MYC Gene Mutations as Causative Pathways for Development and Treatment of Hematological Malignancies

Saeed M Kabrah

Laboratory Medicine Department, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah, Kingdom of Saudi Arabia

Abstract

MYC is a proto-oncogene with deregulation of >50% of human cancers. The dysregulation of MYC cause tumorigenesis, cell growth and proliferation, cell growth, and apoptosis. Novel therapy approaches lead to the direct inhibition of the MYC gene by disruption of MYC/Max complex, MYC destabilization, inhibition of MYC translation and/or transcription. Cetuximab and panitumumab act on the epidermal growth factor receptor (EGFR). Cetuximab is an immunoglobin G1 isotype of a monoclonal antibody that produces antibody-dependent cell-mediated. Panitumumab is an immunoglobulin G2 isotype monoclonal antibody. This antibody acts on different site of EGFR with different degree of affinity. Genome-wide association studies e.g., TWAS determine the aggregate genotypes. Enhancer is cell-specific gene regulation that cluster for binding sites of a transcription factor with spatially coordinated to control the expression of one or more specific target genes. In this review, we will summarize novel drugs in targeting cancerous MYC in haematological malignancy.

Keywords: *MYC gene, enhancer, Genome-wide association studies (GWAS), Cetuximab, Panitumumab, monoclonal antibody.*

Introduction

Considerable literature demonstrated the involvement in the expansion of autoimmune disorder and specific cancer, particularly by proto-oncogene. MYC's future function in disease progression control as well as its integration into disease management has been documented. The three L-MYC, N-MYC and c-MYC are the member of the MYC proto-oncogene family with significant roles in numerous physiological methods i.e., cell cycle regulation and cell division, protein synthesis, cell adhesion, proliferation, cell differentiation, angiogenesis, immune activation, and apoptosis(Beltran, 2014; B.-J. Chen, Wu, Tanaka, & Zhang, 2014; Nie et al., 2012; Posternak & Cole, 2016). Also. MYC is a multifactorial TFs that has a significant function in tumorigenesis. The rearrangement of MYC leads to developments of diffusion large B cell lymphoma (DLBCL) and high-grade B cell lymphoma (HGBL) with the rearrangements of BCL6 and BCL2 by MYC translocation, referred to as double-hit lymphoma (DHL) and triple hit lymphoma (THL) (Landsburg et al., 2016). The World Health Organization (WHO) 2017 update about the DHL and THL prognostic implication that defines the cytogenetically as the

Corresponding author:
Saeed M Kabrah (Ph.D.)
Laboratory Medicine Department, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah, Kingdom of Saudi Arabia P.O.Box 50199 Makkah 21955 Saudi Arabia.
Phone: +966508009555; Fax: +966508009555;
E-mail: smkabrah@uqu.edu.sa

category of "High-grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements" (Grimm & O'Malley, 2019).

The gene regulation is monitored by MYC family member with the basic helix loop helix zipper (bHLHZ) of a transcription factor (TFs). MYC is highly expressed during cell proliferation from foetal development to cell division of adult. The highest level of MYC expressed in the brain tissue during embryogenesis. However, MYC expression is downregulated after embryonic development (Beltran, 2014; Blagosklonny & Pardee, 2002; Fernandez et al., 2003).

There is an interaction between MYC and several proteins to form the multicomponent for the gene expression and transcription regulation and chromatin structure in the normal cell. The dimerization of max protein and MYC protein regulates transcription by binding MYC-box sequence with transcriptional coactivators and also in the regulation of MYC target gene. The interaction of WDR5 with MYC-max leads to the recognition of the target gene. Also, the interaction of MYC-max and coactivators i.e., TF II triggers transcriptional elongation (Beltran, 2014; Blagosklonny & Pardee, 2002; Gandarillas, 2012; Levens, 2013).

The MYC gene stability is influenced by coding mutations that enhance its level over altering basic action (Liu et al., 2006). The sequence of the protein coding is left intact by the chromosomal abnormalities of the MYC gene. MYC acts as oncogenic with its abnormal gene expression. MYC gene moves in Burkitt lymphoma and plasmacytoma with immunoglobins gene (Boxer & Dang, 2001; Levens, 2013). The MYC overexpression is promoted by gene amplification, translocation of chromosomal and mutation in the signalling pathway without any dependence on growth factors stimulation that promotes unstrained proliferation and finally tumorigenesis. Thus, MYC cause extensive transcriptional reprogramming with angiogenesis activation and suppression of host immune response. Therefore, MYC is considered to involve in more than 50% of all human cancer(Dang, 2012; Y. Li, Casey, & Felsher, 2014; Lin et al., 2012).

Haematological Malignancy

Acute Myeloid Leukemia (AML) and Chronic Myelogenous Leukemia (CML)

AML is a malignant disease with significant genetic heterogenicity and failure of bone marrow that leads to immature myeloid cell proliferation. The hematopoietic precursors are arrested in an early stage of development. The occurrence of more than 20% of blasts in the bone marrow distinguishes most AML subtypes from other associated blood disorders (Mughal et al., 2017; Yun et al., 2019). The c-MYC is a downstream target that occurred by molecular abnormalities for the AML patient's prognosis influenced by genetic mutations as shown in figure 1. The MYC expression is highest identified in AML patients that demonstrated poorer overall survival in cytogenetic risk groups(Mughal et al., 2017). The decreased cell growth increased apoptosis with lower MYC expression is a result of the lack of adenylate cyclase that supports AML in human (S. L. Chen et al., 2020; M. Li et al., 2019).

CML is described as a clonal myeloproliferative disorder that is identified by the occurrence of balanced genetic translocation of the Philadelphia chromosome. This increases the proliferation of granulocytes and their immature precursors without the loss of their capacity to differentiate. Around 20% of adults with leukaemia have specifically CML. The CML blood and bone are suggested by the unexplained leucocytosis including immature myeloid cells (Granatowicz et al., 2015). BCR/ABL1 fusion gene is also associated with CML. MYC-Max heterodimer regulates BCR promoter. The BCR and BCR/ABL1

downregulation is significantly caused by MYC expression silencing BCR/ABL1 positive CML cell lines that cause reduced proliferation and induction of cell death. However, MYC overexpression is observed in the CML blast crisis. The beta-catenin MYC target gene activates in blast crisis patients. Thus, MYC overexpression has a significant role in BCR/ABL1 up-regulation leading to blast aggressiveness acquired during CML evolution (Sharma et al., 2015; Wang, Ikura, Eto, & Ota, 2004).

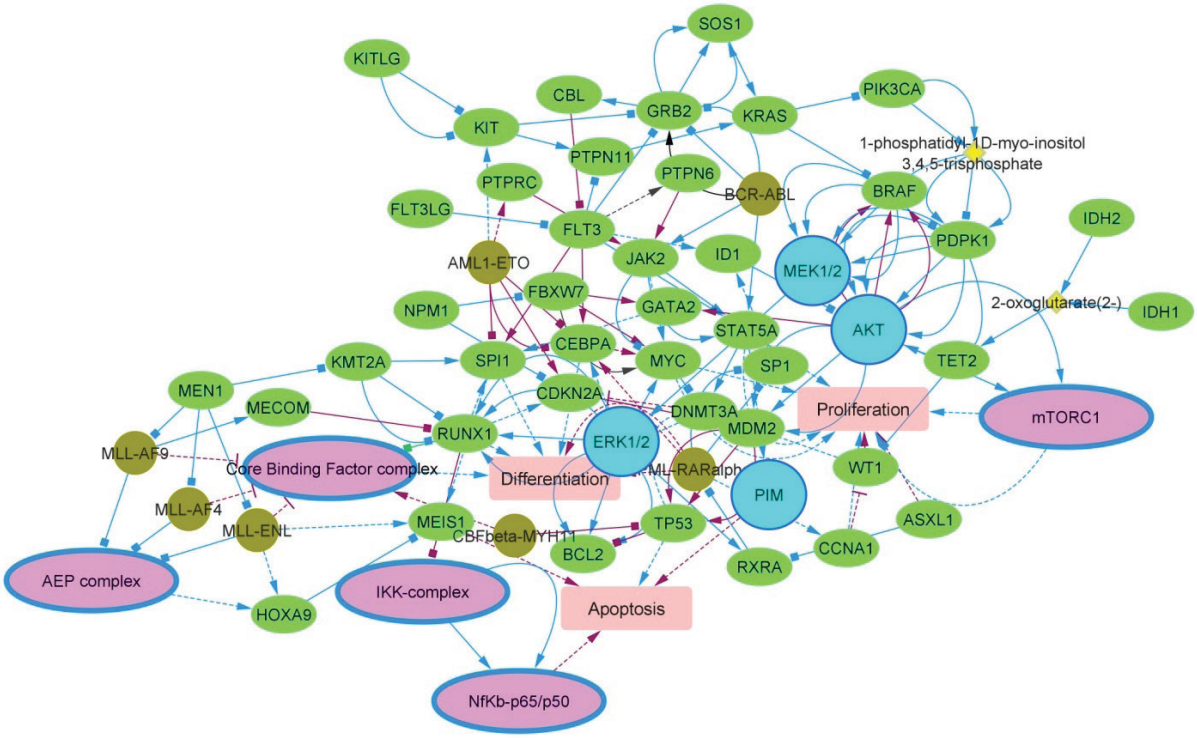

Figure 1: Acute myeloid Leukemia network:

Nodes for all proteins including MYC is shown in green colour circles, fusion proteins are shown in Gray colour, all complexes are shown in large pink circles enclosed with light blue line, protein family proteins are shown in cyan colour circles, small molecules receptors are shown in yellow colour and all the phenotypes are shown in light pink rectangular boxes. Different edges represent the interaction with different molecules. Cyan colour edges show the up regulation of different molecule with the effect of other molecules and vice-versa. Magenta colour edges represent the down regulation of different molecules with respect to each other.

Diffuse Large B-Cell Lymphoma (DLBCL) and Hodgkin's lymphoma

Nodular lymphocyte-predominant Hodgkin's lymphoma and classic Hodgkin's lymphoma are two distinct disease entities of Hodgkin's lymphoma, a rare B-cell malignant neoplasm. DLBCL is the most prevalent lymphoid neoplasm in adults, responsible for 32.5 % of all non-lymphoma Hodgkin's cases diagnosed per year. DLBCL is a heterogeneous disease with variable clinical outcomes to molecular pathogenesis and its biology. DLBCL is divided into three molecular subtypes: germinal core activated B-cell lymphoma, B-cell lymphoma, and primary mediastinal massive B-cell lymphoma. MYC

overexpression is observed in both DLBCL and Hodgkin's lymphoma in which DLBCL patients demonstrated the rearrangements and expression of the MYC and/or BCL2 gene. Burkitt lymphomas and DLBCL have a larger level of MYC staining over other lymphomas (Chisholm et al., 2015; Zelenetz et al., 2016).

Materials and Methods

The GRCh38.p13 long promoter sequence of Human gene chr8:127,735,434-127,742,951(GRCh38/hg38); chr8:128,747,680-128,755,197(GRCh37/hg19 by Entrez Gene); and chr8:128,747,680-128,753,674(GRCh37/hg19 by Ensembl) information were gathered using the gene card human database. The gene databases COSMIC, and Ensembl were used to evaluate the comprehensive and updated information on transcription factors (TFs) leading haematological malignancy due to myc genome changes.

Our study explains the effect of Gefitinib, Erlotinib, Panitumumab, Cetuximab and other compounds that target the MYC gene. Also, we discuss the gene enhancer, genome-wide association study PhenoPred prediction of MYC gene associated diseases and Sorting Intolerant from Tolerant (SIFT).

Results and Discussion

Therapeutic approaches targeting MYC gene

MYC remains the several significant biological pathways involved in cancerous cell proliferation and growth. The MYC-mediated tumorigenesis experimental model demonstrated that MYC cause addiction to established tumours whereas MYC expression deregulation led to failure of addiction. New therapeutic approaches use these MYC induced changes by targeting interruption of MYC-Max dimerization and MYC target genes, inhibition of MYC expression, MYC-Max DNA binding (Palaskas et al., 2011). Other therapeutic approaches focused on targeting MYC target gene i.e., glutaminase (GLS), lactate dehydrogenase A (LDHA), and ornithine decarboxylase (ODC) and also aurora or cyclin-dependent kinases inhibitors (D. Yang et al., 2010). Transgenic murine lymphomas are sensitive to Chk1 inhibitors linked to MYC-induced replicative stress (Murga et al., 2011). The post-translational modifications cause TFs to disorganised segments in controlling the TFs function and stability. The therapeutic approaches depend on protein-protein interaction, DNA binding and disrupting expressions. Here, we summarize the new therapeutic approaches and compounds (Tables 1) that describes the therapeutic targeting on the MYC gene i.e., activation of post-translational modifications, Dimerization of partner protein and MYC transcription.

Table 1: Drugs & Compounds for MYC Gene

Name	Status	Role	Mechanism of Action
Cisplatin 23 102	Approved 25		Inhibits DNA synthesis, a chemotherapy drug, Potent pro-apoptotic anticancer agent; activates caspase-3, Platinum
Gemcitabine 23 102	Approved 25		Ribonucleotide reductase and DNA synthesis inhibitor, Nucleoside Analogs
Aspirin 25	Approved, Vet approved 25	Channel blocker, Target, downregulation	

Cont... **Table 1: Drugs & Compounds for MYC Gene**

Nadroparin 25	Approved, Investigational 25	Target, inhibitor	
rituximab 102	Approved 25		Therapeutic Antibodies
Trametinib 102	Approved 25		MEK 1/2 inhibitor, MEK Inhibitors, Kinase Inhibitors, Mitogen-activated protein/extracellular signal-regulated kinase (MEK) inhibitors
Venetoclax 102	Approved, Investigational 25		Bcl-2 inhibitor, potent and selective
Alisertib 101	Investigational 25	inhibitor, Biomarker	Aurora-A kinase inhibitor, AURKA Inhibitors, Kinase Inhibitors
Dinaciclib 101	Investigational 25	inhibitor, Biomarker	CDK inhibitor, CDK2 Inhibitors, Kinase Inhibitors
10058-F4 88			C-MYC-Max dimerization inhibitor
AMG900 101		Biomarker, inhibitor	AURKA Inhibitors, Kinase Inhibitors, Inhibitors of mitosis Aurora kinase inhibitors
BAY1000394 101		Inhibition, Biomarker	CDK4 Inhibitors, CDK2 Inhibitors

The MYC expression is reduced by epigenetic silencing of the MYC gene. The bromodomain and extra-terminal motif (BET) bromodomains are effective against MYC by the inhibitor of histone methyltransferases, DNA methyltransferases, histone demethylases, and histone deacetylases (Poole & van Riggelen, 2017). The MYC expression is decreased by BET inhibitor by inhibiting the binding of BRD4 at acetylated histones inside the MYC promoter (Kato et al., 2016). G-quadruplexes inhibit the MYC transcription and silences gene expression within the nucleus hypersensitive element (NHE) III region of MYC promoter result in MYC mRNA suppressions and induction of cytotoxicity (Hu et al., 2018).

Some compounds bind directly and inactive downstream MYC function reducing the acquired resistance and better efficacy, bHLHZ is required for MYC dimerization to Max and DNA binding at e-box sequences. MYC/MAX dimer disruptors i.e., 10058-F4 and 10074-G5 binds within the bHLHZ domain and interrupt MYC/MAX dimerization. Struntz et al studied the MYC: MAX stabilization in vitro and in vivo with the use of molecule KI-MS2-008 results in degradation and attenuation of the MYC transcriptional gene (Struntz et al., 2019).

The MYC expression and activity are controlled by several proteins modification, albeit indirect, post-translational therapeutic modifications and method of decreasing MYC function. The mechanism of post-translation modification for the MYC gene include "1) kinases that phosphorylate S62-MYC; (2) phosphatases that dephosphorylate S62-MYC; (3) the PIN1 proline isomerase; and (4) enzymes that affect MYC ubiquitin-dependent proteolysis".

Gefitinib and Erlotinib effect on Apoptosis and c-MYC Expression.

A new therapeutic approach is required for the management of haematological malignancy by targeting one of the biological processes i) apoptosis leading to cell death ii) irreversible cell-cycle blockade iii) terminal differentiation. Target therapy

interrupts the vital cell process and destroys tumour cell. Selective tyrosine kinase inhibitors i.e., imatinib is a targeted therapy for hematologic malignancies. Gefitinib and erlotinib inhibit epidermal growth factor receptor of haematological malignancy (Bell et al., 2005; Herbst et al., 2002; Hidalgo et al., 2001). Stegmaier et al. discovered gefitinib to initiate the cell differentiation in 3 AML e.g., HL60, U37 and Kasumi-1 that inhibits the EGFR expressing cells. Erlotinib is an antineoplastic drug that induces apoptosis on MDS and AML cells (Stegmaier et al., 2005).

Despite A549 non -small cell lung cancer, off-target occurred in the haematological cell lines KG-1, HL60 and P39 due to inhibitory activity of the erlotinib on EGFR causing deficient of EGFR expression. The detection of phosphatidylserine exposure by annexin V-FITC conjugates due to erlotinib induce apoptosis to lead to viability loss in KG-1 cells but P39 and HL60 fail to do so. Phosphoproteome analysis evaluates most KG-1 but fewer P39 and HL60 absolute numbers are reduced by erlotinib. Early phosphatidylserine exposure demonstrated apoptosis, loss of nuclear DNA and nuclear karyorrhexis and pyknosis in incubated KG-1 cell. The autophosphorylation of the cancerous JAK2 kinase on tyrosine is reduced with erlotinib administration (Simone Boehrer et al., 2008). The cytofluorometric analysis proved that erlotinib therapy causes hyperphosphorylation of TF stat-5 by JAK2 on tyrosine. Thus, Phosphoproteome and cytofluorometric analysis validate that erlotinib therapy alone can reduce the constitutive STAT-5 activation in KG-1 cells (S. Boehrer et al., 2008). The RNA interferes with downregulation with JAK2 expression leading to erlotinib-induced apoptosis. The STAT-5 activation was abolished with JAk2 expression alone and simultaneously induce apoptosis in KG-1 cell lines. Similar, the level of apoptosis has induced either erlotinib alone or a combination of erlotinib and JAK2 knockdown. Thus, erlotinib causes apoptosis by inhibiting JAK2, PDGFR knockdown (Abou Dalle et al., 2018). Golub et al. stated proliferation and differentiation arrest as antineoplastic approaches on EGFR inhabitation of gefitinib on haematological malignancy (Stegmaier et al., 2005). Erlotinib and gefitinib destroyed the tumour cell-based on chromatin condensation and fragmentation of nuclear and phosphatidylserine exposure leading to apoptosis. Moreover, these drugs either following ligation of death receptors activating the apical caspase in the death-inducing signal complex (intrinsic pathway) or liberation of the caspase activator cytochrome c in mitochondria outer membrane permeabilization (MOMP), (extrinsic pathway) leading to apoptosis. it is clear that erlotinib activates the intrinsic pathway, based on the finding that mitochondria released cytochrome c (and other death effectors such as endonuclease G) before caspase-3 was stimulated, and that caspase inhibition was unable to avoid mitochondrial outer membrane permeabilization and cell death (Simone Boehrer et al., 2008; Doan et al., 2013; Lainey et al., 2013). Figure 2 describes the gefitinib and erlotinib effect on Apoptosis and c-MYC Expression.

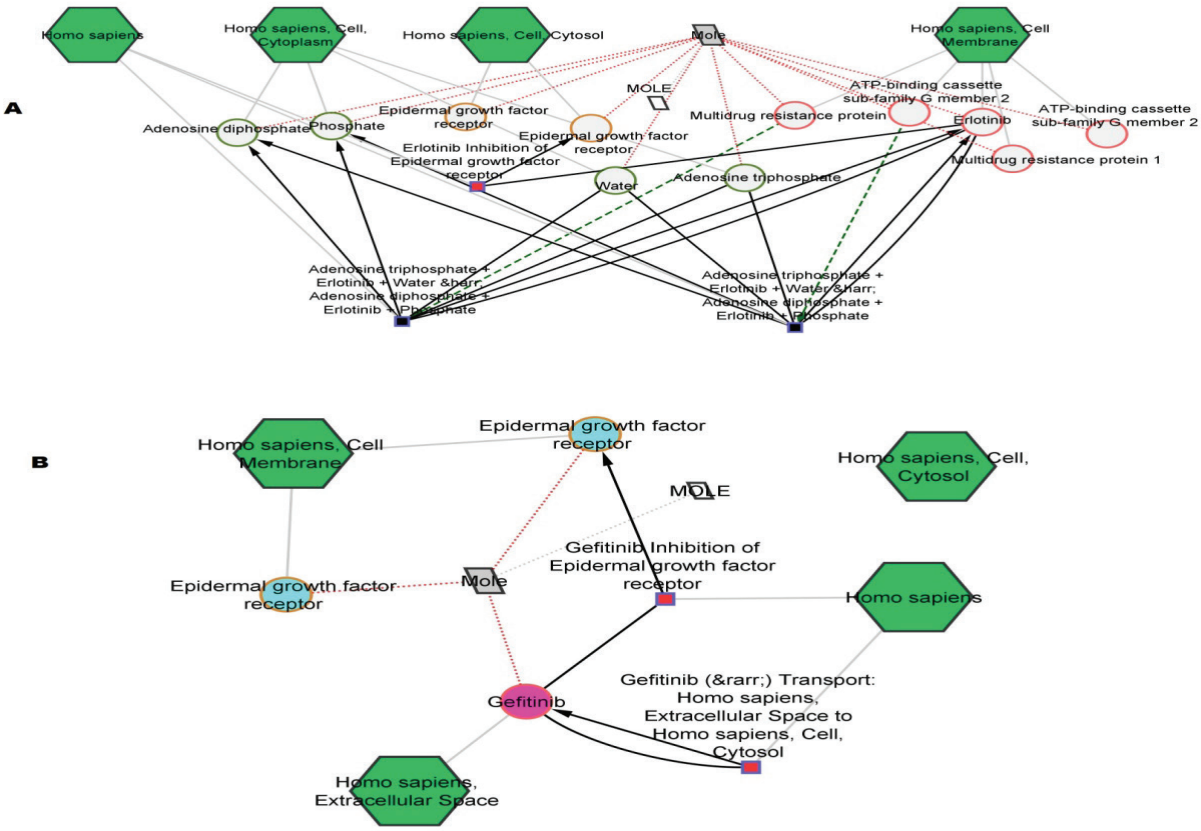

Figure 2: Gefitinib and Erlotinib effect on Apoptosis and c-MYC Expression.

The prooncogenic activities reduced apoptosis, enhanced cell proliferation enhanced angiogenesis and metastatic malignancy are associated with EGFR signalling pathway dysregulation. The receptor binding activates downstream signalling pathway include PI3K/Akt (phosphoinositide 3-kinase/protein kinase B), JAK/STAT (Janus kinase/signal transducers and activators of transcription), and MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase. The frequent activation of these pathway cause survival and proliferation of tumorous cells (García-Foncillas et al., 2019; Kim & Grothey, 2008; Shim, 2011).

The function of monoclonal antibodies cetuximab and panitumumab act by binding to EGFR extracellular domain III that prevents EGFR ligand binding and locking in autoinhibitory monomeric conformation(Shim, 2011; Zhou et al., 2012). Panitumumab and cetuximab are human and mouse/human chimeric monoclonal antibodies respectively. The binding affinity of Panitumumab for the EGFR is 8 times more than Cetuximab. The dimerization and ligand binding activates tyrosine kinase receptors that are internalised by clathrin-dependent endocytosis. The tyrosine kinase activity of activated EGFR is terminated. This process regulates the cell surface receptors number. The deubiquitinating enzymes deubiquitinate ubiquitinated receptors that are again recycled back to the cell membrane. Anti-EGFR therapy resistance has been linked to receptor ubiquitination (Lu et al., 2007). However, cetuximab and panitumumab proved their prognostic effects for the EGFR overexpress that is responsible for haematological malignancy (Kim & Grothey, 2008). Panitumumab and cetuximab compete for the binding

site of EGF. Panitumumab's binds with mutational epitope with ≥50% binding affinity for EGFR residue P349, I438, F412, D355 and P362. Similarly, cetuximab binding affinity for EGFR residue I467, K465, K443, H409, Q408, Q384, S468, P387, D355 and F352 (Voigt et al., 2012). Since D355 is present inside the binding site of all three molecules that cause competition between EGF and monoclonal antibodies. cetuximab binding overlaps with EGF binding site at 5 location i.e., S468, K443, Q409, Q408H, D355 whereas panitumumab binding overlap with 2 locations at D355 and K443 (Voigt et al., 2012). Also, the binding affinity for EGFR is different for panitumumab and cetuximab with dissociation constants of 0.05 nM and0.39 nM respectively (Kim & Grothey, 2008). Thus, figure 3 summarises the pathway of panitumumab and cetuximab.

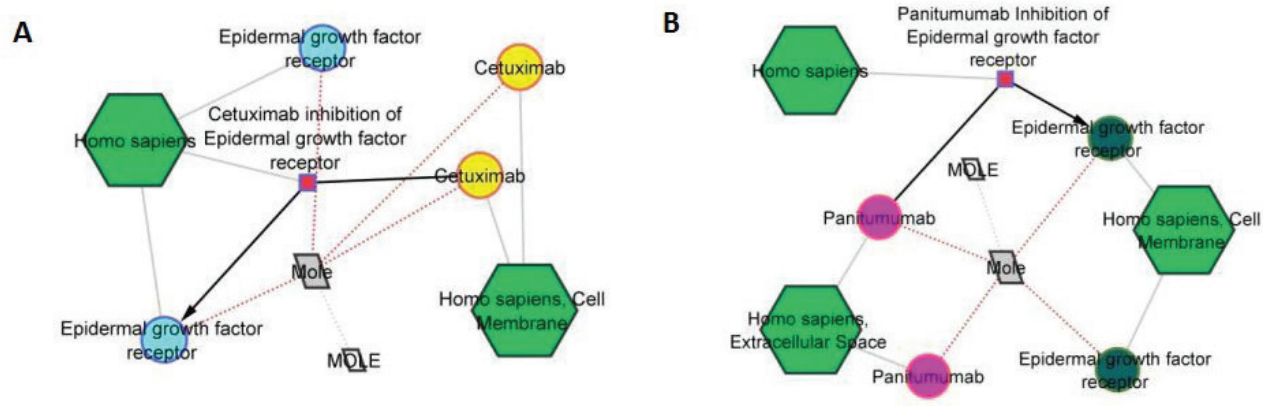

Figure 3: Panitumumab and Cetuximab Drugs action pathway.

Enhancer

Enhancer is usually distributed all over the genome with cis-regulatory DNA sequence. Enhancer is TFs binding elements that regulate the gene expression in a specific spatiotemporal specific manner (Levo & Segal, 2014). Thus, cell and tissue development fate are greatly influenced by enhancer based transcriptional regulation (Taminato et al., 2016). The transcriptional machinery model supports the conformation of chromosome capture that identify direct interaction with the adjacent chromatin regions. Human consists of hundreds of thousand enhancers. Each enhancer is linked with several TFs. Recent development leads to enhancer detection by enhancer reporter assays at the non-coding DNA sequence. The massive parallel reports assays identify variable histone modification marks at different organs (Inoue & Ahituv, 2015). Several genome-wide programmes for enhancer recognition and annotation are based on massive parallel report assays. Active enhancer ensures bidirectional transcriptions that lead to the formation of enhancer RNA (eRNA) products. The most challenging process is linking the enhancer to their target gene (Pennacchio, Bickmore, Dean, Nobrega, & Bejerano, 2013; Shlyueva, Stampfel, & Stark, 2014; Yao, Berman, & Farnham, 2015).

Early discovery used molecular genetics methods to assess enhancer effects on a single gene. Recently, various predictive investigation identified gene enhancer is linked to various TFs binding site as in table 2. Chromosome conformation capture identifies the enhancer and their target gene by

restricting the physical DNA loop. The target gene expression and enhancer variation are identified by expression quantitative trait locus (eQTL) analyses. Enhanceropathies are enhancer related disease occurred either due to TFs mutation intermingling with enhancer or enhancer mutation themselves (Mifsud et al., 2015; Whalen, Truty, & Pollard, 2016). E.g., the Sonic hedgehog gene (SHH) is enhancer mutation diseases that cause developmental abnormalities preaxial polydactyly (Lettice et al., 2003).

Table 2: GeneHancer based predicted genomic regulatory elements related to the MYC gene.

GeneHancer (GH) Identifier	GH Type	GH Score	Gene Association Score	Total Score	Transcription Factor Binding Sites
GH08J127732	Promoter/Enhancer	2.3	528.9	1200.29	394 TFs, HNRNPK, ZNF217
GH08J128181	Enhancer	1.6	23.4	36.88	196 TFs, EP300, FOXK2
GH08J127806	Promoter/Enhancer	1.8	13.9	25.49	140 TFs, ZNF217, TCF12
GH08J127895	Enhancer	1.4	13.2	19.2	297 TFs, ZBTB40, ZNF217
GH08J127793	Promoter/Enhancer	1.8	10.6	19.09	170 TFs, SIN3A, MYC
GH08J128166	Enhancer	1.7	10.5	17.7	354 TFs, LARP7, EP300
GH08J126824	Promoter/Enhancer	1.8	9.6	17.58	49 TFs, CTCF, TCF12
GH08J127972	Promoter/Enhancer	1.6	9.9	16	83 TFs, ZBTB5, RELA
GH08J127924	Promoter/Enhancer	1.5	10.2	15.71	69 TFs, TCF12, FOS
GH08J127758	Enhancer	1.3	11.8	15.34	101 TFs, TCF12, TOE1
GH08J127863	Enhancer	1.3	11	14.58	161 TFs, ZNF217, TCF12
GH08J127888	Promoter/Enhancer	1.4	10.2	14.42	115 TFs, CTCF, SIN3A
GH08J127799	Enhancer	1.2	11.5	13.31	196 TFs, ZNF217, TEAD4
GH08J126876	Promoter/Enhancer	1.2	10.2	12.02	75 TFs, ZNF217, CTCF
GH08J127966	Enhancer	1.1	9.9	10.99	137 TFs, CTCF, TCF12
GH08J128313	Enhancer	1	9.9	10	75 TFs, TCF12, SP1

Cont... **Table 2: GeneHancer based predicted genomic regulatory elements related to the MYC gene.**

GH08J128203	Enhancer	1	9.8	9.55	20 TFs, GATAD2B, ZNF592
GH08J127923	Enhancer	0.8	10.2	7.98	17 TFs, FOXA2,NR3C1
GH08J128162	Enhancer	0.7	9.5	6.72	10 TFs, EP300, SMC3
GH08J128385	Enhancer	0.6	10.1	6.19	15 TFs, GATAD2B, HES1
GH08J128647	Enhancer	0.6	10.1	6.11	13 TFs, ZBTB5, GATAD2B
GH08J127816	Enhancer	1	5.8	6	92 TFs, TCF12, TEAD4
GH08J128041	Enhancer	0.6	10	5.85	4 TFs, FOS, CEBPB
GH08J127886	Enhancer	0.6	10.2	5.68	11 TFs, IRF1, ZNF592
GH08J128649	Enhancer	0.5	10.7	5.62	9 TFs, FOS, FOSL2
GH08J127666	Enhancer	1.4	3.6	5.18	98 TFs, ZNF217, TCF12
GH08J127922	Enhancer	0.5	10.2	5	7 TFs, ZNF316, MAFF
GH08J127763	Enhancer	0.4	11.8	4.96	4 TFs, POLR2A, FOXP2
GH08J127821	Enhancer	0.8	5.7	4.76	24 TFs, USF1, TEAD4
GH08J126874	Enhancer	0.4	10.2	4.27	4 TFs, MEF2B,GATA3
GH08J127813	Enhancer	0.7	5.6	3.89	9 TFs, CTBP1, RBM25
GH08J127245	Enhancer	1.2	2.9	3.45	17 TFs, ZNF426, NFE2
GH08J127826	Enhancer	0.6	5.7	3.13	3 TFs, TCF7L2, ZBTB40
GH08J127292	Enhancer	1.5	1.7	2.64	136 TFs, EP300, ZBTB40
GH08J127396	Enhancer	1.4	1.8	2.57	74 TFs, EP300, CTCF
GH08J127959	Enhancer	1.4	1.4	1.9	191 TFs, PHB2, ZBTB5
GH08J127389	Enhancer	1.1	1.6	1.78	16 TFs, POLR2A, EP300

Cont... **Table 2: GeneHancer based predicted genomic regulatory elements related to the MYC gene.**

GH08J127339	Enhancer	1.1	1.5	1.62	28 TFs, FOS, EP300
GH08J127645	Enhancer	0.9	1.8	1.54	7 TFs, EP300, ZNF263
GH08J127265	Enhancer	0.9	1.5	1.35	4 TFs, POLR2A, JUND

Genome-wide association study

Genome-wide association study (GWAS) is a tool that identifies thousands of single nucleotide polymorphism (SNPs) of the human genome to detect the loci of the gene causing diseases. Linkage disequilibrium (LD) is associated with GWAS as summarised in Table 3. Strong LD demonstrated among SNP and true mutation. GWAS use a hypothesis with the case-control strategy that is based on "common disease–common variation" (Ponder, 2001). The disease-associated SNP marker with allelic frequency is different among the case and control group that aids to determine the SNP locus. The genetic polymorphism present in the human genome is tested by the International HapMap Project. GWAS in advance in the detection of gene loci by coupling with fast-developing high-throughput genotypic technology (Green, Watson, & Collins, 2015). Yang et al studied for the first in Chinese population. The study could not provide significant results of genome-wide analysis and could not be included in the GWAS catalogue (T. L. Yang et al., 2008).

Sud et al. identified 6 potential mutation of chromatin loci i.e., 6q22.33 (rs9482849, 6q23.3 (rs6928977), 3q28 (rs445989), 13q34 (rs112998813), 10p14 (rs3781093), 6q22.33 (rs9482849), for development of Hodgkin's lymphoma due to genetic mutation. These mutations are associated with Hodgkin's lymphoma and diffuse large B-cell lymphoma(Cerhan et al., 2014; Sud et al., 2017). Mitchell et al. identified 8 gene mutation on chromosome 7p15.3 responsible for multiple myeloma (Mitchell et al., 2016).

Table 3: Phenotypes from GWAS CatLog for MYC Gene

Phenotype	Gene Relation	Best Score	Mean Score	# of Snps	# of Studies
glioma	GWAS	64.7	31.8	1	1
colorectal cancer, colorectal adenoma	GWAS	63.5	42.7	3	1
childhood onset asthma	GWAS	23.0	16.3	1	2
prostate specific antigen measurement	GWAS	20.2	14.9	2	1
bladder carcinoma	GWAS	17.7	11.6	2	4
prostate carcinoma	GWAS	17.2	12.6	2	2
cleft palate, cleft lip	GWAS	15.1	15.1	1	1
Eczema	GWAS	14.5	14.5	1	1
colorectal cancer	GWAS	14.2	12.7	3	4

***Cont...*Table 3: Phenotypes from GWAS CatLog for MYC Gene**

hemoglobin measurement	GeneHancer	13.7	13.7	1	1
allergy	GWAS	13.2	13.2	1	1
endometrial carcinoma	GWAS	13.1	9.9	3	2
breast carcinoma	GWAS	13.0	11.8	1	2
Hodgkins lymphoma	GeneHancer	13.0	9.8	1	3
diffuse large B-cell lymphoma	GWAS	12.0	11.2	2	1
ovarian carcinoma	GWAS	11.5	10.0	1	2
asthma	GWAS	10.7	9.2	1	2
renal cell carcinoma	GWAS	10.3	10.3	3	1
body height	GWAS	9.5	8.5	2	2
allergic sensitization measurement	GWAS	9.3	9.3	1	1
pancreatic carcinoma	GWAS	9.0	8.2	2	3
Inhalant adrenergic use measurement	GeneHancer	8.2	8.2	1	1
multiple sclerosis	GWAS	8.1	8.1	1	1
endometrial endometrioid carcinoma	GWAS	8.1	8.1	1	1
platelet crit	GeneHancer	8.1	8.1	1	1
chronic lymphocytic leukemia	GWAS	7.7	7.7	1	1
allergic rhinitis	GWAS	7.4	7.4	1	1
erythrocyte count	GeneHancer	7.4	7.4	1	1
alcohol use disorder measurement, alcohol dependence	GWAS	7.3	7.3	1	1
systemic lupus erythematosus	GeneHancer	6.7	6.6	2	1
tonsillectomy risk measurement	GeneHancer	6.0	6.0	1	1
waist-hip ratio	GeneHancer	5.7	5.7	1	1

Sorting Intolerant from Tolerant (SIFT)

Sorting Intolerant from Tolerant (SIFT) is a protein prediction algorithm that predicts amino acid substitution as deleterious, prioritise nonsynonymous and missense variants as summarized in table 4 (Kumar, Henikoff, & Ng, 2009; Ng & Henikoff, 2002; Sim et al., 2012). A protein can be able to handle an amino acid transition while still functioning normally. It could be able to act naturally, or it could be intolerant to the amino acid. SIFT determines whether an amino acid transition is tolerable or harmful to protein function. SIFT considers protein conservation in homologous sequences as well as the magnitude of the amino acid substitution. It's been seen in a variety of cancer, mutation, and genetic research (Mitsui et al., 2012; Tennessen et al., 2012).

Table 4: List of deleterious variants of MYC predicted by SIFT (Sorting Intolerant From Tolerant) program.

SNP	REF ALLELE	ALT ALLELE	AMINO ACID CHANGE	GENE ID	SIFT SCORE	SIFT MEDIAN	NO OF SEQS AT POSITION	SIFT PREDICTION
rs28933407	C	T	P71S	ENSG00000136997	0.018	2.69	93	DELETERIOUS
rs28933407	C	T	P57S	ENSG00000136997	0.021	2.39	65	DELETERIOUS
rs28933407	C	T	P72S	ENSG00000136997	0.043	2.45	61	DELETERIOUS
rs28933407	C	T	P71S	ENSG00000136997	0.044	2.45	61	DELETERIOUS
rs61752959	G	A	Q33Q	ENSG00000136997	0.609	2.46	50	TOLERATED
rs61752959	G	A	Q48Q	ENSG00000136997	0.614	2.52	54	TOLERATED
rs61752959	G	A	Q47Q	ENSG00000136997	0.615	2.52	54	TOLERATED
rs61752959	G	A	Q47Q	ENSG00000136997	0.68	2.77	74	TOLERATED
rs121918683	A	C	N86T	ENSG00000136997	0.394	2.92	26	TOLERATED
rs121918683	A	C	N101T	ENSG00000136997	0.402	2.9	31	TOLERATED
rs121918683	A	C	N100T	ENSG00000136997	0.403	2.89	31	TOLERATED
rs121918683	A	C	N100T	ENSG00000136997	0.489	3.03	42	TOLERATED
rs121918684	G	C	E53D	ENSG00000136997	0.479	3.09	49	TOLERATED
rs121918684	G	C	E53D	ENSG00000136997	0.491	2.73	43	TOLERATED
rs121918684	G	C	E54D	ENSG00000136997	0.505	2.73	43	TOLERATED
rs121918684	G	C	E39D	ENSG00000136997	0.591	2.63	39	TOLERATED
rs121918685	C	G	P59A	ENSG00000136997	0	2.4	66	DELETERIOUS
rs121918685	C	G	P74A	ENSG00000136997	0	2.46	62	DELETERIOUS
rs121918685	C	G	P73A	ENSG00000136997	0	2.46	62	DELETERIOUS
rs121918685	C	G	P73A	ENSG00000136997	0.003	2.69	94	DELETERIOUS
rs146505192	T	C	F7L	ENSG00000136997	1	3.54	26	TOLERATED
rs146505192	T	C	F22L	ENSG00000136997	1	3.34	25	TOLERATED
rs146505192	T	C	F21L	ENSG00000136997	1	3.79	29	TOLERATED
rs146505192	T	C	F21L	ENSG00000136997	1	3.34	25	TOLERATED
rs200431478	C	T	S362F	ENSG00000136997	0.003	2.46	71	DELETERIOUS
rs200431478	C	T	S361F	ENSG00000136997	0.003	2.46	71	DELETERIOUS

Computational biology aims to predict correctly new gene-disease interactions as summarized in table 5. The so-called guilt-by-association (GBA) technique, in which new candidate genes are discovered by their association with genes already known to be active in the disorder being tested, has proven to be a very effective method. Several different kinds of data can be used to draw this relation. Goh et al. use a network that connects gene with the related disease (Goh et al., 2007). Tian et al. unite genetic interactions and protein interactions for the expression of gene correlation (Tian et al., 2008). Ulitsky et al. merge interactions from yeast two-hybrid experiments and published networks (Ulitsky & Shamir, 2007). Human Reference Protein Database is the most frequently database to determine directly protein-protein interactions (Goel, Harsha, Pandey, & Prasad, 2012).

Table 5: PhenoPred predicted MYC gene associated diseases

Known Disease Gene	
DOID:63 - temp holding	
DOID:162 - cancer	
DOID:462 - Malignant Neoplasms	
DOID:2227 - Malignant neoplasm of lymphatic and hemopoietic tissue	
DOID:2319 - Neoplasm by Special Category	
DOID:8584 - Burkitt's tumor or lymphoma	
DOID:8716 - Lymphosarcoma and reticulosarcoma	
Predicted Disease	Score
DOID:3135 - Malignant neoplasm of bone, connective tissue, skin and breast	5.87
DOID:3094 - Neoplasms, Neuroepithelial	5.42
DOID:171 - Neuroectodermal Tumors	5.17
DOID:3620 - Central Nervous System Neoplasms	5.00
DOID:3195 - Neural Neoplasm	4.98
DOID:1193 - Nervous System Neoplasms	4.92
DOID:3041 - Familial Cancer	4.83
DOID:3093 - Neoplasms, Nerve Tissue	4.70
DOID:3165 - Skin Neoplasms	4.70

Cont... **Table 5: PhenoPred predicted MYC gene associated diseases**

DOID:2994 - Germ cell tumor	4.66
DOID:688 - Neoplasms, Embryonal	4.65
DOID:3095 - Neoplasms, Germ Cell and Embryonal	4.59
DOID:1115 - Sarcoma	4.42
DOID:2627 - Glioma	4.37
DOID:122 - Abdominal Neoplasms	4.36
DOID:208 - Neoplastic Syndromes, Hereditary	4.33
DOID:3023 - Common Tumor	4.27
DOID:4159 - Cancer of Skin	4.25
DOID:685 - Common Carcinoma	4.20
DOID:170 - Endocrine Gland Neoplasms	4.10

Conclusion

The proto-oncogene, MYC dysregulation promotes tumorigenesis, apoptosis, cell proliferation. MYC gene alteration has been detected in haematological malignancy particularly in Hodgkin disease and B-cell neoplasm with aggressive behaviour. The Discovery of novel therapeutics approaches accelerates our understanding of tumorigenesis mechanism in MYC associated haematological malignancy. We have emphasized the transcriptional regulation network of MYC during leukaemia that enlighting the molecular pathway for MYC associated apoptosis, cell growth and cell proliferation. Here we have summarised various pharmacological therapy directly or indirectly inhibiting the MYC (Table 1). Enhancers are specialised regions of the genome that regulate the levels of expression of target genes. They will exist at a great distance from their target gene and loop in complex systems to do so. The field has been attempting to answer the question of which enhancers interfere with target genes for many years, and several experimental approaches to do so have substantial statistical, viability, or reproducibility disadvantages.

Acknowledgment: The author would like to thank the Deanship of scientific research, Umm Al-Qura University, Makkah, Saudi Arabia, for supporting this work.

Data Availability Statement

Research data are not shared. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

Funding : This work was supported by Umm Al-Qura University, Makkah, Saudi Arabia [Grant Code: 18-MED-1-02-0002].

References

1. Abou Dalle, I., Cortes, J. E., Pinnamaneni, P., Lamothe, B., Diaz Duque, A., Randhawa, J., . . . Kantarjian, H. M. (2018). A Pilot Phase II Study of Erlotinib for the Treatment of Patients with Relapsed/Refractory Acute Myeloid Leukemia. *Acta Haematologica, 140*(1), 30-39. doi:10.1159/000490092
2. Bell, D. W., Lynch, T. J., Haserlat, S. M., Harris, P. L., Okimoto, R. A., Brannigan, B. W., . . . Haber, D. A. (2005). Epidermal growth factor receptor mutations and gene amplification in non-small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials. *J Clin Oncol, 23*(31), 8081-8092. doi:10.1200/jco.2005.02.7078
3. Beltran, H. (2014). The N-myc Oncogene: Maximizing its Targets, Regulation, and Therapeutic Potential. *Mol Cancer Res, 12*(6), 815-822. doi:10.1158/1541-7786.Mcr-13-0536
4. Blagosklonny, M. V., & Pardee, A. B. (2002). The restriction point of the cell cycle. *Cell Cycle, 1*(2), 103-110.
5. Boehrer, S., Adès, L., Braun, T., Galluzzi, L., Grosjean, J., Fabre, C., . . . Kroemer, G. (2008). Erlotinib exhibits antineoplastic off-target effects in AML and MDS: a preclinical study. *Blood, 111*(4), 2170-2180. doi:10.1182/blood-2007-07-100362
6. Boehrer, S., Adès, L., Braun, T., Galluzzi, L., Grosjean, J., Fabre, C., . . . Kroemer, G. (2008). Erlotinib exhibits antineoplastic off-target effects in AML and MDS: a preclinical study. *Blood, 111*(4), 2170-2180. doi:10.1182/blood-2007-07-100362
7. Boxer, L. M., & Dang, C. V. (2001). Translocations involving c-myc and c-myc function. *Oncogene, 20*(40), 5595-5610. doi:10.1038/sj.onc.1204595
8. Cerhan, J. R., Berndt, S. I., Vijai, J., Ghesquières, H., McKay, J., Wang, S. S., . . . Chanock, S. J. (2014). Genome-wide association study identifies multiple susceptibility loci for diffuse large B cell lymphoma. *Nat Genet, 46*(11), 1233-1238. doi:10.1038/ng.3105
9. Chen, B.-J., Wu, Y.-L., Tanaka, Y., & Zhang, W. (2014). Small molecules targeting c-Myc oncogene: promising anti-cancer therapeutics. *International journal of biological sciences, 10*(10), 1084-1096. doi:10.7150/ijbs.10190
10. Chen, S. L., Hu, F., Wang, D. W., Qin, Z. Y., Liang, Y., & Dai, Y. J. (2020). Prognosis and regulation of an adenylyl cyclase network in acute myeloid leukemia. *Aging (Albany NY), 12*(12), 11864-11877. doi:10.18632/aging.103357
11. Chisholm, K. M., Bangs, C. D., Bacchi, C. E., Molina-Kirsch, H., Cherry, A., & Natkunam, Y. (2015). Expression profiles of MYC protein and MYC gene rearrangement in lymphomas. *Am J Surg Pathol, 39*(3), 294-303. doi:10.1097/pas.0000000000000365
12. Dang, C. V. (2012). MYC on the path to cancer. *Cell, 149*(1), 22-35. doi:10.1016/j.cell.2012.03.003
13. Doan, P. L., Himburg, H. A., Helms, K., Russell, J. L., Fixsen, E., Quarmyne, M., . . . Chute, J. P. (2013). Epidermal growth factor regulates hematopoietic regeneration after radiation injury. *Nature Medicine, 19*(3), 295-304. doi:10.1038/nm.3070
14. Fernandez, P. C., Frank, S. R., Wang, L., Schroeder, M., Liu, S., Greene, J., . . . Amati, B. (2003). Genomic targets of the human c-Myc protein. *Genes Dev, 17*(9), 1115-1129. doi:10.1101/gad.1067003
15. Gandarillas, A. (2012). The mysterious human epidermal cell cycle, or an oncogene-induced differentiation checkpoint. *Cell Cycle, 11*(24), 4507-4516. doi:10.4161/cc.22529
16. García-Foncillas, J., Sunakawa, Y., Aderka, D., Wainberg, Z., Ronga, P., Witzler, P., & Stintzing, S. (2019). Distinguishing Features of Cetuximab and Panitumumab in Colorectal Cancer and Other Solid Tumors. *Front Oncol, 9*, 849. doi:10.3389/

fonc.2019.00849

17. Goel, R., Harsha, H. C., Pandey, A., & Prasad, T. S. K. (2012). Human Protein Reference Database and Human Proteinpedia as resources for phosphoproteome analysis. *Molecular bioSystems, 8*(2), 453-463. doi:10.1039/c1mb05340j
18. Goh, K.-I., Cusick, M. E., Valle, D., Childs, B., Vidal, M., & Barabási, A.-L. (2007). The human disease network. *Proceedings of the National Academy of Sciences, 104*(21), 8685. doi:10.1073/pnas.0701361104
19. Granatowicz, A., Piatek, C. I., Moschiano, E., El-Hemaidi, I., Armitage, J. D., & Akhtari, M. (2015). An Overview and Update of Chronic Myeloid Leukemia for Primary Care Physicians. *Korean journal of family medicine, 36*(5), 197-202. doi:10.4082/kjfm.2015.36.5.197
20. Green, E. D., Watson, J. D., & Collins, F. S. (2015). Human Genome Project: Twenty-five years of big biology. *Nature, 526*(7571), 29-31. doi:10.1038/526029a
21. Grimm, K. E., & O'Malley, D. P. (2019). Aggressive B cell lymphomas in the 2017 revised WHO classification of tumors of hematopoietic and lymphoid tissues. *Annals of diagnostic pathology, 38*, 6-10.
22. Herbst, R. S., Maddox, A. M., Rothenberg, M. L., Small, E. J., Rubin, E. H., Baselga, J., . . . LoRusso, P. M. (2002). Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: results of a phase I trial. *J Clin Oncol, 20*(18), 3815-3825. doi:10.1200/jco.2002.03.038
23. Hidalgo, M., Siu, L. L., Nemunaitis, J., Rizzo, J., Hammond, L. A., Takimoto, C., . . . Rowinsky, E. K. (2001). Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *J Clin Oncol, 19*(13), 3267-3279. doi:10.1200/jco.2001.19.13.3267
24. Hu, M. H., Wang, Y. Q., Yu, Z. Y., Hu, L. N., Ou, T. M., Chen, S. B., . . . Tan, J. H. (2018). Discovery of a New Four-Leaf Clover-Like Ligand as a Potent c-MYC Transcription Inhibitor Specifically Targeting the Promoter G-Quadruplex. *J Med Chem, 61*(6), 2447-2459. doi:10.1021/acs.jmedchem.7b01697
25. Inoue, F., & Ahituv, N. (2015). Decoding enhancers using massively parallel reporter assays. *Genomics, 106*(3), 159-164. doi:10.1016/j.ygeno.2015.06.005
26. Kato, F., Fiorentino, F. P., Alibés, A., Perucho, M., Sánchez-Céspedes, M., Kohno, T., & Yokota, J. (2016). MYCL is a target of a BET bromodomain inhibitor, JQ1, on growth suppression efficacy in small cell lung cancer cells. *Oncotarget, 7*(47), 77378-77388. doi:10.18632/oncotarget.12671
27. Kim, G. P., & Grothey, A. (2008). Targeting colorectal cancer with human anti-EGFR monoclonocal antibodies: focus on panitumumab. *Biologics, 2*(2), 223-228. doi:10.2147/btt.s1980
28. Kumar, P., Henikoff, S., & Ng, P. C. (2009). Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nature Protocols, 4*(7), 1073-1081. doi:10.1038/nprot.2009.86
29. Lainey, E., Wolfromm, A., Sukkurwala, A. Q., Micol, J.-B., Fenaux, P., Galluzzi, L., . . . Kroemer, G. (2013). EGFR inhibitors exacerbate differentiation and cell cycle arrest induced by retinoic acid and vitamin D3 in acute myeloid leukemia cells. *Cell Cycle, 12*(18), 2978-2991. doi:10.4161/cc.26016
30. Landsburg, D. J., Falkiewicz, M. K., Petrich, A. M., Chu, B. A., Behdad, A., Li, S., . . . Nabhan, C. (2016). Sole rearrangement but not amplification of MYC is associated with a poor prognosis in patients with diffuse large B cell lymphoma and B cell lymphoma unclassifiable. *Br J Haematol, 175*(4), 631-640. doi:10.1111/bjh.14282

31. Lettice, L. A., Heaney, S. J., Purdie, L. A., Li, L., de Beer, P., Oostra, B. A., . . . de Graaff, E. (2003). A long-range Shh enhancer regulates expression in the developing limb and fin and is associated with preaxial polydactyly. *Hum Mol Genet, 12*(14), 1725-1735. doi:10.1093/hmg/ddg180

32. Levens, D. (2013). Cellular MYCro Economics: Balancing MYC Function with MYC Expression. *Cold Spring Harbor Perspectives in Medicine, 3*(12), a022483_erratum. doi:10.1101/cshperspect.a022483

33. Levo, M., & Segal, E. (2014). In pursuit of design principles of regulatory sequences. *Nat Rev Genet, 15*(7), 453-468. doi:10.1038/nrg3684

34. Li, M., Hao, S., Li, C., Xiao, H., Sun, L., Yu, Z., . . . Yin, Y. (2019). Elevated SH3BP5 Correlates with Poor Outcome and Contributes to the Growth of Acute Myeloid Leukemia Cells. *Biomolecules, 9*(9). doi:10.3390/biom9090505

35. Li, Y., Casey, S. C., & Felsher, D. W. (2014). Inactivation of MYC reverses tumorigenesis. *J Intern Med, 276*(1), 52-60. doi:10.1111/joim.12237

36. Lin, C. Y., Lovén, J., Rahl, P. B., Paranal, R. M., Burge, C. B., Bradner, J. E., . . . Young, R. A. (2012). Transcriptional amplification in tumor cells with elevated c-Myc. *Cell, 151*(1), 56-67. doi:10.1016/j.cell.2012.08.026

37. Liu, J., Kouzine, F., Nie, Z., Chung, H.-J., Elisha-Feil, Z., Weber, A., . . . Levens, D. (2006). The FUSE/FBP/FIR/TFIIH system is a molecular machine programming a pulse of c-myc expression. *The EMBO journal, 25*(10), 2119-2130. doi:10.1038/sj.emboj.7601101

38. Lu, Y., Li, X., Liang, K., Luwor, R., Siddik, Z. H., Mills, G. B., . . . Fan, Z. (2007). Epidermal growth factor receptor (EGFR) ubiquitination as a mechanism of acquired resistance escaping treatment by the anti-EGFR monoclonal antibody cetuximab. *Cancer Res, 67*(17), 8240-8247. doi:10.1158/0008-5472.Can-07-0589

39. Mifsud, B., Tavares-Cadete, F., Young, A. N., Sugar, R., Schoenfelder, S., Ferreira, L., . . . Osborne, C. S. (2015). Mapping long-range promoter contacts in human cells with high-resolution capture Hi-C. *Nat Genet, 47*(6), 598-606. doi:10.1038/ng.3286

40. Mitchell, J. S., Li, N., Weinhold, N., Försti, A., Ali, M., van Duin, M., . . . Houlston, R. S. (2016). Genome-wide association study identifies multiple susceptibility loci for multiple myeloma. *Nature Communications, 7*(1), 12050. doi:10.1038/ncomms12050

41. Mitsui, J., Matsukawa, T., Ishiura, H., Higasa, K., Yoshimura, J., Saito, T. L., . . . Tsuji, S. (2012). CSF1R mutations identified in three families with autosomal dominantly inherited leukoencephalopathy. *Am J Med Genet B Neuropsychiatr Genet, 159b*(8), 951-957. doi:10.1002/ajmg.b.32100

42. Mughal, M. K., Akhter, A., Street, L., Pournazari, P., Shabani-Rad, M. T., & Mansoor, A. (2017). Acute myeloid leukaemia: expression of MYC protein and its association with cytogenetic risk profile and overall survival. *Hematol Oncol, 35*(3), 350-356. doi:10.1002/hon.2279

43. Murga, M., Campaner, S., Lopez-Contreras, A. J., Toledo, L. I., Soria, R., Montaña, M. F., . . . Fernandez-Capetillo, O. (2011). Exploiting oncogene-induced replicative stress for the selective killing of Myc-driven tumors. *Nat Struct Mol Biol, 18*(12), 1331-1335. doi:10.1038/nsmb.2189

44. Ng, P. C., & Henikoff, S. (2002). Accounting for human polymorphisms predicted to affect protein function. *Genome Res, 12*(3), 436-446. doi:10.1101/gr.212802

45. Nie, Z., Hu, G., Wei, G., Cui, K., Yamane, A., Resch, W., . . . Levens, D. (2012). c-Myc is a universal amplifier of expressed genes in lymphocytes and embryonic stem cells. *Cell,*

151(1), 68-79. doi:10.1016/j.cell.2012.08.033

46. Palaskas, N., Larson, S. M., Schultz, N., Komisopoulou, E., Wong, J., Rohle, D., . . . Mellinghoff, I. K. (2011). 18F-fluorodeoxy-glucose positron emission tomography marks MYC-overexpressing human basal-like breast cancers. *Cancer Res, 71*(15), 5164-5174. doi:10.1158/0008-5472.Can-10-4633
47. Pennacchio, L. A., Bickmore, W., Dean, A., Nobrega, M. A., & Bejerano, G. (2013). Enhancers: five essential questions. *Nat Rev Genet, 14*(4), 288-295. doi:10.1038/nrg3458
48. Ponder, B. A. (2001). Cancer genetics. *Nature, 411*(6835), 336-341. doi:10.1038/35077207
49. Poole, C. J., & van Riggelen, J. (2017). MYC-Master Regulator of the Cancer Epigenome and Transcriptome. *Genes (Basel), 8*(5). doi:10.3390/genes8050142
50. Posternak, V., & Cole, M. D. (2016). Strategically targeting MYC in cancer. *F1000Res, 5*. doi:10.12688/f1000research.7879.1
51. Sharma, N., Magistroni, V., Piazza, R., Citterio, S., Mezzatesta, C., Khandelwal, P., . . . Gambacorti-Passerini, C. (2015). BCR/ABL1 and BCR are under the transcriptional control of the MYC oncogene. *Molecular Cancer, 14*(1), 132. doi:10.1186/s12943-015-0407-0
52. Shim, H. (2011). One target, different effects: a comparison of distinct therapeutic antibodies against the same targets. *Exp Mol Med, 43*(10), 539-549. doi:10.3858/emm.2011.43.10.063
53. Shlyueva, D., Stampfel, G., & Stark, A. (2014). Transcriptional enhancers: from properties to genome-wide predictions. *Nat Rev Genet, 15*(4), 272-286. doi:10.1038/nrg3682
54. Sim, N. L., Kumar, P., Hu, J., Henikoff, S., Schneider, G., & Ng, P. C. (2012). SIFT web server: predicting effects of amino acid substitutions on proteins. *Nucleic Acids Res, 40*(Web Server issue), W452-457. doi:10.1093/nar/gks539
55. Stegmaier, K., Corsello, S. M., Ross, K. N., Wong, J. S., DeAngelo, D. J., & Golub, T. R. (2005). Gefitinib induces myeloid differentiation of acute myeloid leukemia. *Blood, 106*(8), 2841-2848. doi:10.1182/blood-2005-02-0488 %J Blood
56. Struntz, N. B., Chen, A., Deutzmann, A., Wilson, R. M., Stefan, E., Evans, H. L., . . . Koehler, A. N. (2019). Stabilization of the Max Homodimer with a Small Molecule Attenuates Myc-Driven Transcription. *Cell Chem Biol, 26*(5), 711-723. e714. doi:10.1016/j.chembiol.2019.02.009
57. Sud, A., Thomsen, H., Law, P. J., Försti, A., Filho, M. I. d. S., Holroyd, A., . . . The, P. c. (2017). Genome-wide association study of classical Hodgkin lymphoma identifies key regulators of disease susceptibility. *Nature Communications, 8*(1), 1892. doi:10.1038/s41467-017-00320-1
58. Taminato, T., Yokota, D., Araki, S., Ovara, H., Yamasu, K., & Kawamura, A. (2016). Enhancer activity-based identification of functional enhancers using zebrafish embryos. *Genomics, 108*(2), 102-107. doi:10.1016/j.ygeno.2016.05.005
59. Tennessen, J. A., Bigham, A. W., O'Connor, T. D., Fu, W., Kenny, E. E., Gravel, S., . . . Akey, J. M. (2012). Evolution and functional impact of rare coding variation from deep sequencing of human exomes. *Science, 337*(6090), 64-69. doi:10.1126/science.1219240
60. Tian, W., Zhang, L. V., Taşan, M., Gibbons, F. D., King, O. D., Park, J., . . . Roth, F. P. (2008). Combining guilt-by-association and guilt-by-profiling to predict Saccharomyces cerevisiaegene function. *Genome Biology, 9*(1), S7. doi:10.1186/gb-2008-9-s1-s7
61. Ulitsky, I., & Shamir, R. (2007). Identification of functional modules using network topology and high-throughput data. *BMC Systems Biology, 1*(1), 8. doi:10.1186/1752-0509-1-8
62. Voigt, M., Braig, F., Göthel, M., Schulte, A., Lamszus, K., Bokemeyer, C., & Binder, M.

(2012). Functional dissection of the epidermal growth factor receptor epitopes targeted by panitumumab and cetuximab. *Neoplasia, 14*(11), 1023-1031. doi:10.1593/neo.121242

63. Wang, A., Ikura, T., Eto, K., & Ota, M. S. (2004). Dynamic interaction of p220(NPAT) and CBP/p300 promotes S-phase entry. *Biochem Biophys Res Commun, 325*(4), 1509-1516. doi:10.1016/j.bbrc.2004.10.198
64. Whalen, S., Truty, R. M., & Pollard, K. S. (2016). Enhancer-promoter interactions are encoded by complex genomic signatures on looping chromatin. *Nat Genet, 48*(5), 488-496. doi:10.1038/ng.3539
65. Yang, D., Liu, H., Goga, A., Kim, S., Yuneva, M., & Bishop, J. M. (2010). Therapeutic potential of a synthetic lethal interaction between the MYC proto-oncogene and inhibition of aurora-B kinase. *Proc Natl Acad Sci U S A, 107*(31), 13836-13841. doi:10.1073/pnas.1008366107
66. Yang, T. L., Chen, X. D., Guo, Y., Lei, S. F., Wang, J. T., Zhou, Q., . . . Deng, H. W. (2008). Genome-wide copy-number-variation study identified a susceptibility gene, UGT2B17, for osteoporosis. *Am J Hum Genet, 83*(6), 663-674. doi:10.1016/j.ajhg.2008.10.006
67. Yao, L., Berman, B. P., & Farnham, P. J. (2015). Demystifying the secret mission of enhancers: linking distal regulatory elements to target genes. *Crit Rev Biochem Mol Biol, 50*(6), 550-573. doi:10.3109/10409238.2015.1087961
68. Yun, S., Sharma, R., Chan, O., Vincelette, N. D., Sallman, D. A., Sweet, K., . . . Zhang, L. (2019). Prognostic significance of MYC oncoprotein expression on survival outcome in patients with acute myeloid leukemia with myelodysplasia related changes (AML-MRC). *Leuk Res, 84*, 106194. doi:10.1016/j.leukres.2019.106194
69. Zelenetz, A. D., Gordon, L. I., Wierda, W. G., Abramson, J. S., Advani, R. H., Andreadis, C. B., . . . Sundar, H. (2016). Diffuse Large B-Cell Lymphoma Version 1.2016. *J Natl Compr Canc Netw, 14*(2), 196-231. doi:10.6004/jnccn.2016.0023
70. Zhou, Y., Goenaga, A. L., Harms, B. D., Zou, H., Lou, J., Conrad, F., . . . Marks, J. D. (2012). Impact of intrinsic affinity on functional binding and biological activity of EGFR antibodies. *Mol Cancer Ther, 11*(7), 1467-1476. doi:10.1158/1535-7163.Mct-11-1038