REVIEW

Long non-coding RNA landscape in colorectal cancer

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Increasing numbers of reports have shown the involvement of LncRNAs in the tumour progression in multiple cancers including colorectal and female reproductive cancers such as ovarian and breast. In particular, the profiling of lncRNAs in colorectal cancer (CRC), which is within the top three cancers in both female and male, have identified 556 upregulated and 1040 downregulated lncRNAs as compared to normal tissue. In this highlight, we looked at the mechanism in which some of these lncRNAs can act in CRC development and progression through promoting survival, proliferation and invasion and metastasis. Furthermore, we also look into the possibility of a cytoskeletal protein, gelsolin and its possible interaction with lncRNAs.

Keywords: Colorectal Cancer**;** Long Non-Coding RNA; Proliferation; Invasion; Metastasis; Gelsolin

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Colorectal cancer

Based on the latest GLOBACAN statistics, colorectal cancer (CRC) was estimated to account for 694000 deaths and is one of the top three most common cancers in both females and males [1]. Generally, majority of the CRC are sporadic whereas approximately 20-30% of CRC are inherited form of diseases associated with conditions such as Lynch syndrome and Familial adenomatous polyposis (FAP). The genetic instability associated with CRC includes the most common, chromosomal instability (CIN); microsatellite instability (MSI) and CpG island methylation phenotype (CIMP). CIN is characterized by the major changes in the structure and number of chromosomes whereas MSI is associated with defects in the mismatch repair pathway. CIMP, on the other hand, causes promotor hyper methylation and tumour suppressor genes silencing, leading to epigenetic instability [2,3]. The development of CRC is a multi-step process, which involves the acquisition of multiple mutations such as Adenomatous polyposis coli (APC) and TP53. Several factors such as diet, obesity, tobacco and alcohol use have also been identified to increase the risk of CRC [4]. In

addition, CRC can also be classified into 4 different consensus molecular subtype (CMS) namely, CMS1 (14%, characterized by hypermutation, microsatellite instability and immune activation), CMS2 (37%, epithelial subtype characterized by chromosomal instability and hyperactivity of the Wnt and Myc pathway), CMS3 (13%, epithelial subtype with metabolic dysregulation) and CMS4 (23%, mesenchymal subtype with TGFβ activation, invasion of the stromal and angiogenesis) [5].

Long non-coding RNA (LncRNA)

LncRNAs are RNA molecues of more than 200 nucleotides long in length and generally does not encode for functioning protein. Functionally, the regulation of gene expression by lncRNAs can occur via multiple mechanisms at both DNA and RNA level such as mediating epigenetic modifications through the interaction with chromatin remodeling machinery [6, 7]. For instance, the interaction between lncRNAs such as Xist and chromatin remodeling enzymes such as Polycomb Repressive Complex (PRC) have been shown to result in the inactivation of genes in chromosome X due to widespread methylation. Some other chromatin complexes that have been reported to interact with lncRNAs include DNA demethylation regulator GADD45a and histone demethylase LSD1 [8]. In addition, lncRNAs are also involved in the regulation of transcriptional processes whereby lncRNAs can aid in the recruitment of chromatin modifiers and aid in the formation of enhancer-like complex. Moreover, lncRNAs can also affect post-transcriptional processes via its interference with mRNA splicing processes and as a negative regulator in the inhibition of miRNA activity [6,7,9].

Long non-coding RNA (LncRNA) in colorectal cancer

In the recent years, there have been numerous ongoing researches in uncovering the functional aspects and potential in therapeutic treatments of long non-coding RNAs (LncRNAs) in cancers, which is one of leading causes of incidence and mortality for individuals worldwide. An analysis of the human transcriptome has identified about 68% of expressing genes encoding for lncRNAs and further analysis has enabled the classification of these lncRNAs to be associated with different diseases, including cancer [10, 11]. The importance and mechanistic action of lncRNAs have been looked into by different studies focusing on several different cancers including colon and some of the female reproductive cancers such as breast, cervical, ovarian and endometrium [12]. In an analysis of lncRNA expression profile in CRC, it has identified about 556 upregulated lncRNAs and 1040 downregulated lncRNAs in CRC tissues as compared to normal tissues, whereby UCA1 was most significantly upregulated and lncRNA AK055386 being downregulated. Both were suggested to have an effect in the regulation of cell cycle progression [13]. In addition, there are also other aberrantly expressed lncRNAs such as CCAT1, H19 [14] and HOTAIR [15], which have been suggested to have clinical significance in CRC. LncRNA CPS1-IT1 for instance, which is downregulated in CRC, was found to suppress proliferation, and invasion and metastasis [16]. On the other hand, the upregulation of lncRNA ubiquitin-like plant homeodomain (PHD) and really interesting new gene (RING) finger domain containing protein 1 (UHRF1) Protein Associated Transcript (UPAT) promotes colon cancer tumorigenesis whereby its interaction prevents the degradation of epigenetic factor UHRF1. Stabilization of UHRF1 results in the upregulation of Stearoyl-CoA desaturase 1 and Sprouty 4, which are essential molecues for CRC survival[17]. In addition, there were reports also illustrating how lncRNA can affect cancer cell progression in the different aspects.

lncRNA and Growth & Proliferation

In order for the progression of cancer, cancer cell would need to have the ability to proliferate continuously and this can be acquired with either the evasion of apoptotic signals or with sustained growth signals. LncRNAs have been reported to promote cancer cell proliferation by affecting several cellular processes. lncRNA CRNDE was reported to be highly expressed in CRC tissues and it was identified to bind to miR181a-5p and repress its expression. As miR181a-5p is able to inhibit Wnt/β-catenin signaling by targeting β-catenin/TCF4, upregulation of CRNDE would result in the increase in Wnt signaling, which would in turn promote proliferation [18]. In addition, in CRC, aberrant activation of Wnt signaling can lead to increased production of downstream target c-Myc. c-Myc would in turn upregulate lncRNA MYU and subsequently, MYU complexes with RNA binding protein, hnRNP-K and promote G1-S transition of the cell cycle through the stabilization of Cyclin-dependent Kinase 6(CDK6) [19]. Another effect of lncRNA on proliferation would involve LncRNA-RP11-317J10.2, whereby its downregulation in CRC would promote cell cycle progression with the increase in Cyclin D1, an essential cell cycle progression protein [20]. In CRC, patients with lower lncRNA HOXB-AS3 level correlated with poorer prognosis. Moreover, this lncRNA was also observed to be downregulated in highly metastatic CRC cancer cells. The reduction in lncRNA HOXB-AS3 level resulted in the reduction of HOXB-AS3 peptide, an endogenous peptide encoded by lncRNA HOXB-AS3 that inhibits hnRNP A1-mediated regulation of pyruvate kinase M (PKM) splicing, PKM2 formation and subsequent metabolic reprogramming in CRC cells. Hence, the low level

Table 1. List of lncRNAs in colorectal cancer cell lines using Affymetrix U133P2 platform

Index	Gene	Mean Expr	Standard Deviation	vsGSN_Spear.Rho	vsGSN_Spear.pv	Consensus Subtype.Anova.p	MeanExpr_CMS1	MeanExpr_CMS2	MeanExpr_CMS3	MeanExpr_CMS4
5	ACVR2B-AS1	4.578461653	0.244469102	-0.449538867	0.00194863	0.990286627	4.576117	4.528498	4.561952	4.532177
16	ALKBH3-AS1	4.186143515	0.185024918	0.311067194	0.037535259	0.103145488	4.282104	4.403372	4.248913	4.12042
29	ARHGEF26-AS1	3.619052861	0.840923156	0.406192358	0.005629479	0.41280986	3.38067	3.40619	3.398009	3.935037
36	ASAP1-IT2	4.668174255	0.602911787	0.305797101	0.041067509	0.623589397	4.437332	4.913927	4.837027	4.768028
37	ASB16-AS1	5.500537452	0.605851806	-0.320289855	0.031955155	0.911299842	5.389075	5.25798	5.45398	5.455409
39	ASMTL-AS1	4.907538059	0.312078859	-0.350724638	0.018171576	0.907587909	4.801973	4.800565	4.677503	4.818714
49	BAIAP2-AS1	7.683648149	0.850729961	0.387878788	0.008470746	0.187993143	6.930762	8.295449	7.794788	7.872783
54	BDNF-AS	3.870003496	0.779216402	0.338998682	0.022726793	0.524248643	3.660058	3.637754	3.725352	3.784996
65	BZRAP1-AS1	4.312065585	0.90876151	-0.361791831	0.014604755	0.465569429	4.016981	4.199555	3.755398	4.052064
80	CADM3-AS1	4.384625368	0.16481885	0.413306983	0.004773889	0.809151595	4.408753	4.326222	4.308137	4.409657
95	CATIP-AS1	4.940003776	0.460603059	-0.364295125	0.01388632	0.422527245	4.998086	4.714296	5.166472	4.673326
116	CHKB-AS1	5.557833178	0.377288682	-0.372990777	0.011619738	0.929641586	5.552107	5.420728	5.408765	5.563243
143	DANCR	10.395994901	0.793810697	-0.491567852	0.000605395	0.500721563	10.67674	10.5661	10.47392	9.97383
151	DEPDC1-AS1	4.166452648	0.428188378	-0.364426877	0.013849357	0.284410292	4.25898	4.070752	4.617647	3.990352
184	DPP10-AS3	4.080721561	0.205314121	-0.32687747	0.028404584	0.438632258	4.105314	4.08134	3.860193	4.007328
198	ELFN1-AS1	6.145434336	1.192493792	-0.373649539	0.011461745	0.325313804	6.462381	6.484829	6.114446	5.426983
200	EMC3-AS1	7.041500024	0.562001555	-0.459683794	0.00148936	0.771722566	7.06758	7.18786	7.142899	6.900175
202	ENO1-AS1	4.982844435	0.554985709	-0.430698287	0.003142904	0.41809182	4.527149	5.095978	4.939006	4.890387
203	ENTPD1-AS1	7.261448015	0.756794035	-0.367061924	0.013127486	0.912898663	7.189334	7.339923	6.913244	7.168134
205	EP300-AS1	5.873192753	1.444514744	-0.475625823	0.000959898	0.308438261	6.526896	5.560759	5.020305	5.021396
230	FAM27E3	6.354963006	0.701781125	-0.303162055	0.042932908	0.489768244	6.618687	6.559521	6.033163	6.089667
236	FAM95C	5.544552947	1.282604393	-0.342160738	0.021413142	0.331255857	5.247222	6.166804	4.659209	4.986152
249	FLVCR1-AS1	6.903224958	1.21406065	-0.300395257	0.044965338	0.51835313	7.160119	7.466899	7.220507	6.326991
257	FOXP4-AS1	6.851059846	1.454591043	-0.540843215	0.000125218	0.110189842	6.87759	7.516866	5.756622	5.907094
307	HEIH	8.081976086	0.785127179	0.494598155	0.000553196	0.907332643	8.246104	7.900617	8.172739	7.98093
322	HOXB-AS1	4.229291927	0.803670712	0.304479578	0.041991755	0.15769309	3.994355	4.300616	5.31464	4.029059
338	IL21R-AS1	4.378901718	0.168141453	-0.304347826	0.042085105	0.907676759	4.362462	4.321	4.361672	4.40008
339	ILF3-AS1	8.118211269	0.82025519	-0.47826087	0.00089084	0.394851336	8.35879	8.177816	7.682877	7.681317
340	INE1	4.917504155	0.285172871	-0.371805007	0.011908825	0.588979924	4.717752	4.944956	4.855674	4.826411
342	INTS6-AS1	5.042788807	1.012993063	-0.306324111	0.040702496	0.711915419	4.65093	4.861055	4.214668	4.585751
408	LINC00115	5.167658676	0.772963347	-0.305928854	0.040976006	0.52214504	5.385707	4.896825	4.840493	4.846599
421	LINC00208	4.096497203	0.222777296	0.315810277	0.034573176	0.157991683	4.284512	4.060274	4.013763	3.997024
478	LINC00424	5.093357714	0.201915548	0.306719368	0.04043048	0.619017087	5.179044	5.023784	5.070598	5.101686
490	LINC00470	4.075790124	0.287362024	0.307641634	0.039801555	0.605324076	4.247793	3.980541	4.108874	4.150695

580	LINC00648	4.053965319	1.008841233	0.417786561	0.004295444	0.312132673	3.76783	3.788138	4.550037	4.948382
589	LINC00663	4.964889393	0.661045848	0.319631094	0.032329549	0.1759919	5.088454	4.49709	4.458609	4.977045
623	LINC00852	4.21054026	0.206847361	-0.43030303	0.003173675	0.169735107	4.098439	4.331159	4.331714	4.180044
632	LINC00869	5.374944598	0.378798711	-0.327799736	0.02793473	0.293162771	5.232445	5.51163	5.597788	5.159257
636	LINC00880	4.513250188	0.390603644	-0.37826087	0.010406419	0.711597279	4.427498	4.555247	4.275217	4.632309
669	LINC00930	5.115663327	0.200451845	-0.311330698	0.037365409	0.160132048	5.247613	5.027506	4.913987	4.965428
673	LINC00936	5.955952258	0.871789109	0.516469038	0.000281332	0.146062185	5.63412	5.77864	7.120066	6.33703
675	LINC00938	8.497636589	0.663295875	-0.468247694	0.001179387	0.302824071	8.390444	8.668585	8.657852	7.977719
688	LINC00963	5.328658279	0.630155509	0.357444005	0.015927719	0.524788524	4.939964	5.258535	5.367145	5.116058
689	LINC00967	4.083472174	0.611943308	0.374703557	0.01121278	0.475882985	4.484873	3.865264	3.963928	4.081382
753	LINC01137	4.714100128	0.477710202	0.441633729	0.002389244	0.966468389	4.742036	4.56794	4.604276	4.662079
811	LINC01304	4.314298358	0.203142635	0.399736495	0.006518284	0.2654394	4.398548	4.477429	4.224368	4.267067
815	LINC01314	4.332454764	1.083105431	0.336495389	0.023814069	0.201978437	4.453056	4.174288	5.421322	3.964488
816	LINC01315	6.476087871	1.117642369	-0.411462451	0.004984026	0.345955593	6.825226	6.764993	6.035009	5.866429
845	LINC01424	4.468389457	0.431415689	-0.326613966	0.028540027	0.969037287	4.414031	4.352225	4.499547	4.45689
864	LINC01503	5.343415688	0.966820816	0.409486166	0.00521808	0.972046132	5.476872	5.32216	5.291909	5.565732
880	LINC01535	4.074734564	0.219107154	-0.337285903	0.023466114	0.731490734	4.091295	4.094471	4.043996	3.952672
894	LINC01560	5.567214448	0.74479569	-0.466798419	0.001227413	0.704708482	5.462646	5.852346	5.712946	5.401691
898	LINC01566	5.127514449	0.211735045	-0.335836627	0.024107318	0.594175313	5.203118	5.118081	4.966415	5.087029
917	LINC01620	4.130835171	0.172018856	-0.304479578	0.041991755	0.090298199	4.133541	4.076804	3.917534	4.101622
921	LOH12CR2	4.399160823	0.413611049	-0.345454545	0.020113164	0.554788783	4.290131	4.121865	4.447	4.509953
941	MAPKAPK5-AS1	9.593944408	0.483407358	-0.408168643	0.005379384	0.434591472	9.294761	9.808059	9.361111	9.331939
958	MINCR	6.506235686	0.979429516	-0.489591568	0.000641777	0.172773215	6.285823	6.860871	6.106543	5.693588
962	MIR155HG	4.352287839	1.166339169	-0.319235837	0.032555919	0.386424642	4.223613	3.745139	4.848168	3.960502
969	MIR22HG	7.751996496	1.207641501	0.447957839	0.002030502	0.634801234	7.874913	7.126785	7.896657	8.078812
970	MIR31HG	5.624602011	1.506437803	0.379314888	0.010177269	0.473630612	5.117819	5.279532	6.572974	5.562673
996	MIR924HG	4.695378944	0.780360005	-0.395125165	0.007225427	0.850731763	4.660186	4.507268	4.905629	4.374108
1005	MORC2-AS1	6.681128468	0.501713466	0.311462451	0.03728072	0.935439925	6.659543	6.834537	6.701106	6.802237
1011	MSC-AS1	3.756096392	1.033014489	0.346376812	0.019761307	0.669649215	3.5499	3.458817	3.482382	4.214757
1041	NOP14-AS1	6.377045181	0.532875041	-0.300790514	0.04467029	0.03525814	6.435972	5.778346	6.546497	5.986503
1044	NPTN-IT1	7.407232298	0.999023944	0.364163373	0.013923368	0.08513222	7.390819	7.548109	8.666502	7.387959
1072	PAXBP1-AS1	4.688934448	0.251738452	-0.32397892	0.029924206	0.731461215	4.646056	4.803328	4.57113	4.658983
1074	PAXIP1-AS2	5.139725008	0.453283884	0.339920949	0.02233685	0.775387796	4.902617	5.09797	5.202803	5.041821
1091	PHACTR2-AS1	4.242158597	0.206956512	-0.336758893	0.023697608	0.691977009	4.233417	4.297471	4.231047	4.155969
1095	PINK1-AS	5.865230913	0.695092233	-0.362450593	0.014412696	0.164579085	6.085782	5.593093	5.291449	6.126486
1098	PITPNA-AS1	8.746379795	0.597623048	-0.316073781	0.034414432	0.364041614	8.966186	8.887542	8.405399	8.370357

1107	POU6F2-AS2	3.821788862	1.107826472	0.497496706	0.000507086	0.106101756	3.430234	3.354996	5.382045	4.201577
1121	PRRT3-AS1	7.301787772	1.367291307	-0.302503294	0.043409893	0.708397856	6.814168	7.537882	7.872187	7.010324
1127	PSMG3-AS1	4.965841754	0.522192403	0.305928854	0.040976006	0.814278232	4.978396	4.928715	4.851153	5.201611
1143	RAB30-AS1	8.993523159	0.707115714	-0.384453228	0.009121172	0.939827461	8.892351	9.204113	8.848205	8.934903
1149	RAPGEF4-AS1	4.018630396	0.185949216	-0.41198946	0.004923179	0.065099993	4.032587	4.117815	3.72254	4.016148
1150	RARA-AS1	6.197364502	0.726282093	0.41198946	0.004923179	0.199932625	6.066508	6.442013	6.717456	5.722956
1151	RASSF1-AS1	4.64146225	0.442074807	-0.477338603	0.000914488	0.288135889	4.813029	4.379927	4.723042	4.461724
1152	RASSF8-AS1	4.062911241	0.262007545	0.380632411	0.009896935	0.10382674	4.030662	3.875324	4.06078	4.316523
1165	RNASEH1-AS1	7.759077102	0.768233828	-0.512384717	0.000320308	0.263935838	7.248386	8.131886	8.145346	7.515203
1173	RPARP-AS1	6.409998991	0.908152026	-0.489459816	0.000644271	0.377723488	6.331001	6.571025	5.685196	6.139574
1222	SNHG12	10.6974972	0.807321214	-0.316337286	0.034256289	0.356178064	10.65414	10.75138	10.80198	10.16767
1227	SNHG19	10.2824229	0.879096756	-0.387615283	0.008519318	0.107085856	10.43419	10.38113	10.16502	9.247535
1231	SNHG4	5.345826688	0.87213995	-0.366666667	0.013233677	0.324748714	5.025478	5.78542	4.765513	5.186886
1236	SNHG9	6.307018939	1.091849648	-0.451778656	0.001837648	0.790419535	6.380239	6.292334	6.30848	5.834104
1244	SNORA72	5.522944825	0.599327073	-0.340843215	0.021952532	0.131037978	5.301154	5.858193	5.697543	5.193989
1269	ST3GAL4-AS1	6.198057281	1.128555098	0.344137022	0.020624953	0.683701282	6.10554	6.242035	6.920751	5.949468
1270	ST7-AS1	4.890101189	0.697115598	-0.405270092	0.00574961	0.528338444	4.969011	4.778843	5.552952	4.831874
1278	STK4-AS1	4.729292843	0.231166958	-0.407641634	0.005445111	0.063835279	4.916173	4.808264	4.450904	4.638419
1279	STX17-AS1	8.841131758	0.432452009	0.303293808	0.042838025	0.261876375	9.044904	8.871808	8.421422	9.014238
1280	STX18-AS1	4.160773258	0.417739936	-0.358893281	0.015475875	0.953167737	3.978369	4.094128	4.002783	4.119997
1301	THAP7-AS1	4.429753963	0.428089098	-0.38801054	0.00844655	0.952252312	4.329612	4.326905	4.458366	4.425314
1320	TMPO-AS1	5.068302862	0.667986712	-0.322529644	0.030708931	0.37110402	4.91333	5.138968	5.441775	4.546827
1324	TOLLIP-AS1	5.293022503	0.760619015	-0.321870883	0.031071217	0.703526494	5.296079	5.138785	5.354397	4.833264
1325	TONSL-AS1	4.237907723	0.330989127	0.375362319	0.011059541	0.915980657	4.380319	4.25148	4.394354	4.313657
1326	TP53TG1	6.687746083	1.180811635	0.308432148	0.03926887	0.597081298	6.665982	6.006641	7.412105	6.393167
1338	TTC28-AS1	7.532914452	0.878706379	-0.427931489	0.003363924	0.829505605	7.511613	7.503955	7.452708	7.031614
1349	TUG1	10.31268217	0.813184126	0.312121212	0.036859639	0.680463762	10.47986	10.49709	10.15546	10.67947
1355	UBL7-AS1	6.984452265	0.61547951	-0.300922266	0.044572291	0.164008663	6.683247	6.837062	7.45389	6.694283
1356	UBR5-AS1	6.578248534	0.793574882	-0.390645586	0.007974992	0.547080388	6.368266	6.622673	6.153418	6.080181
1362	URB1-AS1	6.447196468	0.684552165	-0.411857708	0.00493833	0.442034014	6.677593	6.13958	6.081313	6.149383
1364	USP3-AS1	4.588855572	0.598960069	-0.396837945	0.006955386	0.64463246	4.353157	4.400809	4.56618	4.236638
1400	ZNF503-AS2	5.719158532	0.423087559	0.313833992	0.035783081	0.452079973	5.790346	5.685245	5.577466	6.037296
1401	ZNF529-AS1	4.032934112	0.512623039	0.336627141	0.023755779	0.458671601	4.261161	3.771385	4.010541	4.257543
1407	ZNF674-AS1	5.06094323	0.532629987	-0.556521739	7.19E-05	0.398718709	5.39509	5.070095	4.997288	4.875531

of lncRNA HOXB-AS3 would in promote the metabolic reprogramming of CRC cells, with the increased in PKM2 production, to promote survival and tumorigenesis [21].

lncRNA and Invasion and Metastasis

Invasion and metastasis is one of the essential hallmark in

the progression of cancer and the involvement of lncRNA has been discovered gradually. In particular, lncRNA-RP11-317J10.2 was observed to be downregulated in CRC and its silencing resulted in the increase in the invasive capability of CRC cells. It was identified that the silencing of Cyclin D1 abrogated the increased invasive capability of CRC cell induced by LncRNA-RP11-317J10.2 knockdown, suggesting its mechanistic action to be through Cyclin D1 being a downstream target of lncRNA-RP11-317J10.2 in promoting CRC progression [20]. In addition, the upregulation of lncRNA-HNF1A-AS1 was observed in CRC and is essential in cancer progression whereby the loss of lncRNA-HNF1A-AS1 impaired tumor growth and metastasis. LncRNA-HNF1A-AS1 would function as a competitive endogenous RNA (ceRNA) of miR-34a to increase the expression of SIRT1, an NAD-dependent class III deacetylase (HDAC) required for the deacetylation TP53, leading to the repression of TP53 activity. Moreover, the increase in lncRNA-HNF1A-AS1 level resulted in the reduction in levels of TP53, apoptotic proteins and expression of Wnt genes, which can be abrogated with miR34a inhibitors and vice versa. These suggests the importance of lncRNA-HNF1A-AS1 in mediating the suppression of the of miR-34a/SIRT1/TP53 feedback loop. This subsequently resulted in the inhibition of apoptosis and activation of canonical Wnt signaling, which can be suppressed by miR-34a and TP53, promoting the metastatic progression of cancer [22]. Moreover, LINC-PINT, a TP53-regulated lncRNA, was identified to be downregulated in CRC. Mechanistically, the presence of highly conserved residues in LINC-PINT is required for the interaction with PRC2-mediated silencing of invasion-related genes expression with the increase in H3K27me3 level. Therefore, the reduction of LINC-PINT resulted in the increased in the migration and invasive capability of CRC cells [23]. Furthermore, another lncRNA H19, upregulated in mesenchymal like CRC cells and primary CRC tissues, enhances the epithelial mesenchymal transition (EMT) in CRC. lncRNA H19 increases the expression of EMT genes such as Vimentin, ZEB1 and ZEB2 by inhibiting of the activity of miR-138 and miR-200a and hence promoting subsequent cancer progression [24].

Gelsolin and non-coding RNA

Gelsolin, a cytoskeletal molecule which was shown to be expressed differentially in different cancer, have been found to be upregulated in the invasive front of CRC tissues, in particularly in patients with liver metastasis [25]. Furthermore, there are also evidences that suggest the involvement of gelsolin in the invasion and metastasis of CRC whereby the CRC cell with higher gelsolin expression could increase the invasive and migration capability of cells through the Urokinase-Type Plasminogen Activator (uPA) Cascade. The activation of uPAR cascade, which can promote the degradation of the extracellular matrix of cells to promote invasion, could be induced by the higher level of intracellular reactive oxygen species in cells with higher gelsolin levels [25, 26, 27]. Gene expression analysis of lncRNA were carried out in both CRC cell line and tissue using Affymetrix u133 plus2 and RNA-seq respectively and we have identified lists of lncRNA genes that correlates with gelsolin expression. In the CRC cell line based analysis, lncRNA gene expression that correlated more significantly with gelsolin expression did not have significant difference in the expression in the different consensus molecular CRC subtypes (Table 1). On the other hand, the top few lncRNA genes that positively correlated with gelsolin expression, was found to be downregulated in tumor tissue as compared to normal tissue and vice versa. Moreover, in the analysis of CRC clinical data, variation of expression of these lncRNA which correlated more significantly with gelsolin, was more significant across the different molecular subtypes. For instance, mean expression of EMX2OS significantly differs between CMS3 and CMS4 (Table 2). At present, there are no studies that show the interaction between gelsolin and lncRNA. However, the levels of lncRNA were reported to regulate some cytoskeletal related genes. In particular, in breast cancer, MALAT1 silencing resulted in the upregulation of genes such as CTHRC1, a secreted protein that inhibits collagen expression and, CCT4 which is a chaperonin involved in folding tubulin, actin and other cytosolic proteins, leading to reduced motility of lung cancer cell [28]. Moreover, a recent proteomics analysis has identified gelsolin as one of the upregulated proteins in response to overexpression of metastatic inhibitor miR-193a-3p in a highly metastatic lung cancer cell line, suggesting that noncoding RNA can have an effect on gelsolin expression [29]. Gelsolin has not only been identified to express differentially in different cancer, but also been suggested to be down-regulated in early stages of tumorigenesis and re-expressed with cancer progression leading to the increased aggressiveness of cancer in both urothelial carcinoma and oral cancer [26, 30, 31]. Therefore, depending on the cancer cell type and stage, lncRNA could possiblly affect gelsolin expression in different manner to contribute to tumorigenesis.

Conclusions

The emerging studies of lncRNA has enabled us to further understand how the different lncRNAs can act mechanistically and subsequently result in its effect on several hallmarks of cancer such as proliferation and growth, and invasion and metastasis. With the understanding of the biological impacts of LncRNA, there are possibility in looking at lncRNAs being potential therapeutics and

Table 2. List of gene expression of lncRNAs in colorectal cancer tissue samples using RNA-seq

Index	Gene Symbol	Mean Expr	vsGSN_Spear.Rho	vsGSN_Spear.pv	tumor vs normalt-test.p value	tumor vs normal_t-test.FClg2 (T - N)	Consensus Subtype. Anova.p	MeanExpr_CMS1	MeanExpr_CMS2	MeanExpr_CMS3	MeanExpr_CMS4
23	LINC01550	2.288532628	0.548147703	2.42E-31	1.28E-23	-2.324520058	2.28E-13	2.0633586	1.347304202	3.224374	2.422841
36	MIR22HG	6.749478006	0.450533159	1.71E-20	2.34E-42	-1.971378768	1.09E-13	6.6689875	6.101966193	6.377271	7.019228
43	SERTAD4-AS1	3.817946492	0.50065624	1.25E-25	8.09E-15	-1.491236944	5.00E-18	3.2375074	3.236012387	3.605686	4.574794
54	B3GALT5-AS1	2.573686481	0.485310246	5.77E-24	1.32E-40	-4.180139591	0.0081398	2.4542899	1.75540273	1.875464	2.565791
59	CYP1B1-AS1	1.722641844	0.304618532	1.21E-09	7.00E-39	-2.017969748	1.48E-11	0.9825203	1.262618029	2.185726	1.833769
78	SNHG15	8.811901 34	-0.39725552	6.83E-16	6.55E-50	1.683872519	1.19E-10	8.6779316	9.246025717	8.777055	8.713766
95	CECR7	1.788345 78	0.419421163	1.04E-17	1.82E-12	-1.457182845	4.75E-16	1.7197349	1.08369256	1.200203	2.602135
105	DLEU2	5.734611226	-0.300733841	2.00E-09	2.21E-21	1.344419672	6.86E-06	6.1803037	6.079103808	5.455618	5.624955
109	EMX2OS	1.527266456	0.309487816	6.35E-10	0.000233854	-0.876485339	3.83E-24	1.0566682	0.894481295	0.446534	2.824692
132	EPB41L4A-AS2	2.562080531	0.481751007	1.36E-23	1.44E-28	-1.702813903	4.03E-12	2.066005	2.028524123	2.359741	2.983875
143	NR2F1-AS1	4.841678781	0.417810218	1.43E-17	0.000411063	-0.558470131	1.47E-28	4.6806761	4.388500624	4.23592	5.810982
165	HCG4	2.052698864	0.411238472	5.07E-17	6.55E-13	-1.468430996	2.50E-22	1.8654943	1.334865611	1.423268	2.943078
185	TP73-AS1	6.030253513	0.527476389	9.60E-29	7.84E-24	-1.837397547	2.66E-41	5.6372697	5.352653065	4.904931	7.090969
187	AGAP2-AS1	7.250802483	0.357435409	5.91E-13	8.67E-14	0.967825948	3.99E-17	8.0947238	6.918530851	7.503168	7.65048
193	MIR31HG	2.22305603	0.333469786	2.25E-11	5.52E-14	2.094149071	9.46E-15	3.9297626	1.531083984	2.922516	2.85502
212	MIR17HG	6.273620675	-0.378877471	1.74E-14	7.81E-35	2.310073228	1.67E-14	5.8041189	7.119872638	6.065781	6.101154
214	HAND2-AS1	3.303689539	0.410735924	5.58E-17	2.53E-44	-4.618403083	6.79E-42	2.3556342	2.135124585	1.120148	4.863285
216	LINC00092	1.979329548	0.354864573	8.87E-13	1.13E-59	-2.630596566	5.62E-07	1.4701955	1.516806328	1.512136	2.170467
241	PVT1	6.750436105	-0.376575748	2.57E-14	3.77E-76	2.644440653	1.29E-05	6.7231102	7.267085177	6.833664	6.838138
244	RFPL1S	1.594394596	0.470837542	1.80E-22	6.62E-21	-1.455359013	1.54E-30	1.3751769	1.043712975	0.861717	2.44457
256	SCARNA12	2.732310749	-0.359879271	4.01E-13	2.13E-14	1.006339032	4.93E-07	2.5219061	3.045975616	2.556501	2.456889
296	SNHG1	9.544901247	-0.429868647	1.30E-18	1.86E-40	1.619305702	2.09E-07	9.9221915	9.861594826	9.553637	9.341398
297	SNHG3	6.549791777	-0.324281295	8.38E-11	1.70E-26	1.4328795	4.85E-07	6.801419	6.776285609	6.833218	6.211786
298	SNHG4	4.742978398	-0.391769015	1.83E-15	2.43E-27	1.676535815	1.07E-06	4.6700808	5.198254136	4.801147	4.508497
393	SNORA8	8.455702375	-0.303660724	1.37E-09	3.00E-35	1.284204715	0.0003885	8.4789879	8.689290305	8.506673	8.326602

Gene expression analysis of lncRNA in CRC tissues was correlated with gelsolin (GSN) expression using RNA-seq platform. Genes that correlates either positively or negatively with GSN (Rho ≥ 0.3 or Rho ≤ -0.3) are listed in the table, with its p-value (n=382). Fold change of these lncRNA in CRC tissue relative to normal tissue was also tabulated, with p-value shown (tumor (n = 382), normal (n = 51)). Variation of lncRNA gene expression across the 4 molecular subtype of CRC was also carried out and shown in the table.

biomarkers in cancer [32, 33]. In the treatment of CRC, 5-Fluorouracil (5-FU) is one of the more common drugs used mainly in combination, in adjuvant chemotherapy for patients in earlier stages of CRC and chemotherapy treatment of stage IV CRC [34, 35]. However, in one of the recent study, the presences of lncRNAs such as UCA1 and sNAR have been shown to affect the effectiveness of the 5-FU treatment. Downregulation of snaR could decrease the sensitivity towards 5-FU and drug-induced cell death in CRC cells whereas the upregulation of UCA1 in CRC reduces the sensitivity towards 5-FU and drug-induced cell death through inhibiting the activity of miR204-5p as a sponge [36, 37]. Therefore, the complexity of lncRNA in the progression of cancer and its involvement in the treatment and diagnosis of cancer requires further research in order for greater understanding and its subsequent clinical translation.

Conflicting interests

The authors have declared that no conflict of interests exist.

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Authors Contributions

All authors (M.S.O., WP.C., T.Z.T., R.YJ.H., S.C.H., C.T.Y and A.P.K) contributed to the writing of the paper and revision of the manuscript.

Abbreviations

APC: Adenomatous polyposis coli; CCAT1: Colon cancer associated transcript 1; CCT4: Chaperonin Containing TCP1 Subunit 4; CDK: Cyclin dependent kinase; CIMP: CpG Island Methylator Pathway; CIN: Chromosomal instability; CMS: Consensus molecular subtype; CRC: Colorectal Cancer; CTHRC1: Collagen Triple Helix Repeat Containing 1; CPS1-IT1: CPS1 intronic transcript 1; CRNDE: Colorectal neoplasia differentially expressed; EMT: Epithelial mesenchymal transition; EMX2OS: EMX2 Opposite Strand/Antisense RNA; FAP: Familial adenomatous polyposis; GADD5a: Growth arrest and DNA-damage-inducible protein 5 alpha; GSN: Gelsolin; HOTAIR: Hox Antisense Intergenic RNA; hnRNP: Heterogeneous nuclear ribonucleoproteins; LINC-PINT: long intergenic non-protein coding RNA: p53 induced transcript; LncRNA: Long Non-Coding RNA; LSD1: Lysine-specific histone demethylase 1; MALAT1: Metastasis Associated Lung Adenocarcinoma Transcript 1; miRNA: MicroRNA; mRNA: Messenger RNA; MSI: Microsatellite instability; MYU: c-Myc upregulated lncRNA; PKM: Pyruvate kinase muscle isozyme; PRC: Polycomb repressive complex; RNA: Ribonucleic acid; SIRT1: sirtuin (silent mating type information regulation 2 homolog) 1; snaR: small NF90-associated RNAs; TCF: T-cell factor; TGFβ: Transforming growth factor beta; TP53: Tumour protein 53; Xist: X-inactive specific transcript; UCA1: Urothelial Cancer Associated 1; UHRF1: ubiquitin-like plant homeodomain (PHD) and really interesting new gene (RING) finger domain containing protein 1; uPA: Urokinase –type plasminogen activator; UPAT: ubiquitin-like plant homeodomain (PHD) and really interesting new gene (RING) finger domain containing protein 1 (UHRF1) Protein Associated Transcript; ZEB: Zinc finger E-box-binding homeobox; 5FU: 5-Fluorouracil.

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