Akbarzadeh-Khiavi et al, ***BioImpacts*** 2024;14(1):27696
doi: 10.34172/bi.2023.27696
https://bi.tbzmed.ac.ir/

Targeting long non-coding RNAs as new modulators in anti-EGFR resistance mechanisms

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Article Info

Article Type:
Editorial

Article History:
Received: 17 Nov. 2022
Accepted: 15 July 2023
Accepted: 22 Aug. 2023
ePublished: 29 Aug. 2023

Keywords:
LncRNAs
EGFR
Colorectal cancer
Anti-EGFR resistance
Targeting therapy

Summary

Epidermal growth factor receptor (EGFR) is a cell surface protein that plays a vital role in regulating cell growth and division. However, certain tumors, such as colorectal cancer (CRC), can exhibit an overexpression of EGFR, resulting in uncontrolled cell growth and tumor progression. To address this issue, therapies targeting and inhibiting EGFR activity have been developed to suppress cancer growth. Nevertheless, resistance to these therapies poses a significant obstacle in cancer treatment. Recent research has focused on comprehending the underlying mechanisms contributing to anti-EGFR resistance and identifying new targets to overcome this striking challenge. Long non-coding RNAs (lncRNAs) are a class of RNA molecules that do not encode proteins but play pivotal roles in gene regulation and cellular processes. Emerging evidence suggests that lncRNAs may participate in modulating resistance to anti-EGFR therapies in CRC. Consequently, combining lncRNA targeting with the existing treatment modalities could potentially yield improved clinical outcomes. Illuminating the involvement of lncRNAs in anti-EGFR resistance mechanisms of cancer cells can provide valuable insights into the development of novel anti-EGFR therapies in several solid tumors.

Authors' Biosketch

Mostafa Akbarzadeh-Khiavi is an Assistant Professor of molecular medicine at the Liver and Gastrointestinal Diseases Research Center (LGDRC) and RCPN at Tabriz University of Medical Sciences, working on the development of advanced nano-formulated enzymes/antibodies used for the targeted drug delivery. Currently, he is involved in a project on cellular and molecular mechanisms of chronic disease and new strategies for diagnosing and treating them.

Azam Safary is an Assistant Professor of medical biotechnology at the Connective Tissue Diseases Research Center (CTDRC) and Research Center for Pharmaceutical Nanotechnology (RCPN) at Tabriz University of Medical Sciences, working on the cellular and molecular mechanisms of immune-mediated inflammatory diseases, new strategies for the detection and prevention of them, nano-formulated therapeutic enzymes, and biotechnological aspects of recombinant proteins.

Professor Yadollah Omidi has a Ph.D. degree in Pharmaceutical Sciences (2003, Cardiff University, UK) and completed a postdoctoral program (2004) at Cardiff University. He is currently working as a full professor at Nova Southeastern University College of Pharmacy, Florida. Prof. Omidi's research in advanced targeted diagnosis and therapy of diseases have resulted in over 300 published papers in international journals, 27 book chapters, and a few patents. His H-index is 61 and i10-index is 238. He has consecutively been listed among top 1% highly cited scientists worldwide by WoS-ESI.

Epidermal growth factor receptors (EGFRs) overexpressed by various solid tumors are involved in the initiation, progression, and metastasis of different malignancies such as breast cancer and colorectal cancer (CRC).[1,2] EGFRs are considered clinically valid oncomarkers which can be targeted to inhibit/eradicate cancer cells using various advanced treatment modalities such as monoclonal antibodies (mAbs), Ab-armed nanomedicines, Ab-drug nanoconjugates, hybrid Ab scaffolds like bispecific constructs, aptamer-decorated

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nanosystems, gene therapy, and so forth.[1-7] Specific binding of epidermal growth factors (EGF) to EGFRs results in their dimerization and activation of downstream signaling mechanisms such as MAPK/ERK, PI3K/AKT/mTOR pathways leading to the regulation of cancer cell proliferation, invasion, and angiogenesis.[8,9] Anti-EGFR mAbs such as cetuximab (CET) were shown to substantially improve the overall survival of metastatic CRC (mCRC) patients with wild-type KRAS genotypes.[10] However, in mCRC patients, the therapeutic response to anti-EGFR therapy can be limited due to the development of multiple resistance mechanisms.[11] Numerous genetic factors contribute to the development of resistance mechanisms in cancer cells against anti-EGFR mAbs. These factors include:

- EGFR gene copy number: The number of copies of the EGFR gene can influence the response to anti-EGFR mAbs.
- Protein expression of EGFR ligands: The levels of ligands that bind to EGFR, such as EGF and TGF-alpha, can impact the efficacy of anti-EGFR mAbs.
- HER2 and MET gene amplification: Amplification of HER2 and MET genes, which are involved in signaling pathways related to EGFR, can contribute to resistance against anti-EGFR mAbs.
- Activation of EGFR downstream cascade signaling pathways: Mutations or alterations in downstream signaling pathways of EGFR, such as KRAS, NRAS, BRAF, and PIK3CA, can lead to resistance against anti-EGFR mAbs.
- Loss of PTEN and STAT3 phosphorylation: Inactivation of the tumor suppressor PTEN and abnormal phosphorylation of STAT3 might be associated with resistance to anti-EGFR mAbs.
- Epithelial-mesenchymal transition (EMT) occurrence: EMT, a process where epithelial cells acquire mesenchymal characteristics, seems to be linked to resistance against anti-EGFR mAbs in cancer cells.

These factors appear to contribute collectively to the emergence of resistance mechanisms in cancer cells, reducing the effectiveness of anti-EGFR mAbs.[12,13] Besides, the role of non-genetic factors is a highly debated issue even though little is known about the exact resistance mechanism of such a phenomenon. All in all, it is necessary to explore new strategies for improving the cytotoxic impacts of anti-EGFR mAbs, enhancing apoptosis in CRC, and overcoming drug resistance mechanisms in mCRC patients.[14]

In recent studies, the crucial functions of small non-coding RNAs (sncRNAs) and long non-coding RNAs (lncRNAs) have gained significant attention, particularly in relation to tumor progression and the development of resistance mechanisms against anti-EGFR mAbs in CRC.[15] Of these, lncRNA biomacromolecules are considered complex ncRNAs structures, which have been indiscriminately described as RNA molecules longer than 200 nucleotides with no translation into proteins.[16] These biomacromolecules appear to modulate CRC via altering the expression of genes, triggering chromosomal remodeling, orchestrating transcriptional/post-transcriptional impacts, and self-translation of lncRNAs into polypeptides.[17,18] Additionally, lncRNAs can prevent therapeutic-induced cell death, stimulate the EMT phenomenon, and promote non-cell-autonomous resistance mechanisms.[19] Table 1 lists some of the aberrant expressions of specific lncRNAs together with their potential biological and clinical relevance during colorectal carcinogenesis.[20,21]

Remarkably, lncRNAs are believed to be potential modulators of genes related to the cancer cells resistance mechanisms, which might (i) influence intracellular drug concentrations, (ii) prompt alternative signaling pathways, and (iii) modify drug efficacy by hindering cell cycle regulation and DNA damage response. All in all, they are probably responsible for developing resistance to anticancer agents, especially anti-EGFR mAbs.[31] LncRNAs may induce CET-resistance in mCRC through different mechanisms, including (i) the EGFR mutations and disrupting the CET binding to EGFR (lncRNA POU5F1P4),[37] (ii) the mutations of the EGFR downstream pathways (lncRNA CRART16),[38] (iii) the activation of Wnt/β-catenin signaling (lncRNA MIR100HG),[26] and (iv) the activation of the parallel pathway such as MET (lncRNA UCA1).[39] Remarkably, lncRNA CRART16 was reported to elicit CET-resistance in CRC cells most likely by functioning as a miR-371a-5p sponge and thereby enhancing the expression of erythroblasts Leukemia viral oncogene Homolog 3 (ERBB3) through the miR-371a-5p/ERBB3/MAPK pathway.[38] The downregulation of lncRNAs LNC00973 seems to improve CET resistance in mCRC cells most likely by regulating the metabolism of glucose.[29] Besides, lncRNA HCG18 appears to facilitate the progress of the CRC resulting in CET-resistance through upregulation of PD-L1 and also suppressed CD8+ T lymphocytes cells via sponging miR-20b-5p.[28] The upregulation of exosomal lncRNA UCA1,[29] and downregulation of lncRNA POU5F1P4 were shown to be involved with the emergence of drug resistance in CET-sensitive CRC cells.[37] Recent studies have supported lncRNAs' roles in anti-EGFR drug-resistance inducing based on lncRNAs-mRNAs, or lncRNAs-miRNAs-mRNAs regulatory networks through the EGFR, RAS, and PI3K/AKT signaling pathways.[40] Fig. 1 illustrates the possible involvement of lncRNAs on EGFR-related signaling pathways.

Collectively, the mechanisms underlying the CRC resistance to anti-EGFR therapy are the most complicated issue, and the lncRNAs spectrum associated with this resistance mechanism remained largely unknown due to the paucity of lncRNAs-specific microarray/RNA sequencing analysis. Upon some published data, lncRNAs

Table 1. Long non-coding RNAs and colorectal cancer

LncRNAs	Expression level	Potential function and mechanism	References
MALAT1	Upregulated	Promoted proliferation, invasion, and migration through activating PRKA kinase anchor protein 9 (AKAP-9)	22
H19	Upregulated	Downregulation of its target tumor suppressor retinoblastoma (RB) and hence regulation of the CRC development	23
CCAT1	Upregulated	Promoted CRC progression by regulating the miR-181a-5p expression	24
CCAT2	Upregulated	Enhance the proliferation and metastasis of CRC cells by engaging in direct interactions with TAF15, facilitating the transcriptional activation of RAB14, and triggering the AKT/GSK3β signaling pathway.	25
PANDAR	Upregulated	Enhanced CRC progression by EMT pathway	26
UCA1	Upregulated	Promoted progression of CRC via the miR-143/MYO6 axis	27
MEG3	Downregulated	SOCS3-mediated repression of the malignant proliferation of colonic stem cells by activation of miR-708 and hence inhibition of CRC progression	28
PCAT6	Upregulated	Inhibited apoptosis of CRC cells through regulation of anti-apoptotic protein ARC expression via EZH2	29
BCAR4	Upregulated	Enhanced CRC progression via activating Wnt/β-catenin signaling	30
TUSC7	Downregulated	Promote cell migration and invasion in CRC via regulation of miR-23b/PDE7A Axis	31
MAPKAPK5-AS1	Upregulated	Enhanced CRC progression by cis-regulating the nearby gene MK5 and acting as a let-7f-1-3p sponge	29, 32
RP9P	Upregulated	Promote CRC progression by modulating miR-133a-3p/FOXQ1 axis	33
u50535	Upregulated	Promoted CRC growth and metastasis by regulating CCL20	29
PVT1	Upregulated	Promoting CRC tumorigenesis through miR-16-5p stabilization and interaction with the VEGFA/VEGFR1/AKT Axis	27
NEAT1	Upregulated	Promoted progression of CRC via modulation of the KDM5A/Cul4A and Wnt signaling pathway	34
FTX	Upregulated	Enhanced migration and invasion of CRC cells by miRNA-590-5p/RBPJ axis	35
XIST	Upregulated	Enhanced growth and metastatic potential of colorectal cancer cells by directly affecting miR-486-5p and facilitating the activation of neuropilin-2, a critical regulator of epithelial-mesenchymal transition (EMT)	36

can affect the therapeutic efficacy of anti-EGFR mAbs mainly through intracellular signaling even though their specific mechanisms are yet to be fully addressed. Notably, the interaction between ncRNAs and their crosstalk with anti-EGFR resistance-related pathways needs to be fully understood. To specifically target and inhibit the overexpressed lncRNAs, various therapeutic approaches can be developed. First, antisense oligonucleotides (ASOs), antagomirs, small interfering RNAs (siRNAs), short hairpin RNAs (shRNAs), miRNA sponges, and CRISPR/Cas9-based genome editing technique, which can be used to directly interfere with the expression or function of the overexpressed lncRNAs, leading to their inhibition or degradation. Second, treatment strategies that involve the use of tumor suppressor lncRNAs. Some lncRNAs have the ability to suppress tumor growth and progression. By introducing or enhancing the expression of tumor suppressor lncRNAs, it may be possible to regulate the functional expression of oncomiRs and restore normal cellular functions. Third, small molecule inhibitors, which specifically target the functional domains or binding sites of overexpressed lncRNAs, can be developed. Fourth, screening natural compounds and extracts for their ability to inhibit overexpressed lncRNAs can be another approach. Finally, nanoscale formulations such as Ab-drug nanoconjugates can be employed. These involve coupling therapeutic agents, such as small molecule drugs or antibodies, to nanoparticles with potential to specifically target and suppress the cells or tissues expressing the lncRNAs. Altogether, therapeutic strategies for targeting overexpressed lncRNAs include the use of antisense oligonucleotides, RNA interference, genome editing, exploitation of tumor suppressor lncRNAs, and nanoscale treatment modalities like Ab-drug nanoconjugates. These approaches hold promise in combating cancers associated with aberrant lncRNA expression. Despite the recent progress in ncRNA-based therapeutics, understanding the precise role of lncRNAs and related molecular mechanisms in anti-EGFR therapy and CET resistance in mCRC requires deep insights.

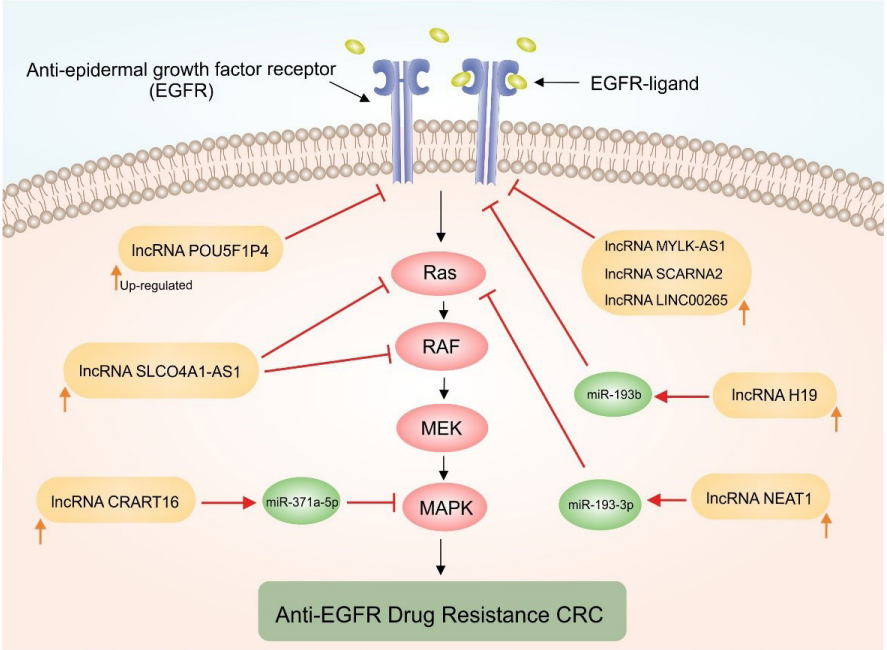

Fig. 1. Schematic representation of the upregulation impacts of certain lncRNAs on the EGFR-related signaling pathways. Epidermal growth factor receptor (EGFR), as a cell surface receptor, regulates cell growth, proliferation, and survival. Dysregulation of EGFR signaling is commonly observed in cancer, leading to uncontrolled cell growth and tumor progression. A complex network of genes and miRNAs can be modulated, including those associated with the RAS/RAF/MEK/ERK pathways. LncRNA CRART16 upregulates ERBB3 expression through miR-371a-5p, lncRNA NEAT1 downregulates miR-193a-3p, and lncRNA H19 attenuates miR-193b-mediated inhibition. These functions activate the EGFR/RAS/RAF/MAPK pathways and contribute to anti-EGFR resistance in CRC.

In this regard, mismatched base pairing to non-target mRNAs, unexpected effects on normal tissue, and especially off-target effects are still tremendous challenges that need to be addressed. Thus, further evaluations are required to improve therapeutics' specificity, delivery, and tolerability using lncRNAs. Moreover, lncRNAs can be applied in monitoring and forecasting treatment response and resistance to personalized treatments to improve clinical outcomes.

Authors' Contribution

Conceptualization: Mostafa Akbarzadeh-Khiavi, Azam Safary, Yadollah Omidi.
Data curation: Mostafa Akbarzadeh-Khiavi, Azam Safary.
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Visualization: Mostafa Akbarzadeh-Khiavi, Azam Safary, Yadollah Omidi.
Writing–original draft: Mostafa Akbarzadeh-Khiavi, Azam Safary, Yadollah Omidi.
Writing–review & editing: Mostafa Akbarzadeh-Khiavi, Azam Safary, Yadollah Omidi.

Competing interests

None to be stated.

Ethical statement

The present study was approved by the Ethics Committee of Tabriz University of Medical Sciences (Ethical No. IR.TBZMED.REC.1401.338).

Funding sources

The support provided by the Liver and Gastrointestinal Diseases Research Center at Tabriz University of Medical Sciences (grant #69709) to MAK is acknowledged.

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