

# Role of NF-KB1 in Regulation of Micro RNA

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**Abstract – NF-KB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a collective name for the complexes formed by five NF-KB-Rel family members which control transcription of DNA. NF-KB1 (p50) is a member of NF-KB protein family which is known to regulate a wide range of genes those are involved in various physiological processes viz. immune and inflammatory responses, apoptosis, stress, cell proliferation and developmental process. This review is based on the detail bioinformatic analysis of NF-KB1 regulation on microRNA. Basically the miRNAs are small non-coding RNA shown to be involved in many biological and cellular processes. The NF-KB1 as a transcription factor regulates 29 microRNA genes by binding to its promoter region. Most of these microRNAs are associated with various types of cancers, including lung, prostate, breast and gastrointestinal cancer.**

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## INTRODUCTION

NF-KB is is an complex formed by five NF-KB-Rel family members namely NF-KB1(p50), NF-KB2(p52), Rel-A(p65), Rel-B, and c-rel (1). NF-KBs family regulates the expression of many genes involved in various physiological processes viz. cell proliferation, survival, inflammation, apoptosis and immunity (2). All these dimeric subunits retained in cytoplasm in a complex with inhibitory peptide (Ikbs) (1). Upon stimulation by various pathogens and their products, mitogens, stress, cytokines they migrate to nucleus with their interacting partner in either homodimer or heterodimer form to perform target gene expression. Unlike the other subunits, p50 doesn't have transactivation domain (TAD) and hence cannot regulate target gene expression of its own.

Transcription factors (TFs) usually control gene expression by binding with either promoter or enhancer region of respective genes encoding either protein or encoding microRNAs (miRNA) precursors. microRNAs are genes encoding ~22 bp long, small non-coding RNAs, also known as miRs. TFs can regulate the expression of specific miRNAs and in turn miRNAs can also target respective TF mRNAs. Multiple miRNAs have been shown to alter NF-KB activity targeting either IKK complex or NF-KB individual subunits (3-5). NF-KB is known to have a major role in regulation of various miRNAs viz mir-9, mir-16, however, in this review we demonstrate for the first time, the regulation of set of miRNAs as well as their targets by NF-KB1partner protein.

The NF-KB-miRNA network has been shown to regulate various physiological and pathological

conditions such as inflammation, immune, and stress-like responses (6). Aberrant miRNAs expressions have been detected during inflammation and cancer.

## REGULATION OF miRNA BY NF-KB1

NF-KB1 subunits have both positive as well as negative regulation of its wide range of target gene expression (1). NF-KB1 homodimers are known to suppress target genes (7) where-as NF-KB1 binding with other NF-KB subunit can activate various gene expressions. Here, we have shown that NF-KB1 is regulating 29 microRNAs in human (table 1). The genomic location of total 29 miRNA regulated by NF-KB1 is provided in table 2. The NF-KB1 targeting these microRNAs were retrieved using TransmiR v2.0 (8) database. Here, we consider only the literature-curated TF-miRNA regulation and repression. From human microRNA disease database (HMDD) (9), we found many of these miRNAs are associated with cancer. There is also feedback regulation by various miRNA which is a new emerging concept of its regulation. Two of these 29 microRNAs (miR-9 and miR-16) acts as feedback loop mechanism (Figure 1). These two and other miRs regulating NF-KB1 is also provided in table 3. Both these miRNAs bind to the 3' UTR of NF-KB1 gene and regulates its expression. It is also known that miR-16 significantly inhibits myoblast proliferation and promotes apoptosis (10). Another miRNA (miR-9) inhibits the growth of the gastric adenocarcinoma cell line MGC803 *in vitro* and *in vivo* (10). We predicted miR-340 have two binding sites in the 3'UTR of the NF-KB1 gene which could be a potential miRNA to inhibit the

expression of this gene. Previous studies suggest that miR-340 inhibits the tumor cell proliferation and induces apoptosis (11). We also found it regulates 279 protein coding gene expressions. From computational and functional analysis, we found that most of these genes were positively regulating the immune system process and there carried out molecular functions like cytokine receptor binding.

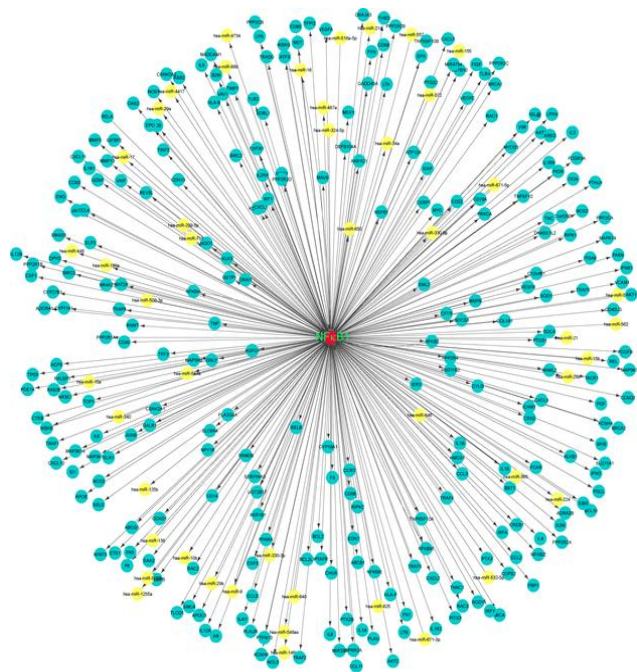


Figure1. The combinatorial NF-KB1 regulatory network.

The nodes in the network represent the NF-KB1 (red), mRNAs (cyan) and miRNAs (yellow). The edges denote the physical interaction and direction of regulation.

Functional annotation of microRNAs regulated by NF-KB1

In order to identify the disease association of microRNA genes which are regulated by NF-KB1, we subjected these microRNAs to miRNet tool. It is a user-friendly, integrated tool suite designed for comprehensive analysis and functional interpretation of miRNAs. We found majority of these microRNAs are associated with lung cancer, prostate cancer, breast cancer, hematological disease, pancreatic cancer, squamous cell carcinoma, head and neck, muscular disorder, ovarian cancer, colorectal cancer and gastrointestinal cancer. In order to understand the functional role of these microRNA, its targets were identified using four standard and widely used miRNA target prediction programs: miRanda, TargetScan, PITA and PICTAR. We included the experimentally validated miRNA targets from miRTarBase and miRecords databases. We consider the genes which are predicted by all the four prediction programs. A total 2808 genes are regulated by 29 microRNAs.

Table 1. NF-KB1 regulating microRNAs and protein coding genes

NF-KB1 regulating miRNA	NF-KB1 regulating protein coding genes
hsa-miR-10b, hsa-miR-1255a, hsa-miR-125b, hsa-miR-146a, hsa-miR-155, hsa-miR-16, hsa-miR-17, hsa-miR-199a, hsa-miR-21, hsa-miR-224, hsa-miR-29a, hsa-miR-29c, hsa-miR-330-3p, hsa-miR-34a, hsa-miR-365, hsa-miR-4417, hsa-miR-448, hsa-miR-4734, hsa-miR-487a, hsa-miR-5088, hsa-miR-544a, hsa-miR-548ac, hsa-miR-711, hsa-miR-889, hsa-miR-9	A2M, ABCB1, ABCG1, ACP5, ADORA1, ADRA2B, AGFG1, AKR1B1, AKR1C1, AKT1, AKT1, AKT2, AKT3, APOC3, APOE, AR, ARHG, ARLGIP5, ASB2, ATF3, ATP12A, B2M, BCL10, BCL2, BCL2L1, BIRC2, BIRC3, BRCA1, BRCA2, BST1, C12orf61, C1orf200, CCL11, CCL2, CCL3, CCL3, CCL4, CCL4, CCL5, CCL5, CCND1, CCND2, CCR7, CD104, CD22, CD40, CD40LG, CD69, CD79A, CD80, CD83, CD86, CDH13, CFTR, CHUK, CNTN1, COL1A1, COP2, CREB1, CSF1, CSF3, CSN2, CSNK2A1, CSNK2A2, CSRP1, CTSS, CXCL1, CXCL10, CXCL11, CXCL2, CXCL3, CXCL5, CYLD, CYP11A1, CYP19A1, CYP27B1, DEFB104A, DNAA3, DNASE1L2, DPYD, EBB3, EDN1, ELF3, ELK1, EML2, ENG, EPO, EPX, ETS1, F3, F8, FAS, FASN, FBP1, FCAR, FCGR3A, FIGF, FNI, FOS, FYN, GADD45A, GALR1, GDNF, GNLV, GSTP1, HLA-B, HLA-F, HMOX1, HSD11B2, HSPB1, ICAM1, ID1, IER3, IFNB1, IFNG, IGF2, IGL@, IKKB, IKBK, IL10, IL12A, IL12B, IL12B, IL1A, IL1B, IL1B, IL1R1, IL1R1, IL1R2, IL1R2, IL2, IL2RA, IL4, IL4I1, IL5, IL6, IL6, IL8, IL8, IRF1, IRF4, ITGA6, JAG2, JUNB, KCN4, KCN8, KCNMA1, KLK3, KLB1, LPXN, LTA, LTB, LYN, MADCAM1, MAM2, MAP3K1, MAP3K14, MAP3K7, MAP3K8, MAP3K8, MAPK14, MAT2A, MAVS, MET, MICA, MIR30, MIR4734, MMP13, MMP3, MMP9, MSX1, MYB, MYC, MYOD1, NFAT5, NFKB2, NFKBIA, NFKBIA, NFKBIB, NFKBIE, NFKBIZ, NOD1, NOD2, NOL3, NOS1, NOS2, NPY1R, NOO1, NR3C1, NR4A2, OAS2, OGN, ORAI1, PDCL, PDETA, PDGFB, PGF, PIGR, PITX3, PLA2G4A, PLAU, PLAUR, PPARA, PPP2A, PPP2CB, PPP2R1A, PPP2R1B, PPP2R2A, PPP2R2B, PPP2R2C, PPP2R2D, PPP2R4, PRKCA, PTAFR, PTGS1, PTGS2, PTHLH, PTK2B, PTPN13, PTX3, RAB35, RAC1, RAC2, RAC3, RALBP1, REL, RELB, REV3L, RIPK1, RIPK2, RNMT, RRM2B, SAA2, SDCA, SELE, SERPINA3, SLC11A1, SLC6A4, SMAD3, SMC4, SOCS3, SOD1, SORL1, SPRR2A, TACR1, TFF3, TFP2, THBD, TIMP1, TIN2, TLCD1, TLR2, TLR2, TLR4, TNC, TNF, TNF, TNFRSF10A, TNFRSF10B, TNFSF10, TNNC1, TOPI, TP53, TRADD, TRAF1, TRAF2, TRAF3, TRAF4, TRAF5, TRAF6, UGT2B17, VAV1, VCAM1, VEGFA, VEGFB, VEGFC, VIM, VIPR1, VWF, WTI, XIAP, ZBTB10

Table 2. Location of the 29microRNA regulated by NF-KB1

ID	Accession	Chromosome	Start	End	Strand
hsa-mir-16-1	MI0000070	chr13	50048973	50049061	-
hsa-mir-17	MI0000071	chr13	91350605	91350688	+
hsa-mir-21	MI0000077	chr17	59841266	59841337	+
hsa-mir-24-1	MI0000080	chr9	95086021	95086088	+
hsa-mir-29a	MI0000087	chr7	130876747	130876810	-
hsa-mir-29b-1	MI0000105	chr7	130877459	130877539	-
hsa-mir-29b-2	MI0000107	chr1	207802443	207802523	-
hsa-mir-16-2	MI0000115	chr3	160404745	160404825	+
hsa-mir-10b	MI0000267	chr2	176150303	176150412	+
hsa-mir-199a-2	MI0000281	chr1	172144535	172144644	-
hsa-mir-214	MI0000290	chr1	172138798	172138907	-
hsa-mir-219a-1	MI0000296	chr6	33207835	33207944	+
hsa-mir-23b	MI0000439	chr9	95085208	95085304	+
hsa-mir-27b	MI0000440	chr9	95085445	95085541	+
hsa-mir-30b	MI0000441	chr8	134800520	134800607	-
hsa-mir-125b-1	MI0000446	chr11	122099757	122099844	-
hsa-mir-9-1	MI0000466	chr1	156420341	156420429	-
hsa-mir-9-2	MI0000467	chr5	88666853	88666939	+
hsa-mir-125b-2	MI0000470	chr21	16590237	16590325	+
hsa-mir-146a	MI0000477	chr5	160485352	160485450	+
hsa-mir-29c	MI0000735	chr1	207801852	207801939	-
hsa-mir-340	MI0000802	chr5	180015303	180015397	-
hsa-mir-424	MI0001446	chrX	134546614	134546711	+
hsa-mir-448	MI0001637	chrX	114823454	114823564	+
hsa-mir-503	MI0003188	chrX	134546328	134546398	-
hsa-mir-506	MI0003193	chrX	147230720	147230843	+
hsa-mir-548d-1	MI0003668	chr8	123348034	123348130	-
hsa-mir-548d-2	MI0003671	chr17	67471489	67471585	+
hsa-mir-1276	MI0006416	chr15	85770496	85770578	-
hsa-mir-1908	MI0008329	chr11	61815161	61815240	+
hsa-mir-3200	MI0014249	chr22	30731557	30731641	+
hsa-mir-3620	MI0016011	chr1	228097263	228097341	+
hsa-mir-4485	MI0016846	chr11	10508270	10508326	-

Table 3. microRNAs and Transcription factors regulating NF-KB1

microRNA targeting NF-kB1	Transcription factor targeting NF-kB1
hsa-miR-138	IKKBK
hsa-miR-15a	IKBK
hsa-miR-15b	NFKB1
hsa-miR-16	NFKB2
hsa-miR-299-5p	NFKBIA
hsa-miR-324-5p	NFKBIB
hsa-miR-340	RELA
hsa-miR-508-3p	
hsa-miR-516a-5p	
hsa-miR-532-5p	
hsa-miR-557	
hsa-miR-559	
hsa-miR-562	
hsa-miR-572	
hsa-miR-625	
hsa-miR-640	
hsa-miR-646	
hsa-miR-671-3p	
hsa-miR-671-5p	
hsa-miR-9	

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