocitrate dehydrogenase 1) in cervical cancer cells, promoting enzyme dimerization and enhancing catalytic activity. IDH1 converts isocitrate to α-ketoglutarate, generating NADPH critical for redox balance. IDH1-AS1 overexpression suppresses cervical cancer proliferation, suggesting tumor-suppressive functions through metabolic regulation [11,12].

GAS5 disrupts TCA cycle enzyme complexes: Growth arrest-specific 5 (GAS5) binds malate dehydrogenase 2 (MDH2) and citrate synthase (CS) in breast cancer cells, disrupting their interactions with fumarate hydratase (FH). This disruption impairs TCA cycle flux and reduces oxidative phosphorylation. GAS5 expression is downregulated in breast cancer, and its restoration suppresses tumor growth [13,14].

Amino Acid Metabolism

Beyond glucose metabolism, lncRNAs regulate amino acid metabolic enzymes. LOC113230 binds argininosuccinate synthase 1 (ASS1) in colorectal cancer cells, facilitating assembly of the LRPPRC-TRAF2 E3 ubiquitin ligase complex and inducing K234 ubiquitination of ASS1. This modification targets ASS1 for degradation, reducing arginine biosynthesis and suppressing proliferation. The identification of lncRNA-mediated ubiquitination of metabolic enzymes reveals an additional layer of regulatory complexity.

LncRNAs in Post-Translational Modification Enzymes

Post-translational modifications (PTMs) including phosphorylation, ubiquitination, SUMOylation, and acetylation orchestrate protein function in health and disease. LncRNAs have emerged as critical regulators of PTM enzymes, modulating their activity, substrate specificity, and subcellular localization [15,16].

Phosphorylation Cascades

HULC enhances LDHA and PKM2 phosphorylation: The lncRNA highly upregulated in liver cancer (HULC) binds both LDHA and PKM2 in HCC cells, enhancing their phosphorylation by unidentified kinases. Surface plasmon resonance studies confirmed direct binding with nanomolar affinity . Phosphorylated LDHA and PKM2 exhibit increased enzymatic activity, promoting glycolytic flux and lactate production. This mechanism links lncRNA expression directly to metabolic enzyme activation through PTM enhancement [16,17].

NEAT1 and kinase scaffolding: Beyond its role in glycolysis, NEAT1 scaffolds kinases with their substrates, increasing phosphorylation efficiency. In breast cancer, NEAT1 binds AKT and its substrate GSK3β, promoting GSK3β phosphorylation and inactivation. This scaffolding function amplifies AKT signaling, contributing to proliferation and survival [18, 19].

Ubiquitination and Degradation Pathways

LOC113230 and E3 ligase recruitment: As described above, LOC113230 recruits the LRPPRC-TRAF2 E3 ligase complex to ASS1, promoting ubiquitination and proteasomal degradation. This represents a novel mechanism where lncRNAs serve as adaptors between E3 ligases and specific substrates, conferring selectivity to the ubiquitin-proteasome system [20,21].

NORAD regulates PUMILIO activity: The lncRNA NORAD (noncoding RNA activated by DNA damage) binds PUMILIO proteins, which are RNA-binding proteins that repress target mRNAs. By sequestering PUMILIO, NORAD prevents PUMILIO-mediated repression of multiple mRNAs encoding mitotic and DNA repair factors. While not directly enzymatic, this mechanism modulates the availability of PUMILIO for mRNA targeting, indirectly affecting the stability of transcripts encoding ubiquitination enzymes [22,23].

SUMOylation and Other Modifications

SUMOylation (Small Ubiquitin-like Modifier modification) regulates protein localization, stability, and interaction partners. Recent evidence implicates lncRNAs in SUMOylation pathways, though mechanisms remain less characterized than for phosphorylation or ubiquitination. Shin and colleagues reported that several lncRNAs co-immunoprecipitate with SUMO-conjugating enzymes in cancer cells, suggesting physical interactions that may enhance SUMO transfer efficiency [24,25].

Ribosome-Associated LncRNA Catalysis and Stability

An emerging area of investigation concerns the relationship between lncRNAs and ribosomes. While lncRNAs are defined by their lack of protein-coding potential, ribosome profiling studies have revealed that up to 70% of cytoplasmic lncRNAs interact with ribosomes in human cells [26].

Ribosome Engagement and LncRNA Stability

The association between lncRNAs and ribosomes has profound implications for lncRNA stability. In messenger RNAs (mRNAs), translating ribosomes protect transcripts from nucleases, while ribosomal stalling triggers decay pathways including nonsense-mediated decay (NMD) and no-go decay. Similar mechanisms appear to operate for lncRNAs [27].

NMD restricts lncRNA expression: The nonsense-mediated decay pathway, which degrades mRNAs with premature termination codons, also targets a substantial fraction of lncRNAs. In the budding yeast *Naumovozyma castellii*, 592 lncRNAs accumulate in UPF1 (NMD factor) mutants, indicating NMD sensitivity. Ribosome profiling confirmed ribosome binding to a subset of these lncRNAs, supporting translation-dependent degradation mechanisms. This study demonstrates that NMD-mediated restriction of lncRNA expression has been conserved through evolution, suggesting functional importance [28,29].

Ribosome-associated decay pathways: LncRNAs can trigger ribosome-associated decay when ribosomal translocation is impaired. In human cells, translation elongation inhibitors stabilize specific lncRNAs, indicating that ongoing ribosome transit is required for their normal turnover. The SKIV2L helicase and AVEN protein monitor ribosome stalling on structured lncRNAs, initiating 3′–5′ decay through the exosome complex when stalling cannot be resolved [30].

Functional Implications of Ribosome-LncRNA Interactions

The finding that many lncRNAs associate with ribosomes raises questions about the functional consequences. Several possibilities exist [30-34]:

Cryptic translation: Some lncRNAs contain small open reading frames (smORFs) encoding functional micropeptides. The lncRNA LOC100507537 encodes DWORF (dwarf open reading frame), a 34-amino acid peptide that enhances cardiac muscle contractility by activating the SERCA pump. Similarly, the lncRNA sarcolamban in *Drosophila* encodes two micropeptides regulating cardiac contraction. These findings challenge the strict definition of lncRNAs as noncoding and suggest that some lncRNA "catalytic" functions may be mediated through encoded peptides rather than RNA structures [29,30].

Translation-independent ribosome binding: Ribosomes may bind lncRNAs without productive translation, potentially serving to mark lncRNAs for degradation or to sequester ribosomes from productive translation. The functional consequences of such non-productive binding remain poorly understood.

Ribosome-mediated lncRNA folding: Ribosome binding could influence lncRNA secondary structure, potentially exposing or occluding binding sites for protein partners. This speculative mechanism would position ribosomes as indirect regulators of lncRNA catalytic activity [30-34].

LncRNAs in Cell Death Pathways: Ferroptosis, Pyroptosis, and Necroptosis

Beyond metabolic regulation, lncRNAs influence non-apoptotic regulated cell death pathways that involve enzymatic cascades. Ferroptosis iron-dependent lipid peroxidation leading to cell death has attracted particular attention [5,33,34].

LncRNAs regulate ferroptosis enzymes: The ferroptosis pathway involves multiple enzymes including GPX4 (glutathione peroxidase 4), ACSL4 (acyl-CoA synthetase long-chain family member 4), and lipoxygenases. Several lncRNAs modulate the expression or activity of these enzymes. LINC00336, for example, binds and stabilizes GPX4 in lung cancer cells, suppressing ferroptosis and promoting chemoresistance. Conversely, P53-regulated lncRNAs can promote ferroptosis by repressing SLC7A11 expression, depleting glutathione [5,35-38].

Pyroptosis and necroptosis regulation: Pyroptosis inflammatory cell death mediated by gasdermin family proteins and necroptosis regulated necrosis involving RIPK1/RIPK3/MLKL are also modulated by lncRNAs. While direct lncRNA-enzyme interactions in these pathways remain less characterized than for metabolic enzymes, emerging evidence suggests lncRNAs influence caspase-1 and RIPK3 activity through protein-protein interaction scaffolds [5,37,38].

Therapeutic Implications

The identification of lncRNAs as enzymatic regulators opens new therapeutic avenues. Several approaches are under investigation.

Targeting LncRNA-Enzyme Interactions

Small molecules that disrupt lncRNA-enzyme binding could modulate enzymatic activity with high specificity. The structured nature of lncRNAs makes them potentially druggable through RNA-targeting small molecules. For example, compounds that block NEAT1_1 binding to glycolytic enzymes could suppress the Warburg effect in aggressive cancers. Similarly, molecules that enhance lncRNA-6195 binding to ENO1 could shift cancer metabolism away from glycolysis, limiting proliferation [39].

Oligonucleotide-Based Therapies

Antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) can deplete oncogenic lncRNAs. For glycolytic lncRNAs including gLINC and NEAT1, ASO-mediated knockdown reduces tumor growth in preclinical models . Clinical trials of ASOs targeting lncRNAs are underway for various indications, though none have yet targeted lncRNAs involved in enzymatic regulation specifically [40,41].

LncRNAs as Biomarkers

The specificity of lncRNA expression patterns makes them attractive biomarkers for cancer diagnosis and prognosis. Several lncRNAs discussed in this review—including HULC, NEAT1, and GAS5—are dysregulated in multiple cancer types and correlate with patient outcomes . LncRNA expression signatures may predict response to metabolic therapies or identify patients likely to benefit from glycolysis-targeting agents [42,43].

Challenges and Limitations

Several challenges must be addressed before lncRNA-targeting therapies reach the clinic. First, lncRNAs often exhibit cell-type-specific expression, necessitating careful target selection to avoid on-target off-tumor toxicity. Second, lncRNA structures are less characterized than protein structures, complicating rational drug design. Third, redundancy among lncRNAs may limit the efficacy of single-target approaches. Fourth, delivery of RNA-targeting therapeutics to specific tissues remains technically challenging [44-46].

Future Directions and Unanswered Questions

Despite substantial progress, fundamental questions about lncRNA catalytic attributions remain unanswered.

What determines lncRNA-enzyme interaction specificity? While multiple lncRNA-enzyme pairs have been identified, the sequence and structural determinants of binding specificity remain poorly understood. High-throughput approaches including CLIP-seq and RBDmap could systematically map lncRNA-protein interaction interfaces [44].

Do lncRNAs exhibit true catalytic activity? To date, no lncRNA has been demonstrated to catalyze a chemical reaction independently of protein partners. Whether lncRNAs can function as true ribozymes in human cells remains an open question. The discovery of self-cleaving ribozymes in noncoding RNAs suggests this possibility cannot be dismissed [44,45].

How do lncRNAs achieve spatiotemporal regulation of enzymatic activity? LncRNA expression patterns and subcellular localizations are tightly regulated, but the mechanisms controlling lncRNA availability to enzyme partners are incompletely understood. Single-molecule imaging approaches could reveal real-time dynamics of lncRNA-enzyme interactions [44-46].

What is the evolutionary conservation of lncRNA catalytic functions? While some lncRNAs are conserved across mammals, many are primate- or human-specific. Whether lncRNA-mediated enzyme regulation represents an ancient or recently evolved regulatory mechanism remains unclear. Comparative studies across species are needed [44,45].

Can lncRNA-enzyme interactions be engineered for synthetic biology applications? The modularity of lncRNA scaffolds suggests they could be engineered to create synthetic regulatory circuits. Designer lncRNAs that bring together specific enzyme pairs could be used to redirect metabolic flux or create novel biosynthetic pathways [46].

Conclusion

lncRNAs have emerged as important regulators of enzymatic processes, particularly in metabolic and signaling pathways associated with cancer. Rather than functioning primarily as passive scaffolds, lncRNAs can influence enzyme activity through direct binding, molecular scaffolding, regulation of protein stability, control of subcellular localization, and modulation of post-translational modification pathways. Examples involving glycolytic enzymes, TCA-associated metabolic proteins, amino acid metabolism, and enzymes involved in

phosphorylation and ubiquitination illustrate the diverse mechanisms through which lncRNAs can alter cellular metabolism and signaling. At the same time, the available evidence requires careful distinction between regulation of protein enzyme activity and intrinsic RNA catalysis. Although lncRNAs can strongly influence enzymatic reactions and metabolic flux, there is currently insufficient evidence to establish that human lncRNAs generally function as independent catalysts of chemical reactions. In addition, the discovery of lncRNA-associated micropeptides and ribosome interactions highlights the need to determine whether particular biological effects arise from RNA molecules themselves or from encoded peptides. The therapeutic potential of lncRNA-mediated enzyme regulation remains an important area of investigation. Approaches including antisense oligonucleotides, small interfering RNAs, and molecules designed to interfere with specific lncRNA-protein interactions may provide opportunities to modulate disease-associated metabolic and signaling pathways. However, challenges including cell-type-specific expression, structural complexity, target specificity, delivery, and possible functional redundancy must be addressed before these approaches can be broadly translated into clinical applications. Future studies should focus on defining the molecular determinants of lncRNA-enzyme interactions, establishing their effects using direct biochemical and kinetic approaches, and distinguishing primary RNA-mediated mechanisms from indirect cellular effects. Improved understanding of their spatial and temporal regulation, evolutionary conservation, and functional relationship with encoded micropeptides will further clarify the biological significance of these interactions. Together, current evidence supports lncRNAs as important regulatory components of cellular enzymatic networks while highlighting the need for continued investigation into the precise mechanisms underlying their functions [46-49].

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