Review

Multi-Omics Mining of LNC-RNAs With Biological and Clinical Relevance in Cancer

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Multi-Omics Mining of lnc-Rnas with Biological and Clinical Relevance in Cancer

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Abstract: In this review, we will cover a general overview of the current panorama on lncRNAs with an actual or potential role as biological markers in cancer. We will discuss examples of multi-omics approaches that integrates information on somatic aberrations, gene expression and epigenomics, with the scope of providing a more comprehensive view of the functional impact of lncRNA profiles and how these paradigm can be exploited for the discovery and selection of lncRNAs with a functional role and their use as variables informing on progression and prognostic and help guiding the selection of therapeutic strategies for cancers. Finally, we propose a perspective for future evolution of the study of lncRNAs and the discovery of their functional and harnessing their potential to assist in clinical management of malignancies.

Keywords: long non-coding RNAs ; cancer; multi-omics

1. INTRODUCTION

The advent of next generation sequencing and other breakthrough technologies for the study of the human genome has thoroughly transformed the way basic and clinical research in cancer is conducted [1,2]. As a consequence of these fast-moving advances, we have been able to produce large volumes of data from an assortment of multiple omics layers (i.e., genomics, epigenomics, transcriptomics, proteomics, metabolomics and microbiomics) from different tissue and cell models for the study and translational research in cancer [3,4]. In particular, the exponential advances in sequencing technology have allowed researchers to explore the complexity and diversity of human transcriptomes [5,6]. One population of RNA molecules that has received special attention in recent years are the long noncoding RNAs (LncRNAs), molecules without protein-coding capacities but with versatile and pleiotropic functions [7,8], with well-defined action mechanisms linked to different hallmarks of cancer [9–11]. LncRNAs are increasingly being recognized as potential pharmacological targets and as diagnostic and prognostic biomarkers [12–14]. Indeed, advances in RNA-seq and other large-scale methodologies represent a valuable resource to deepen our knowledge of the molecular aspects of LncRNAs and their roles in cancer biology [15,16]. So far, most studies have mostly centered on detecting aberrant expression changes of LncRNAs. However, given the complex and pleiotropic functions of LncRNAs, we must recognize that to truly harness the potential of these transcripts to reveal complex functional aspects and their associations with extrinsic and intrinsic factors that influence susceptibility, incidence, and survival of different types of cancer we need to incorporate new frameworks of multidimensional analysis as has been proposed for the study of other complex diseases [17]. In this context, multi-omics analysis approaches that combine and integrate protein-coding gene expression with other dimensions of molecular information such as genomics and epigenomic, have improved our capacity to obtain significant understanding of the

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molecular aberrations underpinning the oncologic characteristics in different types and subtypes of tumors (e.g., cancer cell fate and survival) [4,18]. Likewise, a multi-omics framework progressively incorporated into research is helping us to delineate the way LncRNAs perform their functions and how they impact on cancer development [19]. As a new paradigm, these approaches might boost research to produce sufficient evidence to ascribe them a causal relationship to malignancy presence and most importantly, a clinical value as diagnostics, prognostic and predictive markers in cancer [20,21]. Therefore, in the following sections we present and discuss recent scientific evidence describing how the availability of more powerful technologies in genomics and transcriptomics has been applied for the study of functional and biological aspects of LncRNAs in cancer research, with a special focus on benchmark features that have brought an increasing awareness on the potential roles LncRNAs have as informative molecules of carcinogenesis. We particularly discuss different modalities and approaches for the integration of multi-omics data and how they are being leveraged to boost the discovery and characterization of LncRNAs as potential markers of tumor progression, and the current challenges in translating these advances into the clinical setting.

2. THE REVOLUTION OF NON-CODING TRANSCRIPTOME IN CANCER STUDIES

Growing evidence has demonstrated that large amounts of LncRNAs are contained within the human genome. The most recent release of LNCipedia, a public database for LncRNAs sequence and annotation contains 107,039 high-confidence transcripts, which do not show any coding potential, belonging to 49,372 LncRNAs genes [22]. Undoubtedly, the flourishing number of LncRNAs has aroused scientific interest in the study of their biological features and roles over the last years [11]. On the basis of the fact that they play critical roles in various processes necessary for body cells functions, many studies have addressed and demonstrated the relationship between LncRNAs and disease [21]. In particular, experimental evidence of the relevance of LncRNAs as markers for cancer has been accumulating over the last decades. Among the most prominent examples of LncRNAs whose aberrant expression is associated with cancer development we can find descriptions of MALAT1 [23], HOTAIR [24] and PCA3[25]. Since its discovery, MALAT1 has become the paradigm of functional alterations of a LncRNA in cancer, and has been proposed as a potential biomarker with a vital role in several tumors such as non-small cell lung adenocarcinoma (NSCLC) [26] gastric cancer [27] and colorectal cancer [28]. The oncogenic LncRNA HOTAIR holds also a promising value as a biomarker of response for breast [29] and hepatocellular carcinoma [30]. Meanwhile, PCA3 in urine has been used as a marker of prostate cancer aggressiveness to guide medical decisions on patient treatment and has been available since its approval by the FDA [31,32]. Apart from PCA3, till date there's no other LncRNA that has been given clearance by FDA either for diagnostic, prognostic or response to treatment prediction in any type of cancer. Despite the accomplished examples of MALAT1, HOTAIR in cancer research and the use of PCA3 in the clinical setting, discovering more associations between LncRNAs and diseases and even more, characterizing them as biomarkers or targets of therapeutic agents has become an increasingly challenging task. It is in this juncture that integrative analysis of large scale data has represented a game changer. In this respect, a number of scientific examples which leverage analysis strategies to investigate the relation of somatic alterations, including somatic mutations and copy number variation profiles, with transcriptome changes, including networks of expression perturbations of protein coding genes, microRNAs and in particular aberrations of LncRNAs, to unveil properties of the latter as cancer drivers or markers with potential utility in prognosis and prediction to response to therapy.

3. LncRNAS ASSOCIATED TO CANCER DRIVER SOMATIC MUTATIONS PROFILES

Cancer is characterized by the somatic acquisition of different cellular alterations that lead to selective advantages such as unrestricted growth, suppression of apoptosis and enhanced metabolism [33]. Genomic instability has been widely recognized as one of the leading hallmarks of cancer [34]. More recently, in particular with the aid of high-throughput sequencing, research has revealed the complexity of somatic DNA aberrations landscapes of cancer genomes [35]. As a matter of fact, the definition of particular somatic mutation profiles have long been a keystone for

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characterizing cancer patients and leading to the discovery of specific cancer driver genes [36], which in turn can help to estimate inherited risk, prioritize therapy and prognosis, and understand pharmacological response to drug treatments [37]. It comes as not surprise that given the protein-centric view that has been prevalent over the past years in many branches of molecular biology, cancer studies have focused to a greater extent on exploring mutations occurring in protein-coding regions, despite the fact that exome represents a very small fraction (1-2%) of the human genome. Excitingly, with the expansion of our knowledge about other functional regions within human genome other than regions with protein-coding loci, now a growing number of discoveries have sprout out demonstrating that recurrent somatic mutations in non protein-coding regions can be also informative features which are paving the way to discover causal associations between LncRNAs functions and oncogenesis [38]. Leveraging whole genome sequencing data, researchers have been able to better characterize the presence, frequency and functional impact of somatic mutations in non-coding regions of cancer genomes [39]. To our current understanding, the most robust evidence observed has shown that cancer driving point mutations and structural variants are less frequent in non-coding genes and regulatory sequences than in protein-coding genes. However, it is expected that more driver aberrations will be discovered in the coming years as data of more cancer genomes will become available. Despite the challenges this effort entails, availability of data from larger-scale cancer sample sequencing projects, such as the TCGA project, along with more refined integrative computational genomics methods have increased exponentially in the past years, and we are already witnessing the discovery of driver somatic mutations in non-coding regions with an actual impact on the function of genes other than protein-coding genes [40–43]. For example, with the aim of exploring not only protein-coding elements, but also non-coding genomic regions, Rheinbay et al. developed a capture assay that covers exons, promoter elements, and additional regulatory regions and they sequenced 360 primary breast tumors and patient-matched normal samples. Importantly, they observed that cancer driver mutations in regulatory non-coding regions can actually occur at similar frequencies as in coding regions. However, they also found promoter elements with significant burden or clustering of mutations, including promoters of LncRNA genes, among which were RMRP8 and NEAT1. Of note, 3 out 4 mutations present in the promoter element of NEAT1 produces a reduction of its expression, which remarkably add to other loss of function alterations involving NEAT1 in breast cancer [44]. This study presents one of the most sophisticated integrative efforts conducted so far and the approach used by the authors put the emphasis in the discovery of somatic alterations occurring not precisely on the loci encoding transcripts of LncRNAs but the regulatory regions controlling their transcription. Nonetheless, other approaches integrating multiple omics data have been proposed to characterize somatic point mutations in LncRNA coding loci which produce an eventual gain or loss of function (Figure 1).

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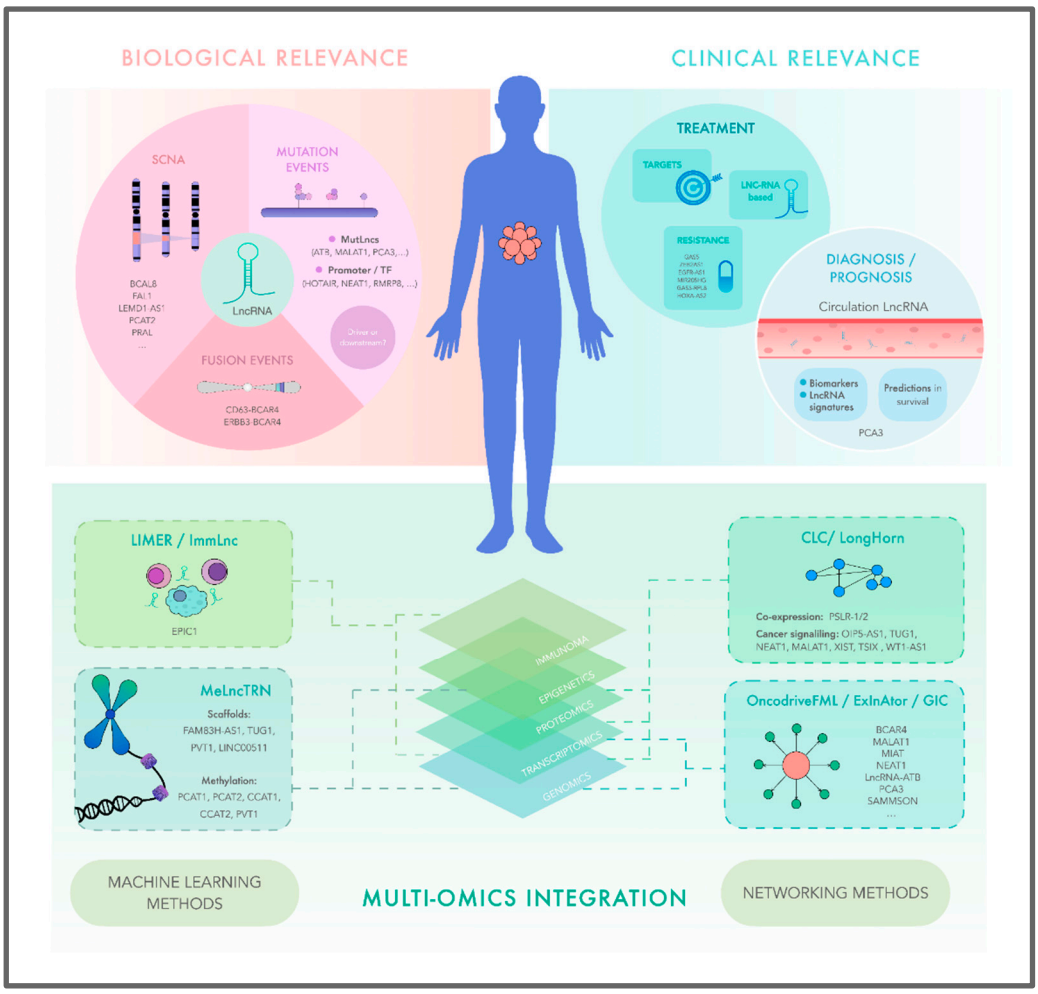

Figure 1. Overview of multi-omics integration for the understanding and application of lncRNA in cancer. Technologies and the era of big data offer new insights into the biological role of lncRNA across all types of cancer and, as a consequence, this new information brings us light to integrate them into precision medicine to be able to achieve better clinical decisions in diagnosis, prognosis and treatment.

4. APPROACHES TO PRIORITIZE CANCER DRIVER LNCRNAS USING SOMATIC MUTATIONS PROFILES

From the omics and bioinformatics point of view, we can broadly classify approaches that have been developed to prioritize LncRNAs with a possible association to cancer in at least two categories, (1) Integrative analysis of somatic variants with a cancer driver potential which have an impact on the functional activity of LncRNAs associated to prognosis in cancer patients [45–49], and (2) post-analysis integration strategies centered on the relationship between genome instability and LncRNAs with aberrant expression associated to tumor prognosis [50–56]. As a representative study to evaluate the potential impact of somatic mutations in human LncRNAs (denominated MutLncs) and their functional significance in cancer, Gao et al. interrogated mutation profiles in genomic regions harboring LncRNA and their vicinity, across 17 cancer types and used an integrative pipeline to describe the significance of MutLncs contribution to cancer [45]. Interestingly, they discovered different cancer-specific networks of co-occurring MutLncs, considering mixing effects, that is, the influence of a pairwise combination of multidimensional data including DNA methylation, TF expression and miRNA expression. Notably, the study found that a number of MutLncs in co-occurring pairs are correlated with patient survival especially in human skin cutaneous melanoma (SKCM) and glioblastoma (GBM) tumors [45].

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The complexity of cancer genomes goes beyond a number of specific targetable driver mutations and other features like tumor mutational burden (TMB) and mutational signatures are being increasingly incorporated in bioinformatics analysis aimed at unveiling therapeutic and prognostic insights in cancer [57], therefore is not unexpected that many studies that integrates somatic mutation profiles and transcriptome expression data to identify LncRNAs with a potential biomarker role in cancer have emerged in recent years [50–53,58] (Table 1). For example, in a work in colon cancer, researchers used a post-analysis integration strategy to characterize patients by their somatic mutations profiles and subsequently, analyze transcriptome data and information on survival from the same set of patients, they were able to to derive a score computed on a 7 genome instability-associated LncRNA signature that is able to distinguish high-risk patients which are characterized by high somatic mutation, high microsatellite instability, significantly poorer clinical outcomes and specific tumor immune infiltration [54]. Using a similar approach in cervical cancer (CESC), Zhang and cols. produced a mutator hypothesis-derived computational model in which they first grouped patients on the basis of cumulative number of somatic mutations, then they screened for expression differences of LncRNAs and found a genomic instability-associated LncRNAs signature with potential to determine the survival rate of patients, helping to differentiate CESC tumors of high and low risk [55]. Remarkably, TMB has become an emerging marker for checkpoint inhibitor-based immunotherapy [59]. In a recent study which integrates RNA sequencing data, mutation profiles, and corresponding clinical information from a TCGA colon cancer (COAD) dataset, the authors assessed the TMB of COAD samples to assign them into low and high TMB groups. Then, they used a machine learning approach to construct a of 14-LncRNA based classifier index which was related related to 3 immune checkpoints (i.e., PD1, PD-L1, and CTLA-4). Interestingly, the classifier obtained was significantly associated with TMB levels and could accurately predict overall survival of COAD patients [60].

The number of studies discussed so far give us a vision of various modalities of integrative multi-omics analysis employed as powerful strategies to identify and characterize LncRNAs as informative features that allow the diagnosis, prediction and prognosis. Nonetheless, from the perspective of searching for other biological and environmental factors (e.g., sex hormones, smoking, occupational risk, nutrition habits, etc) associated with the risk of cancer development, patient survival rate and treatment response, the complex interplay between LncRNAs and these environmental and other clinical factors driving the carcinogenesis process and determining cancer patients outcomes has raised challenging questions for researchers, which could not be answered without an integrative genomics approach. For example, Lung adenocarcinoma (LADC), the most common type of lung cancer, is largely caused by chronic tobacco smoking. However, there are roughly 25% of cases occurring in non-smoker persons. Of note, this proportion of non-smoker LADC is associated with being female and the etiology remains an elusive question. In a recent study to uncover genomic evidence of smoking-associated mutagenesis, the researchers implemented an integrative multilevel analysis, using Whole-genome sequencing and RNA-seq data to decipher the mutational processes and the complex genomic rearrangements driving the development of LADC. One of the intriguing findings of this multi-omic analysis effort, was the discovery of a recurrent fusion gene, composed by the gene ERBB3 and the LncRNA anti-oestrogen-resistance 4 (BCAR4), which was present in two tumors of female cases in which a low to no contribution of mutational signature 4 (i.e., S4-low LADCs), a signature associated with direct DNA damage by tobacco smoke mutagens, was observed [61]. Recently, other comprehensive integrative genomic analyses have led to the discovery of different fusion variants involving BCAR4 in lung adenocarcinoma [62–64]. Interestingly, the CD63–BCAR4 fusion was discovered in a never-smoking female patient by another genome-wide study on non-small cell lung cancer (NSCLC) [65]. Here, the authors encountered that the expression of both transcripts within this fusion were highly activated. When we consider the fact that a higher expression of BCAR4 has also been established as an independent predictive factor for tamoxifen resistance and poor progression-free survival in breast cancer patients with ER+ [66], the relevance of these complex rearrangements involving BCAR4 in other types of tumors, such as lung cancer, becomes perhaps more evident from the clinical standpoint, and demonstrate the utility of using

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highly multidimensional molecular analysis to undercover targetable alterations which otherwise would be overlooked.

5. COPY-NUMBER VARIATIONS IN GENOMIC REGIONS ENCODING LNCRNAS

Genomics and mathematical analysis of patterns of somatic alterations have indeed become a powerful strategy to identify cancer driver genes. In this regard, although somatic point mutations and small insertions and deletions (INDELS) have been the primary focus in cancer genomic studies, copy number variations (CNV) are also important forms of DNA aberrations, also termed somatic copy number alterations (SCNAs), that encompass larger genomic regions often harboring key genes involved in development and progression of many cancers [67,68]. Not surprisingly, most large-scale genomic analyses conducted to date have successfully identified almost exclusively protein-coding cancer driver genes located in these regions of focal amplification and deletion [69–71], and just relatively recently the first systematic analysis reporting the identification of LncRNAs that are also contained within focal CNV in cancer genomes started to emerge [72–75]. In the light of the evidence pointing out that almost 3 quarters of the human genome can be transcribed to RNA [76] and that only 2% of the human transcriptional landscape encode a protein, the necessity to understand the functional impact of SCNAs on LncRNAs has become more evident. In one of the first comprehensive characterizations of the impact of cancer driver LncRNAs in regions of SCNAs alterations, Hu et al. implemented the bioinformatic integration of SCNAs and expression analysis across 12 different types of cancer. In developing their approach, the researchers scanned wide-genome data in search for focal alterations, which often exhibit high-amplitude variation and mapped known LncRNA loci to those regions of focal gain or loses. Interestingly, about 17.8% of LncRNAs encoded loci with SCNAs were expressed in 40 cancer cell lines that represent 5 different types of tumors, among which they discovered FAL1 as a potential oncogenic LncRNA associated with clinical outcomes in patients with ovarian cancer. In a follow up study, the authors confirmed the SCNAs in FAL1 in OC and observed it was also present in other 5 tumor types [68,77–79]. One key aspect to be considered in the characterization of LncRNAs as tumorigenic drivers is highlighted by the author's approach which arises from the reasoning that a prerequisite for distinguishing drivers from passengers SCNAs involving LncRNAs loci is that lncRNAs transcripts encoded in those loci have to be present (i.e., in sufficient amount to be detected) in cancer cells of interest. In fact, this is true to other kinds of genomic alterations too. In this respect, the identification of SCNAs of LncRNA loci which are actively transcribed in a particular cell at a particular moment can help guide the characterization of LncRNA molecules with an actual functional and role as driver of tumorigenesis and potential clinical utility, as has been further demonstrated by the study of Hu et al. and other studies [73,74,77,80–83] (Table 1). A second consideration that emerges in the light of the cited approaches to really understand the contribution of LncRNAs as drivers of cancer and its dysregulation relies on estimating the relation that exist between copy number values of significant SCNAs harboring LncRNAs loci and the levels of expression of their corresponding LncRNA transcripts that are present in a certain type of cancer. As a matter of fact, this aspect is consistent with our knowledge that differential gene expression of protein-coding cancer driver genes are significantly correlated with CNV [68,84]. As a consequence, researchers have come to delineate the correlation between SCNAs and the expression levels as useful parameters to define the gain or loss of function of LncRNAs with oncogenic or tumor suppressor functions and potentially associated to the clinical outcome for different tumors [68,74,77–79,83,85]. Cancer is a heterogeneous disease that includes a diversity of tumors from the same or different organs and tissues, displaying differences in cellular compositions, biological and molecular features [86] and much of our understanding about cancer heterogeneity and its clinical implications have been improved by new developments in genomics[87]. Some studies have so far addressed the integration of multi-omics data including LncRNAs expression and SCNA with the scope of defining molecular profiles that capture the diversity of tumor subtypes with different prognosis and responses to treatments [88–90]. As a worth noting example, in large-scale genomic analysis in high-grade serous ovarian carcinoma (OV), Akrami et al. investigated the correlation between SCNA profiles and the expression of LncRNAs and were able to find the LncRNA OVAL (RP11-522D2.1) as

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a target of focal DNA amplification. Of note, this alteration is detected specifically in OV and is concordant with the increase in OVAL transcript expression [91]. It is important to be aware that this relationship might be more intricate and SCNAs alterations present in a tumor can be associated with the aberrant expression of LncRNAs other than the ones that are encoded within their loci. For example, other mechanisms might be operating to disrupt their activity, such as the occurrence of a breakpoint event within the boundaries of promoters and regulatory sites of a particular LncRNAs or genomic alterations directly perturbing their protein-coding gene targets for such LncRNAs [70]. In this regard, more research is still awaited to unveil the complicated interaction between LncRNAs, protein-coding genes, miRNAs and other kinds of functional elements potentially drivers of cancer.

Table 1. List of studies analyzing or integrating multiple molecular features explored with high throughput strategies (multi-omics) and their potential effect as molecular markers or biological targets in different cancer types.

LncRNA	Potential association based on biological or clinical data	Relation with other Omics features	Reference
ESR1, TRPS1, ERG, RUNX1, SNHG16, HOTAIR	cancer development and progression	somatic mutations on lncRNA TF binding site	[45]
RMRP8, NEAT1	breast cancer (BRCA)	somatic mutations on lncRNA promoter	[44]
ENSG0000021403, ENSG00000261650, ENSG00000281406, G001643	Relapse in colorectal cancer (CRC)	Mutations accumulated in lncRNA loci	[49]
LINC00460, AC156455.1, AC015977.2, 'PRDM16-dt', AL139351.1, AL035661.1, LINC01606	Poor overall survival risk in renal cell carcinoma (RCC)	High Somatic mutation-associated lncRNAs signature	[50]
LINC00460, LINC01234	Poor overall survival risk in clear cell renal carcinoma (CCRC)	High Somatic mutation-associated lncRNAs signature	[51]
FAM30A, CACNA1C-AS1, LINC02595	Poor overall survival risk in AML	High Somatic mutation-associated lncRNAs signature	[52]
AC007996.1, AC009237.14, AP003555.1, AL590483.1	Poor overall survival risk in CRC	High Somatic mutation-associated lncRNAs signature	[53]
ZNF503-AS1, AL353747.2, AC129492.1, AP003555.1, AC009237.14	Poor overall survival risk in CRC	High Somatic mutation-associated lncRNAs signature	[54]
AC107464.2, MIR100HG, AP001527.2	Poor overall survival risk in cervical cancer (CESC)	High Somatic mutation-associated lncRNAs signature	[55]
AC002511.2, LINC00501, LINC02055, LINC02714, LINC01508, LOC105371967,	Poor overall survival risk in hepatocellular carcinoma (HCC)	High Somatic mutation-associated lncRNAs signature	[56]

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RP11_96A15.1, RP11_305F18.1, RP11_342M1.3, RP11_432J24.3, U95743.1			
C116351.1, ZFPM2-AS1, AC145343.1, MIR210HG	Poor overall survival risk in hepatocellular carcinoma (HCC)	High Somatic mutation-associated lncRNAs signature	[58]
FAL1	Oncogenic lncRNA	SCNA related lncRNA	[73]
BCAL8	Poor overall survival risk BRCA	SCNA related lncRNAs	[74]
RUSC1-AS1, LINC01990, LINC01411, LINC02099, H19, LINC00452, ADPGK-AS1, C1QTNF1-AS1	Poor overall survival risk in CESC	SCNA related lncRNAs	[77]
PRAL	Tumor suppressor	SCNA related lncRNA	[78]
LOC101927604, LOC105377267, CASC15, LINC-PINT, CLDN10-AS1, C14orf132, LMF1, LINC00675, CCDC144NL-AS1, LOC284454	low disease-free survival in CRC	SCNA related lncRNA	[79]
RP11-571M6.8	immunosuppressive function in GBM	SCNA related lncRNA	[80]
RP11-1020A11.1	Poor overall survival risk in bladder carcinoma	SCNA related lncRNA	[80]
CTD-2256P15.2	Treatment with methyl ethyl ketone (MEK) inhibitors prediction in LUAD	SCNA related lncRNA	[80]
LINC00896, MCM8-AS1, LINC01251, LNX1-AS1, GPRC5D-AS1, CTD-2350J17.1, LINC01133, LINC01121, and AC073130.1	Poor overall survival risk in LUSC	SCNA related lncRNA	[81]
RP11-241F15.10	Tumor suppressor in osteosarcoma	SCNA related lncRNA	[82]
ALAL-1	Related to lower levels of immune infiltration LUSC	SCNA related lncRNA	[83]
LOC339803, F11-AS1, PCAT2 TMEM220-AS1	Poor overall survival risk in HCC	SCNA related lncRNA	[85]
ENSG00000261582	Poor overall survival risk in LUAD and CESC	SCNA related lncRNA	[89]
PCAN-R1 (Ensembl ID ENSG00000228288), PCAN-R2 (Ensembl ID ENSG00000231806)	Oncogenic in PRAD related to Poor overall survival risk	SCNA related lncRNA	[89]

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LOC101927151, LINC00861, LEMD1-AS1	Poor overall survival risk in OV	SCNA related lncRNA	[90]

6. THE ADVENT OF MACHINE LEARNING TO DEEPEN THE FUNCTIONAL AND BIOLOGICAL ROLES OF LNCRNAS IN CANCER

Machine learning methods have been used more and more frequently in attempts of better understanding the biology of molecules such as the LncRNAs. These methods have a general classification in supervised and unsupervised learning. The former include dimensional reduction and clustering, while the latter include regression and classification. In the context of the LncRNA landscape, one of the challenges that has arisen is the accurate identification of true LncRNAs from other species of RNAs, along with defining their biological roles. The main approach for the identification of LncRNAs is based on its coding potential and length, later on, other features were integrated such as: existence of an open reading frame (ORF), nucleotide composition, kmers, secondary structure, codon usage, ribosome release score, conservation scores and others. The most common algorithms to integrate the information includes logistic regression, random forest (RF), support vector machine (SVM) and deep learning. From a mechanistic point of view, to gain a better understanding of the role of LncRNAs in complex diseases such as cancer, in addition to the coding potential, some computational frameworks rely on machine learning methods, such as the Genetic Importance Calculator (GIC), which takes into account LncRNAs interaction with other omics levels. Through these methods it is possible to accurately find unknown LncRNA interactions. The number of methods that have been developed for these purposes has increased steadily in the last years and discussing them all is beyond the scope of this review. However, some of the limitations and strengths of these methods have been comprehensively revised elsewhere [92–94].

In recent years, a number of strategies have emerged based on the use of deep learning and complex network analysis to uncover the relevant dysregulations of LncRNAs and the potential value to identify relationships with cancer diagnosis, prognosis and treatment [17,95–99]. One of the limitations of this type of algorithm is the lack of reliable and verified negative samples; they use known biomolecule-disease associations, which cannot be applied to new diseases. And in addition, all the data have different calculation rules, which can lead to inaccuracy [100]. Furthermore, the link between LncRNAs and cancer goes beyond the identification of molecules that may be actively participating in the disease. Other aspects have been explored, such as the identification of biomarkers capable of predicting prognosis or even responses to drugs [101]. For this scope, the combination of different approaches has been proposed like the least absolute reduction and selector operation (LASSO) and support vector machine recursive feature elimination (SVM-RFE)[100,102]. In general, the methods for identification of LncRNA, prediction of their functions, relationship with disease, even as part of precision medicine tools for prognosis and drug response predictions, continue to improve by using higher level features, as well as generating more and new information to feed the algorithms for better classifications. Despite all efforts, the integration of all available information in a biologically meaningful way remains a challenge.

7. MULTI-OMIC NETWORKS APPROACHES REVEAL LNCRNA BIOLOGICAL RELEVANCE ON CANCER BIOLOGY

As previously discussed, technological and computational advances in recent decades have allowed the identification of thousands of LncRNAs whose molecular alterations are associated with different types of cancer. A major challenge is that initial efforts to discover cancer-related LncRNAs took advantage of classical functional genomics approaches primarily by characterizing the global transcriptomic landscape, evolutionary conservation, or proximity to known cancer genes, and while these analytical strategies provided valuable insights, altered transcriptional profiles alone do not indicate a causal role in cancer programs. At present, different biological evidence describing well-known cancer-associated LncRNAs have been presented in the literature, most of them focused on the function of a single LncRNA linked to malignant transformation through its roles in gene regulation and its impact on cancer hallmarks.

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Despite the intense research on the mechanisms underlying altered LncRNAs, our understanding of the global biological impact of LncRNAs regulations in tumors remains limited [103]. It is challenging to holistically describe the complex biological processes of many LncRNAs and their cooperative mechanisms using traditional biochemical and molecular approaches. Therefore, the availability of multi-omic data from genomics (mutations and CNV), transcriptomics (mRNA, noncoding RNA), proteomics, epigenetics (chromatin methylation and architecture), and metabolomic studies has opened new strategies to advance the understanding of LncRNAs roles in health and diseases by creating tools to integrate this data at the system level.

In this section, we will review the progress made in understanding multi-omics biological features through machine learning and artificial intelligence approaches and provide an overview of novel advances in revealing the regulatory bases underlying the functionalities of LncRNAs through various molecular and cellular biological levels.

7.1. Describing new LncRNAs drivers in cancer through multi-omic integration

Apart from some limited and well-known LncRNAs, the landscape of cancer LncRNAs is far from being complete. The diverse functional repertoire of LncRNAs in cancer can be explored by: 1) their function as driver genes resulting from early mutations that are positively selected during tumorigenesis; or 2) as downstream genes, resulting from non-genetic changes in expression, localization, or molecular interactions [104]. Although both categories contribute to cancer phenotypes, most efforts to discover cancer LncRNAs only take advantage of differential expression approaches. To overcome this, several computational methods have recently been developed to identify LncRNA driver genes by analyzing coordinate omic alterations to detect signals of positive selection (Figure 1, bottom panel).

One of the first statistical methods for driver-gene discovery was OncodriveFML[105], which identifies tumor-related LncRNAs by interrogating somatic mutations of coding and non-coding regions and gene expression. Compared to other methods, OncodriveFML calculates a functional impact score for which it uses a local mutational background, in specific regions to define positive selection signals in genes across tumor tissues. The method considers that the mutational background is influenced by the chromatin architecture, the replication timing and the transcription factor binding sites and, therefore, considering this local background, as well as the mutational and expression patterns, this computational tool can discover LncRNAs contained in potential genomic driver regions involved in tumorigenesis. Calculation of this method on whole-genome tumor data sequenced by TCGA and Cancer Genome Project made it possible to identify MALAT and MIAT as two LncRNAs that exhibit an excess of high-impact mutations.

Another integrative method to predict LncRNA drivers relevant in tumorigenesis is ExInAtor [106] that identifies genes with high somatic single nucleotide variants load across tumor genomes using DNA mutational patterns (local trinucleotide background model) and expression data as proxies for functionality. ExInAtor was computed over 1112 entire genomes from 23 cancer types deposited in GENCODE and predicted 15 high-confidence LncRNAs drivers, from which 9 are novel LncRNAs and 6 known cancer-related transcripts, including PCA3, MALAT1, BCAR4, LncRNA-ATB and SAMMSON. Most of the above mentioned LncRNAS were found to be tumor-specific, although NEAT1 and MALAT1, were identified in a Pan Cancer context, reaffirming their roles in tumorigenesis. The set of none previously reported driver LncRNAs includes: MIR100HG, AP000469.2, RP11-308N19.1, RP11-455B3.1, RP11-332J15.1, RP11-707A18.1, RP11-6c14.1, RP11-1101K5.1, RP11-354A14.1, RP11-189E14.4 (fig 2b). These novel candidates are evolutionary conserved, expressed in normal tissue and present elevated gene length. They also tend to be proximal to cancer SNPs and are encoded in CNV regions, pointing to their role in tumorigenesis. The authors highlight MIR100HG that is highly conserved, present canonical histone modifications in the promoter region and transcription factors binding sites.

More recently, to enhance the discovery of cancer-related LncRNAs and gain insights into their biology, the Cancer LncRNA Census (CLC) was presented as a tool to provide functional or genetic evidence of LncRNAs roles in cancer by the integration of genomic and transcriptomic data linked to

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cancer in different mammals species [104]. Until now, it is not completely clear whether mutated LncRNAs can drive tumorigenesis and whether such altered functions could be conserved during evolution. Therefore, CLC considers as a relevant feature the conserved functions between humans and mice that could be strong evidence for the biological role of the LncRNAs, both in cancer and under physiological conditions. Application of this computational model revealed the colocalization of cancer LncRNAs with known protein-coding cancer genes, 10 tumor-causing mutations were identified in 8 LncRNA orthologs, including DLEU2, GAS5, MONC, NEAT1, PINT, PVT1, SLNCR1, XIS some of them already reported in cancer.

The integration of DNA, RNA, and protein alterations and the way they cooperatively interact are providing new evidence for the relevance of LncRNA dysregulation in cancer, and therefore uncharacterized LncRNA models have been developed to define cancer cues. For instance, LongHorn [107], a recently presented computational method that integrates genomic, transcriptome and proteomic alterations and predicts LncRNA regulatory networks dysregulated in cancer pathways, by modeling their impact on transcription factors, RNA-binding proteins, and microRNAs activity, LncRNA-promoter binding sites and post-transcriptional activation/inihibition. Computing this method for 14 cancer types from TCGA predicts multiple LncRNA candidates whose dysregulation affect other known cancer genes and pathways, mainly in tumor specific context and influence tumor etiology. OIP5-AS1, TUG1, NEAT1, MALAT1, XIST, and TSIX, were inferred to regulate cancer signaling in multiple tumor contexts. Additionally, analyses of the LncRNA networks pointed to the enrichment of LncRNA binding sites in the promoter regions of messenger RNAs, enhancing the transcriptional effects of the LncRNAs. Functional experimental analyses in breast and gynecologic cancer cells showed that knock-down of OIP5-AS downregulated PTEN, boosting cell proliferation. Similarly, WT1-AS silencing downregulated predicted targets including: BCOR, FOXO4, PBX1, WT1 and ZEB1 in ovarian cell lines models, while TUG1 exogenous downmodulation negatively regulates CELF1, CSF1, FGFR2, NRAS, PDGFC and SOS1. The above characterization confirmed most of the predictions performed with LongHorn.

An interesting approach presented by Mitra and collaborators to predict biological dependencies of uncharacterized LncRNAs is centered in the identification of co-essential modules through the integration of copy number, epigenetic, and transcriptomic data of LncRNA landscape of exogenous knockouts or activation screens established with CRISPR approaches [108]. Applying this model to multi-omic cancer cells lines data the authors estimated 289 LncRNA-gene co-expression networks that recapitulates known proliferation-regulating LncRNAs and predicts novel LncRNAs related with proliferative signaling that are poorly characterized such as PSLR-1/2 that induce a G2 arrest throughout the modulation of FOXM1 transcriptional network and their exogenous expression inhibits proliferation and colony formation in in-vitro models.

Although DNA methylation dysregulation is associated with cancer, the molecular mechanisms of how methylation and transcriptional LncRNA patterns are reciprocally modulated in cancer remains largely unknown. A novel integrative analysis framework, called MeLncTRN (Methylation mediated LncRNA Transcriptional Regulatory Network), integrates transcriptome, DNA methylome and copy number variation profiles, to identify the regulatory circuits directed by epigenetically-driven LncRNAs across 18 cancer types. Analysis of 5970 TCGA tumor samples defined that the association between LncRNAs and DNA methylation mechanisms is common and conserved across multiple cancer types, for instance a complex interplay between LncRNAs and epigenetic modulators such as the DNA cytosine methyltransferases DNMT1, and histone modification proteins, such as EZH2, occurred. For example, FAM83H-AS1, TUG1, PVT1, and LINC00511 act as scaffolds to enhance EZH2 or DNMT1 binding and consequently repress the expression of their mRNA targets[109]. This observation expands the understanding of LncRNAs roles in the transcriptional regulation circuits in addition to their miRNA sponge activity as a competitive endogenous RNA (ceRNA) [110].

Emerging evidence has also indicated the underlying crosstalk between LncRNA and genomic instability, a relevant hallmark of cancer. Novel approaches integrating chip-seq, WGS and WES data revealed an unexpected relationship between oncogenic LncRNAs and epigenetic alterations that

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contributes to chromosome fragility in cancer. To characterize the LncRNA-based mechanism by which aberrant epigenetic signatures can be generated, the authors used as a conceptual proxy the subtelomeric chromosome locus 8q24 that contains the cMYC gene and a large histone H3 variant (CENP-A) domain, both altered in cancer cells of diverse solid tumors. This region also encodes for 5 unique LncRNAs sequences, namely, PCAT1, PCAT2, CCAT1, CCAT2, and PVT1, that negatively modulated the occupancy of CENP-A at the chromosomal locus. Their results stated a competition between LncRNAs transcription and R-loop occupancy that highly contributes to the maintenance of CENP-A invasion that ultimately impairs chromosome stability [111].

One oncological milestone already mentioned is TMB, related to the infiltration of diverse immune cell populations that can enhance or limit cancer programs [112]. Recently, increasing evidence has revealed that LncRNAs can play fundamental roles in the regulation of the immune system, but only few immune-related LncRNAs have been described in cancer. Therefore, novel approaches to shed light have been developed [113,114]. Through an integrative analysis of the LncRNA expression, tumor immune response signatures and genome-wide DNA methylation data in 9,626 tumor samples across 32 cancer types, the tool lincRNA-based immune response (LIMER) [115] revealed 7528 lincRNAs associated with tumor immune signature. Of interest, EPIC1 was detected as a relevant immune-related LncRNA inversely correlated with MHC expression and CD8+ T activation and infiltration. In-vitro and in-vivo models demonstrated that EPIC induces tumor immune evasion and resistance to immunotherapy by the epigenetic suppression of tumor cell antigen presentation through EZH2 interaction. Another interesting tool is ImmLnc [113], which systematically infers candidate LncRNA modulators of immune-related pathways by matching gene and LncRNA expression profiles. The tool prioritizes cancer-related LncRNAs by comprehensively characterizing LncRNA landscape and its correlation with the immunome. One of the first insights is that tumors originating from similar tissues are likely to share LncRNA immune regulators. Further, novel subtypes identified through ImmLnc show distinct mutation burden, immune-cell infiltration, expression of immunomodulatory genes, response to chemotherapy, and prognosis.

8. THERAPEUTIC HARNESSING OF LNCRNAS THROUGH MULTI-OMIC ONCOLOGY: PERSPECTIVE OF THE FUTURE APPLICATION OF LNCRNAS

The field of research on LncRNAs has developed rapidly over the past decade, moving beyond understanding their fundamental biological traits to actually harness their clinical relevance. Consequently, LncRNAs have been proposed as biomarkers and therapeutic targets that have been actively explored. In this section, we will review emerging strategies for the therapeutic exploitation of LncRNA.

It would be convenient to start by discussing the value of circulating LncRNAs as biomedical tools that allow the detection and monitoring of various diseases. Despite the important progress in translating the clinical utility of circulating molecules such as proteins, metabolites or free mRNA as biomarkers, there are still relevant limitations, which is why the LncRNA study has been postulated as a new source of biological information that presents relevant advantages over other circulating analytes, such as a greater resistance to degradation, stability in biofluids due to their secondary structures and their transport in extracellular vesicles, all these characteristics presented them as reliable cancer biomarkers [116,117].

The PCA3 case is a good example to illustrate the potential use of LncRNAs as informative biomarkers in cancer clinics. In 1999, Bussemakers and colleagues discovered that the ncRNA prostate cancer antigen 3 (PCA3), which they initially named Differential Display Code 3 (DD3), was overexpressed in prostate cancer tissues compared to not neoplastic prostate tissues. Of relevance, PCA3 was found to be virtually specific for prostate cancer. In a follow-up study, the tissue specificity of PCA3 was confirmed and its diagnostic performance validated. Interestingly, PCA3 has shown greater specificity and sensitivity than prostate-specific antigen, one of the most relevant biochemical tests for the detection of prostate cancer. Subsequently, it was shown that PCA3 levels could be quantitatively determined in urine sediments obtained after prostate massage, and finally, in 2012, PCA3 was approved as an auxiliary biomarker in the molecular diagnosis of PCa in the European

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Union, Canada and the United States and is currently marketed as a diagnostic Progensa test by Hologic Gen Probe (Marlborough, MA, USA) [32]. Interestingly, PCA3 noncoding RNA is involved in the control of prostate cancer cell survival and modulates androgen receptor signaling [25]

Although PCA3, to date, is the only LncRNA that has received FDA clearance for diagnosis, prognosis, or prediction of treatment response in any type of cancer, there are other reports describing new potential LncRNA biomarkers with high sensitivity and specificity for detecting specific neoplasms (Table 1) [118], and, thus the diagnostic and monitoring utility of circulating LncRNAs biomarkers has not yet reached its full potential.

A rapidly growing area of interest in the field of oncology is the drug resistance phenomena that is the major limiting factor to achieving cure in cancer patients. Emerging preclinical evidence supports that LncRNA expression patterns predict response to anticancer drugs [101]. By comparing publicly available transcriptional profiles of different RNA species at baseline and after drug treatment of hundreds of compounds in cancer cell lines, many LncRNAs such as GAS5 and ZEB2AS1 were shown to exceptionally predict sensitivity to various anticancer drugs. Therefore, LncRNAs could explain new signals of how cancer cells become resistant to anticancer therapies and represent a new source of biomarkers. Additionally, recent evidence showed that the LncRNAs EGFR-AS1 and MIR205HG, could significantly improve response prediction to erlotinib and gefinitib, even better than EGFR somatic mutations and amplifications, suggesting a critical role of these LncRNAs in cancer precision medicine [119].

Given the ability of LncRNAs to act as competitive endogenous RNAs (e.g., siRNAs or miRNA sponges), they could potentially govern resistance-related biological processes. By calculating a ceRNA network, including LncRNA and mRNA, various drug resistance-related modules were identified as novel drug resistance markers*. For example, the ceRNA pair GAS5-RPL8 regulates drug resistance since GAS5 down-expression enhances miRNA-inhibition of RPL8, which has been reported associated with chemotherapy resistance[120]. Integration of multiomics data reveals another relevant ceRNA module made up of HOXA-AS2, which is regulated by EIF4A3, FMR1, and HNRNPA2B1, mainly downregulated in BRCA patients, leading to adriamycin resistance. These changes also downregulated the expression of miR-107 [121]. Taken together, these studies demonstrate the potential viability of LncRNAs as a complementary biomarker and drug and molecular target.

The therapeutic targeting of non-coding RNAs is an attractive approach to treat cancer. Although none LncRNA-based therapy has been introduced into clinics, the functional diversity of LncRNAs poses an opportunity for their therapeutic modulation, through transcriptional and post-transcriptional inhibition, steric blockade of promoters or secondary structures, exogenous synthetic LncRNAs, and editing tools as CRISPR-Cas systems [122,123]. Each of these approaches has its own challenges, and future studies are needed to demonstrate their therapeutic efficacy.

9. CONCLUSIONS.

LncRNAs and their implications for cancer is currently a very active area of research, and we can consider that it is at its early stages. The number of LncRNAs that has been described as effectively having role in the molecular and biological pathways on cancer is still limited and probably most of them will play a secondary role in driving carcinogenesis, however, in order to achieve a more clear and effective landscape of LncRNAs in cancer clinics, different challenges need to be faced, such as assessing whether LncRNA biomarkers will work in cross-validation samples in clinical studies, how they are related to cellular heterogeneity, the dynamic changes in their expression and the strength of their association with other molecular aberrations over time. Despite these ongoing challenges, a growing number of preclinical studies have demonstrated the potential of LncRNA-based therapies and the plausibility of their diagnostic and therapeutic applications, bringing them closer to a clinical transference. As the number of massively screened tumors increases, the development of statistical and mathematical methods to discover LncRNA-drivers becomes increasingly important. With the advent of new technological resources such as single cell and spatial-based genomics and transcriptomics, and the popularization and ease of access to machine

learning frameworks, multi-omics data integration approaches will further establish itself as a powerful paradigm in the study of LncRNAs in cancer. These methods will contribute to complementing our set of resources to unveil the relationships between LncRNAs and other biological factors that critically modulate cancer cell fitness, demonstrating novel resources for studying tumor-relevant LncRNAs by dedicated multi-omics computational tools. It is highly desirable that in the foreseeable future, researchers make efforts to become native users of these technologies to keep up with the current and future challenges in cancer LncRNAs field.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used Conceptualization, I.S-G. and S.L.R-C.; investigation, I.S-G., S.L.R-C. and B.R-Z.; writing—original draft preparation, I.S-G., S.L.R-C. and B.R-Z.; writing—review and editing, I.S-G., S.L.R-C. and B.R-Z.; All authors have read and agreed to the published version of the manuscript. Please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

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