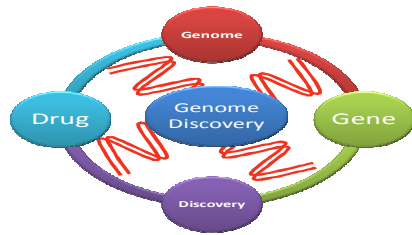


**The TA-p73 functions as  
a Lung tumor  
suppressor by increasing  
the expression of  
miRNA, Let-7**

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# Introduction

I have previously proposed that E2F-1-TA-p73-dependent tumor suppressor pathway could inhibit the development of lung adenocarcinoma.

This hypothesis is strongly supported by a recent finding showing that TA-p73 specific knockout mice are prone to lung adenocarcinoma. However, the p73-dependent tumor suppressor pathway remains ill defined.

# Hypothesis

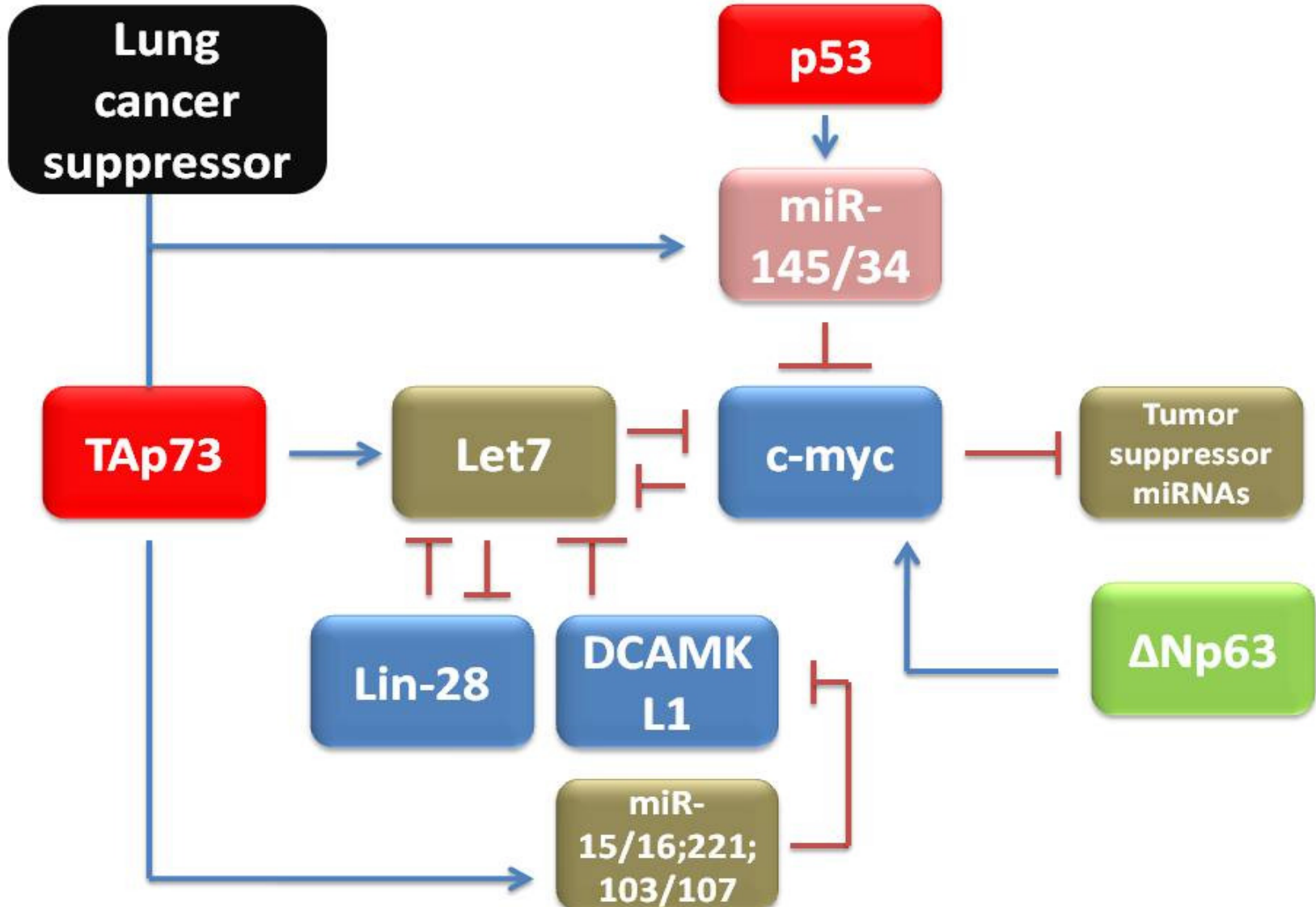
It has been shown that let-7 cluster is highly expressed in normal lung. Loss of let-7 expression: a) is common in Non-small cell lung carcinoma; and b) enhances lung tumor formation, indicating that it could function as a lung tumor suppressor. Based on these facts, I hypothesized that let-7 could be a transcriptional target of TA-p73.

# Result-1

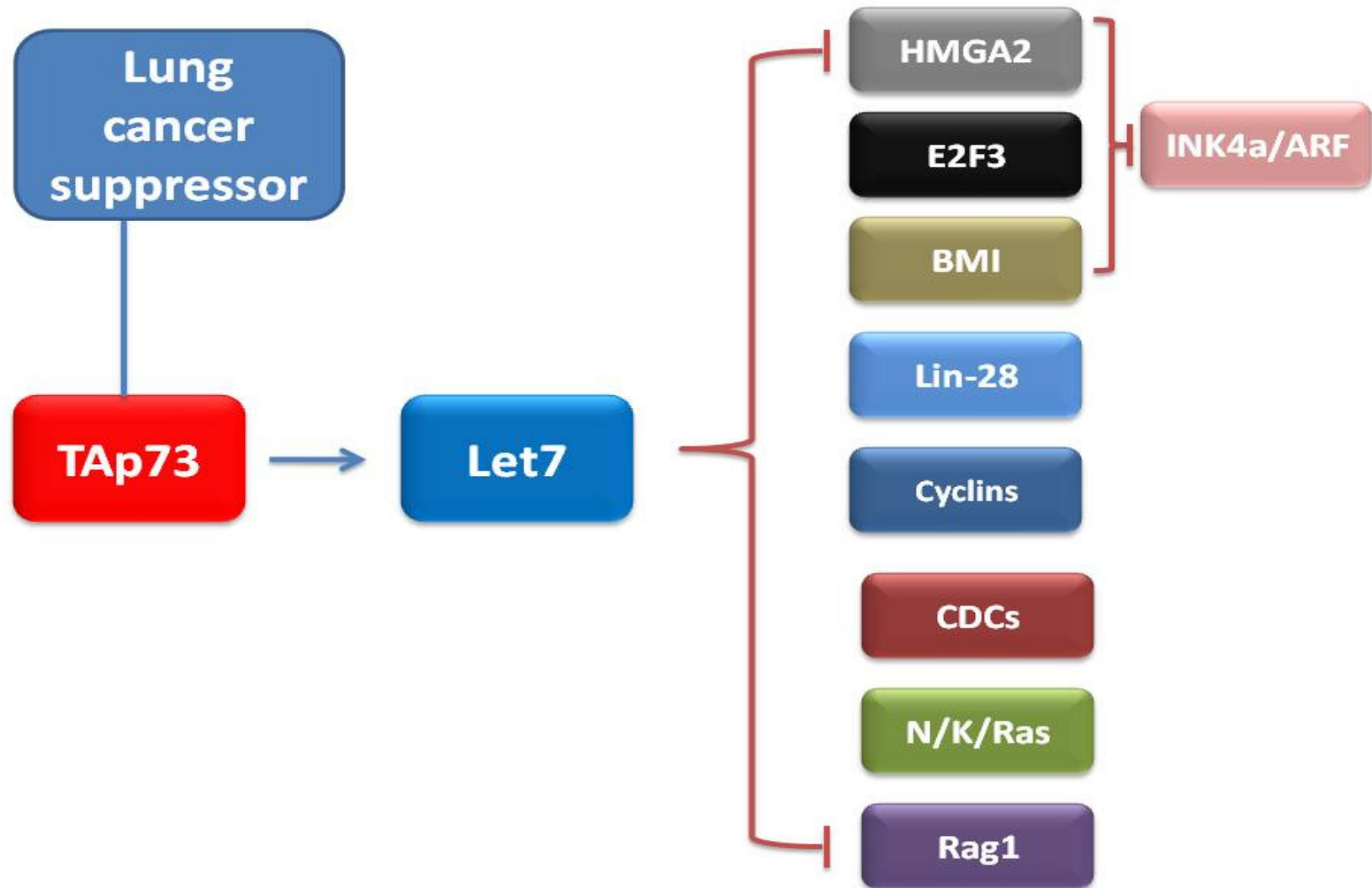
To confirm this hypothesis, I have analyzed the let-7 cluster promoters using TRASFAC bioinformatics software. This analysis suggests that Let-7c contains three perfect p53-RE half-sites and five nearly perfect p53RE sites (Table 1). In addition, other let-7 cluster miRNAs appear to contain several p53-REs (Table 2-11), suggesting that Let-7 miRNA cluster could be a transcriptional target of p73/p63/p53.

## Result-2

Furthermore, negative regulators of let-7 biogenesis, such as lin-28, c-myc and DCAMKL-1, are suppressed by p53-miRs, such as let-7, miR-145, miR-34, miR-15/16, miR-103/107 and miR-221, suggesting that p73/p63/p53, by suppressing the expression of lin-28, c-myc and DCAMKL-1, it could increase the expression of let-7 (figure 1). By increasing the expression of let-7, p73 could suppress the expression of its targets, such as N/H/K-ras, HMGA2, cyclins, MCMs, BUBs, IL-6, NFkB, STAT3, lin-28 and CDCs (figures 2, 3 & 4 ); thereby it could inhibit the initiation of lung tumors.

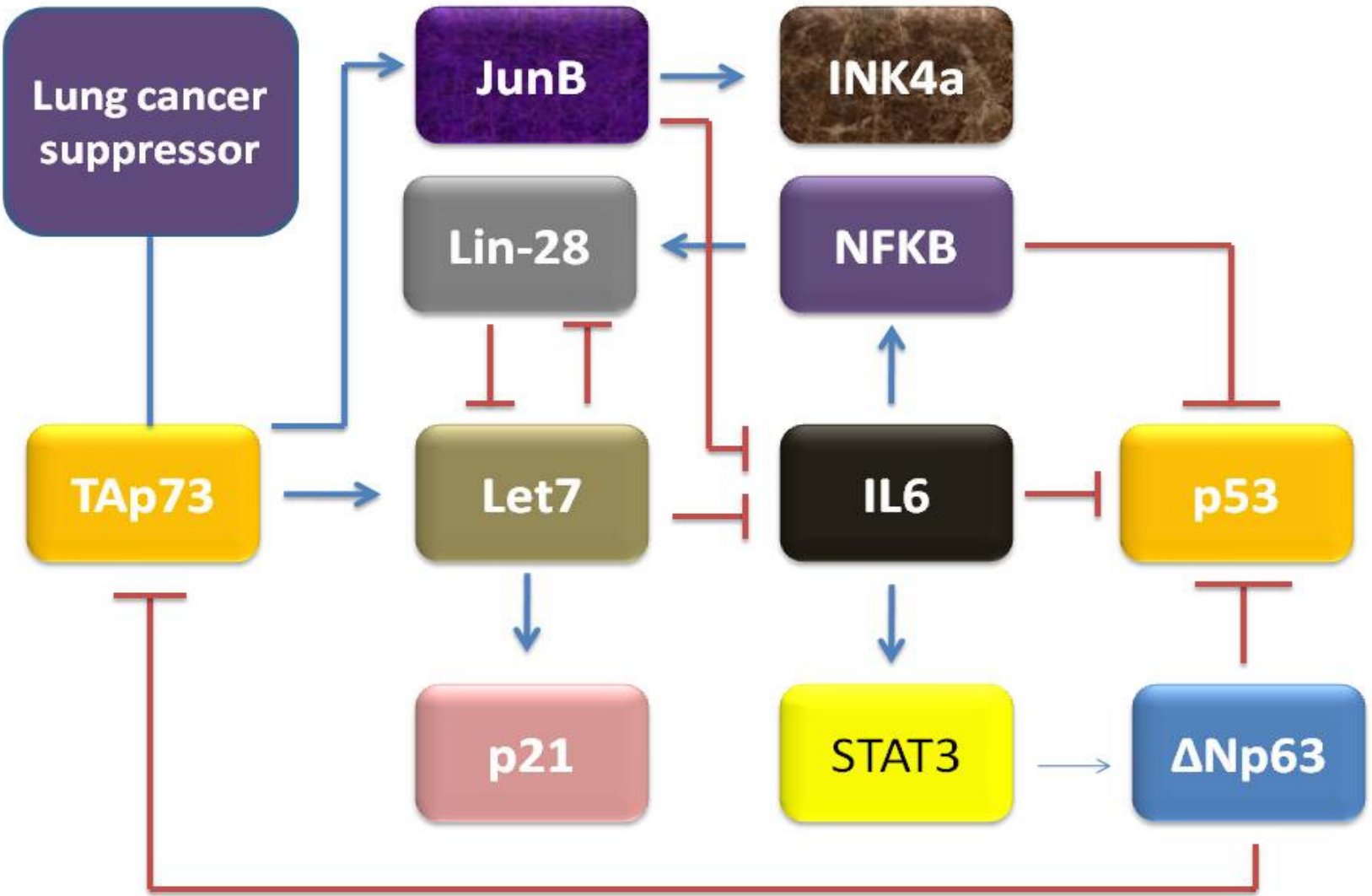


**Fig. 1 TA-p73 tumorsuppressor inhibits the negative regulators of let-7**

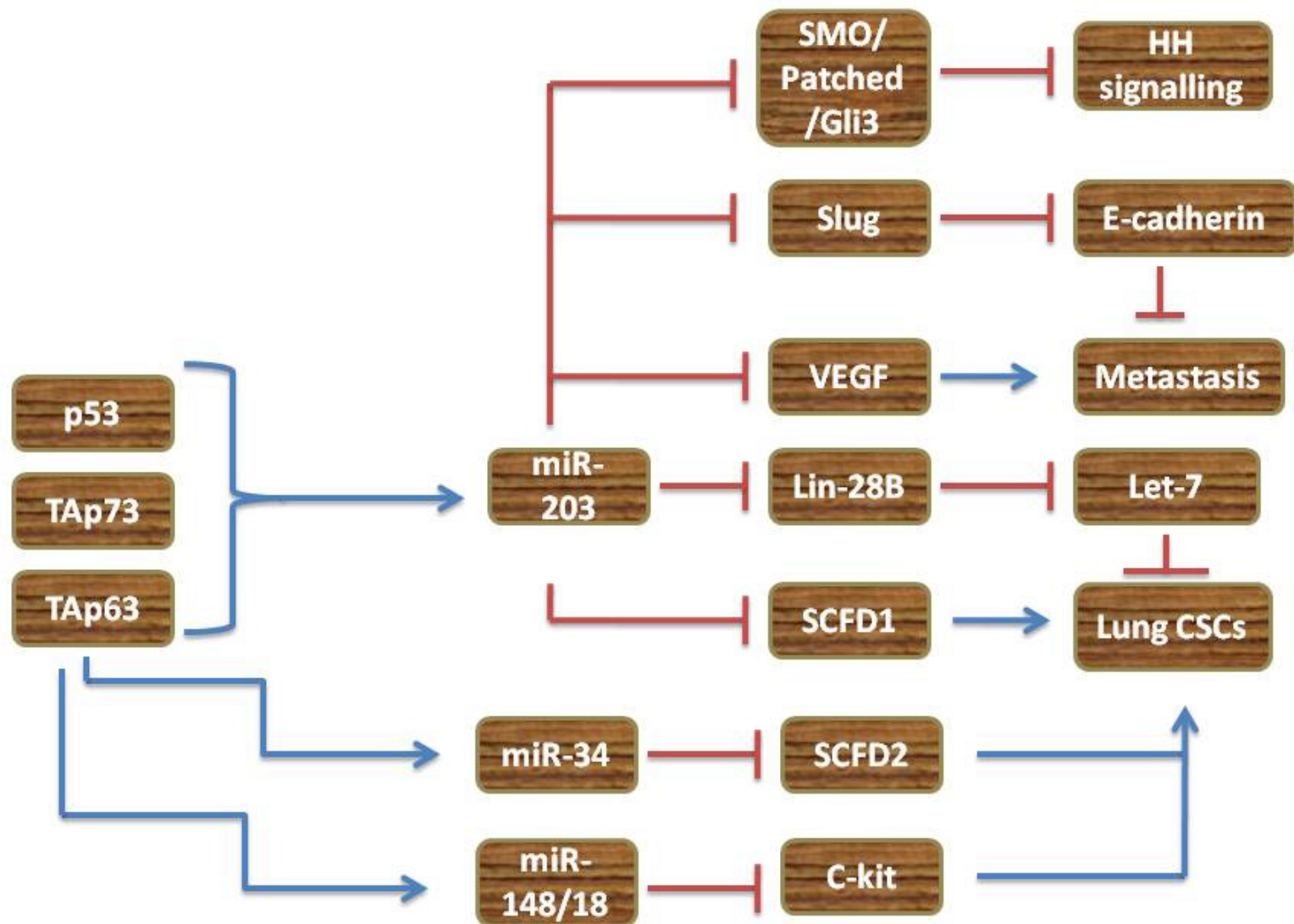


**Fig. 2 The targets of TA-p73-let7 tumor suppressor pathway**





**Fig. 3** The TA-p73-let-7-IL6-NFkB/STAT3 tumor suppressor pathway



**Fig. 4. The TA-p73/p63-let-7/miR-203 tumor suppressor pathway inhibits lung cancer stem cell proliferation and metastasis**

No.	Position	p53/p63/p73 responsive elements
1	-259 to -278	(aat <u>cttg</u> taa)(ata <u>catg</u> gtt)
2	-3133 to -3142	(aaa <u>catg</u> ttt)*
3	-3232 to -3251	(aag <u>catg</u> tga)(cac <u>caag</u> gtt)
4	-3981 to -4003	(gtg <u>ctgg</u> gat)tac(agg <u>catg</u> agc)

**Table 1 Human let-7a-1 promoter contains p53/p63/p73REs**

No.	Position	p53/p63/p73 responsive elements
1	-3 to -22	(agc <b>cattg</b> tga)(ctg <b>catg</b> ctc)
2	-1258 to -1279	(agg <b>ctagt</b> gg)aa(taa <b>catg</b> aag)
3	-1922 to -1944	(aga <b>cttg</b> gaa)ata( <b>catctt</b> gagt)
4	-4061 to -4079	(atc <b>catg</b> gggac <b>catg</b> agc)

**Table 2 Human let-7a-2 promoter contains p53/p63/p73REs**

No.	Position	p53/p63/p73 responsive elements
1	-100 to -121	(gtg <u>cg</u> gtg)cc(tgc <u>cg</u> agcct)
2	-216 to -236	(tcg <u>cat</u> gcct)g(tgt <u>ctt</u> gctg)
3	-1156 to -1189	(acc <u>cg</u> agg)cg(gag <u>ctt</u> gcag)tg(agc <u>cg</u> agatc)
4	-1399 to -1420	(tag <u>cat</u> gccg)tt(taa <u>ctt</u> ggca)
5	-1861 to -1903	(ggc <u>ctt</u> gagg)(gaa <u>cac</u> gggg)t(ctt <u>cg</u> cgacc)cc(agg <u>cg</u> agatg)
6	-2266 to -2290	(agt <u>cag</u> gagc)ccaga(gtg <u>cg</u> tgctt)
7	-3217 to -3236	(agc <u>cat</u> gtct)(ctt <u>ctt</u> gtct)

**Table 3 Human let-7a-3promoter contains p53/p73/p63REs**



No.	Position	p53/p63/p73 responsive elements
1	-41 to -62	(agg <b>caggggc</b> )tg(gtg <b>ctggg</b> cg)
2	-234 to -253	(aca <b>ctgggtc</b> )(cca <b>catggca</b> )
3	-376 to -396	(ctg <b>cgagtat</b> )(tgg <b>cgttgccc</b> )
4	-431 to -453	(cac <b>caggaga</b> )agg(cac <b>cgagggg</b> )
5	-479 to 501	(cat <b>caggccc</b> )ag(gct <b>catgggt</b> )
6	-1203 to -1226	(cca <b>cttgctg</b> )tgt(gac <b>cttgac</b> )
7	-1036 to -1058	(gtg <b>cggttg</b> )cc(tgc <b>cgagcct</b> )
8	-2352 to 2373	(tcg <b>catgcct</b> )g(tgt <b>cttgctg</b> )
9	-2600 to 2623	(aca <b>cggtccc</b> )aga(gag <b>caagcag</b> )
10	-2787 to -2807	(agg <b>cgagatg</b> )(atg <b>ctgggac</b> )
11	-3822 to -3847	(atc <b>ctggagt</b> )gcagc(cct <b>catgccc</b> )
12	-4153 to -4173	(agc <b>catgtct</b> )(ctt <b>cttgctt</b> )
13	-4660 to -4680	(act <b>caaggac</b> )(agg <b>cttggt</b> )

Table 4 Human let-7b promoter contains p53/p63/p73 REs

No.	Position	p53/p63/p73 responsive elements
1	-1980 to -1989	aaa <u>catg</u> ctt
2	-3472 to -3481	aaa <u>cttg</u> ttt
3	-3615 to -3624	gag <u>catg</u> ttc
4	-1348 to -1366	(aat <u>catg</u> cca)t(tat <u>cg</u> gcca)
5	-1594 to -1623	(aaa <u>cg</u> tgat)g(tgg <u>ctg</u> gctt)
6	-2583 to -2603	(tat <u>cg</u> tgttt)t(ctt <u>ctc</u> gatc)

**Table 5 Human let-7c promoter contains p53/p63/p73 REs**

No.	Position	p53/p63/p73 responsive elements
1	-53 to -77	(gaa <u>catgacc</u> )taatt(taa <u>cagg</u> tta)
2	-322 to -344	(agc <u>ctgggtg</u> )aca(gag <u>cgagact</u> )
3	-403 to -425	(act <u>ctggggg</u> )ctg(agg <u>caggaga</u> )
4	-716 to -738	(taa <u>ctgggtt</u> )ggg(cac <u>catggct</u> )
5	-1717 to 1736	(acc <u>catgaag</u> )(gcc <u>catgttt</u> )
6	-3326 to -3344	(atg <u>catgatgta</u> <u>caggact</u> )

Table 6 Human let-7d promoter contains p53/p63/p73 REs



No.	Position	p53/p63/p73 responsive elements
1	-1902 to -1925	(gggcatgctg)gga(accaggcct)
2	-2772 to -2793	(ggtcaagggt)g(agccgtgcca)
3	-2904 to -2922	(gggcgagctgcccgagccc)
4	-3197 to -3222	(cga <del>cgcg</del> ggagc <del>cgcg</del> ggagc <del>cg</del> tgagt)
5	-4701 to -4723	(aac <del>cg</del> tg <del>tcc</del> )ccg(ccc <del>ctt</del> g <del>ctc</del> )

**Table 7 Human let-7e promoter contains p53/p63/p73REs**

No.	Position	p53/p63/p73 responsive elements
1	-462 to -482	(aac <u>caggatt</u> )(acc <u>gaggag</u> )
2	-649 to -668	(aat <u>cttgtaa</u> )(ata <u>catggtt</u> )
3	-3316 to -3336	(gtt <u>cgagacc</u> )(agc <u>ctggcca</u> )
4	-3574 to -3584	<u>(aaacatgttt)</u>
5	-3622 to -3642	(aag <u>catgtga</u> )(cac <u>caaggtt</u> )

Table 8 Human let-7f-1 promoter contains p53/p63/p73 REs

No.	Position	p53/p63/p73 responsive elements
1	-426 to -449	(att <u>cttg</u> cta)gaa <u>t(gatcatg</u> atc)
2	-1813 to -1833	(atg <u>cttgaca</u> )a(ggc <u>caaga</u> aat)
3	-3188 to -3217	(aga <u>catg</u> att)(ctg <u>cttga</u> ac)(aaa <u>catg</u> gaa)
4	-3959 to -3979	(cgt <u>caagt</u> ta)g(aat <u>cgag</u> ttc)
5	-4218 to -4239	(caa <u>cttg</u> atg)at( <u>ttgctt</u> gatt)

Table 9 Human let-7f-2 promoter contains p53/p63/p73 REs

No.	Position	p53/p73/p63 responsive elements
1	-212 to -221	aaa <b>catgtct</b>
2	-2339 to -2348	aag <b>caagcct</b>
3	-3128 to -3137	aga <b>cttgttt</b>
4	-3372 to -3381	agg <b>cttgctt</b>
5	-1016 to -1037	(gtt <b>caagcga</b> )t(gct <b>cttgctt</b> )
6	-1719 to -1741	(aca <b>cttgata</b> )ca(cag <b>caagtga</b> )
7	-4151 to -4175	(agt <b>cttgctc</b> )tgtt(gcc <b>caggcta</b> )

Table 10 Human let-7g promoter contains p53/p63/p73REs

No.	Position	p53/p63/p73 responsive elements
1	-1 to -26	( <b>tcc</b> <u>cg</u> <b>tg</b> cct)ccccga( <b>cac</b> <u>cat</u> <b>ggcc</b> )
2	-156 to -181	( <b>ggg</b> <u>cg</u> <b>cg</b> ccg)ggagt( <b>agc</b> <u>cg</u> <b>ag</b> ccg)
3	-416 to -439	( <b>ctc</b> <u>ct</u> <b>ag</b> cgg)gcg( <b>aag</b> <u>cg</u> <b>cg</b> gga)
4	-443 to -471	( <b>gcg</b> <u>cg</u> <b>ag</b> cgg)cgcagctcg( <b>gga</b> <u>cg</u> <b>tg</b> gcg)
5	-803 to -823	(gcg <u>cg</u> <b>ag</b> acg)(ggt <u>ct</u> <b>t</b> gt)
6	-1702 to -1712	( <b>aaa</b> <u>cat</u> <b>g</b> ctt)
7	-2872 to -2896	( <b>agg</b> <u>ca</u> <b>ag</b> ata)atgt( <b>gag</b> <u>ca</u> <b>ag</b> gca)

Table 11 Human let-7i promoter contains p53REs

# Conclusion

Together, this study proposes for the first time the TA-p73/p63-let-7-INK4a/ARF functions as a lung tumor suppressor pathway.