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Role of Chronic Psychological Stress in microRNA Biogenesis and microRNA Regulated Signal Transduction Pathways During Cancer

Mohammad Rakibul Alam[1, *], Mohammad Rubayet Ahsan[2], Rezowan Kabir[3], Sourav Biswas Nayan[4], Mahbub E. Sobhani[2]

[1]Department of Molecular Medicine, Kyungpook National University, Daegu, Republic of Korea
[2]Biotechnology and Genetic Engineering Discipline, Khulna University, Khulna, Bangladesh
[3]Biomedical Engineering Department, Military Institute of Science and Technology (MIST), Mirpur Cantonment, Dhaka, Bangladesh
[4]Department of Food Engineering, North Pacific International University of Bangladesh, Manikganj, Bangladesh

Abstract

The role of RNA in the central dogma of life has been changed after the discovery of evolutionary conserved, single stranded petite RNA molecule named microRNA (miRNA). miRNA is an essential regulator of gene expression that controls both physiological and pathological process in the progression of cancer. In order to reveal the role of miRNA, we have studied major signalling pathways including: IGF1R, AKT, MAPK, and WNT pathways. miRNA has significant role in activating these pathways as well as down-regulating apoptotic proteins i.e. PTEN, FOXO, p 53, p 21, p 27, puma, Bim, GSK3β, AXIN, APC, CK1α, RUNX3, SOX, NLK and up-regulating oncogenic proteins i.e. Ras, VEGF, ctnnB. During chronic psychological stress, body elevates the production of glucocorticoids (GCs) via hypothalamic pituitary adrenocortical (HPA) axis which ultimately facilitates tumorigenesis through regulation of signal transduction pathways. Binding with Glucocorticoid receptor, GCs activates the oncogenic transcription factor c-Myc that binds directly to the E-box sequence of Drosha promoter to produce mature miRNA and eventually leads cellular proliferation and cancer development. This paper reviews chronic psychological stress induced GCs secretion, and propose molecular mechanism of GCs regulated mature miRNA production and miRNA mediated regulation of cellular signal transduction pathways during cancer.

Keywords

Chronic Psychological Stress, Glucocorticoid, miRNA Biogenesis, IGF1R/AKT/MAPK/WNT Signalling Pathways

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1. Introduction

Psychological stress is a physiological or emotional reactions experienced when a person observes that demand go beyond the personal and social resources the individual is capable to organize. Concerning global issues, humans have always experienced period of excessive stress such as natural catastrophe, poverty, war, and epidemics. Based on the duration and intensity, stress could be categorized towards acute stress and chronic stress. Usually in emergencies acute stress is exists and persists for period of minutes to hours, such as fighting or escaping. The emotional cognitive system is activated by changing the arrangement and consequences of specific molecules and tissues in the brain, and we make decisions for stress-coping mechanisms [1]. Concurrently, the body produces GCs for a short time to improve flexibility and sensitivity that is often beneficial to the body. On the other hand, chronic stress lasts for several hours per day for weeks, months or years and causes ill health. Finally, the consequences of stress lead the harsh physiological condition

* Corresponding author
E-mail address: roqeeb.kubge10@gmail.com (M. R. Alam)

with insomnia, gastrointestinal disorders, anxiety, and depression, that positively regulated the risk of mental illness, cardiovascular disease, and cancer [2, 3].

A population-based study revealed that every year around one million new cancer cases take place due to stressful mental condition among people aged 20-39 years [4]. The connection between chronic psychological stress and cancers has stimulated gradually with extensive curiosity and concern in the global medical community. Therefore, numerous research groups have conducted research in association with stress and cancers like prostate, breast, gastric, lung, and skin cancer, and made remarkable insight by demonstrating that chronic stress can lead cancer development and progression [2, 5, 6] and regulate miRNA transcription, processing, sub-cellular localization and functioning [7].

miRNA is a major class of tiny RNA molecule, discovered in *Caenorhabiditis elegans* in 1993, generally found in most eukaryotes, including humans. miRNA encodes about 1-5% of the human genome as well as regulates as a minimum 30% of protein coding genes. Till date, very few are acknowledged about the functions and targets of miRNA molecules among identified 1000 distinct miRNAs within the human genome [8, 9]. Mature miRNA is synthesized through sequential processing of primary miRNA (pri-miRNA), which integrates into the effector complex RNA induced silencing complex (RISC). Finally, gene expression is regulated by mature miRNA through binding with target mRNA and promoting their degradation and/or translational repression [8].

By regulating the function of oncogenes and tumour suppressor genes miRNA plays a crucial role in diverse biological processes including cell proliferation, development, differentiation, metastasis, and apoptosis inhibition. Moreover, miRNA influences major signal transduction pathways are likely to be a well-situated strategy for disclosing relevant connection between miRNA and cancer formation [10]. Through the phosphorylation of PI3K and PIP3 AKT signalling is activated and facilitates tumorigenesis through down regulating apoptotic factors, besides up-regulating anti-apoptotic factors and influencing the activation of transcription factors [11]. AKT also suppresses tumour suppressor complex TSC1-TSC2 for consenting the activation of mTOR signalling, which positively regulates protein synthesis by phosphorylating the eukaryotic initiation factor eIF4E-binding protein 1 (4E-BP1) and the p70 ribosomal S6 kinase 1 (S6K1) [12]. In the canonical WNT signal transduction, the presence of Wnt signal provides assemblage of β-catenin in cytoplasm and influences nuclear transmission and formation of β-catenin, TCF/LEF complex which finally leads the tumour formation through stimulating numerous transcription factors. According to the recent findings, the newly identified miRNAs are the important molecular regulators of these tumour forming signalling pathways [13, 14].

During chronic psychological stress the increased secretion of GCs modulates immune functions to increase the susceptibility of cancer [15]. GCs promote growth and metastasis by up-regulating the oncogenic transcription factor c-Myc that binds to approximately 10-15% genes in the genome and regulates genes encoding both protein and non-coding RNA [16, 17]. Emerging evidence has demonstrated that, drosha is a c-Myc target gene; c-Myc is directly binds with drosha promoter to activate the expression of Drosha which is the key component of the miRNA processing machinery [17, 18]. Therefore in this review, we will discuss about GCs influencing mature miRNA formation and its regulatory role on different signal transductions of tumorigenesis.

2. Functional Relevance of Stress Hormones in Cancer

During chronic psychological stress the homeostasis disrupting situation is generated in central nervous system. Two highly controlled information processing cascades i.e. the hypothalamic-pituitary-adrenal (HPA) and the sympathetic nervous system (SNS) generally maintain stress response [2, 16]. Activated HPA increases the production of corticotrophin releasing hormone (CRH) from the hypothalamus that promotes elevated secretion of adrenocorticopic hormone (ACTH) from anterior pituitary. ACTH in turn, encourages the GCs hormone release from adrenal cortex. GCs are low molecular weight lipolytic molecule, stress induced steroid hormone and extensively used as anti-inflammatory as well as immunosuppressive agents [2, 16].

The psychological stress operated regulation of cancer cells are mediated by more complicated processes, and the pathophysiological mechanisms remain mostly unknown. Therefore, elucidation of the direct impacts of stress hormones, speciaty GCs on cancer cells would be the remarkable impact in advancement of exploring the molecular mechanism of cancer progression from stressor. Previously, researcher have used *in vivo* and *in vitro* approaches to demonstrate the impacts of psychological stress on cancer cells are mostly operated by the key stress hormones (EPI and NEPI) and β-adrenergic receptors (β-AR), especially the β2-AR [19, 20]. β-AR signals can stimulate numerous intracellular proliferative and migratory signalling pathways, such as the cyclic adenosine monophosphate (cAMP)/ protein kinase A (PKA), the mitogen-activated protein kinase (MAPK)/extracellular

signal-regulated kinase (ERK1/2) and phosphatidylinositol-3-kinase (PI3K)/AKT signalling pathways [21, 22].

Furthermore, G-protein-coupled receptors (GPCR) or receptor tyrosine kinases (RTK), β-AR signals straight activate the RTKs, or rise in matrix metalloproteinases (MMPS) through homodimerization and heterodimerization with other ARs, that can finally release growth factors to activate the RTKs indirectly in tumour cell. GCs can function in interaction with stress hormones to promote cancer progression. Dexamethasone, prednisone and cortisone, for example, can stimulate cell survival and chemoresistance in a number of solid tumours [23]. The mechanism consists of direct augmentation of cell growth, survival, and immunosuppression as well.

Glucocorticoid receptors (GRs) are responsible to play an influential role in a series of human malignancies. Upon activation, GRs function as a transcription factor, resulting enhancement of growth and survival of cancer cells either via binding to GC response elements (GRE) in the regulatory sequences of target genes or through hindering the functions of other transcription factors such as activator protein-1 (AP-1), signal transducers and activators of transcription 5 (STAT5) and NF-κB [24]. Moreover, GCs can also positively regulate the activation of proto-oncogene c-Myc, anti-apoptotic protein Bcl-xL, cytosolic caspase inhibitor cIAP2 and β2-AR to modulate growth, proliferation and metastasis of cancer cells (Figure 1) [16, 25, 26]. Recent evidences have revealed that expression of cell cycle genes such as Wee1, Cyclins as well as c-Myc is directly under the regulation of the circadian transcriptional complex (CTC). Hereafter, this finding depicts that psychological stress is a vital regulator to the disruption of circadian rhythms [27]. However, the detailed mechanism that dictates in the functions of psychological stress on central circadian rhythms and the molecular clock remain to be shed light on.

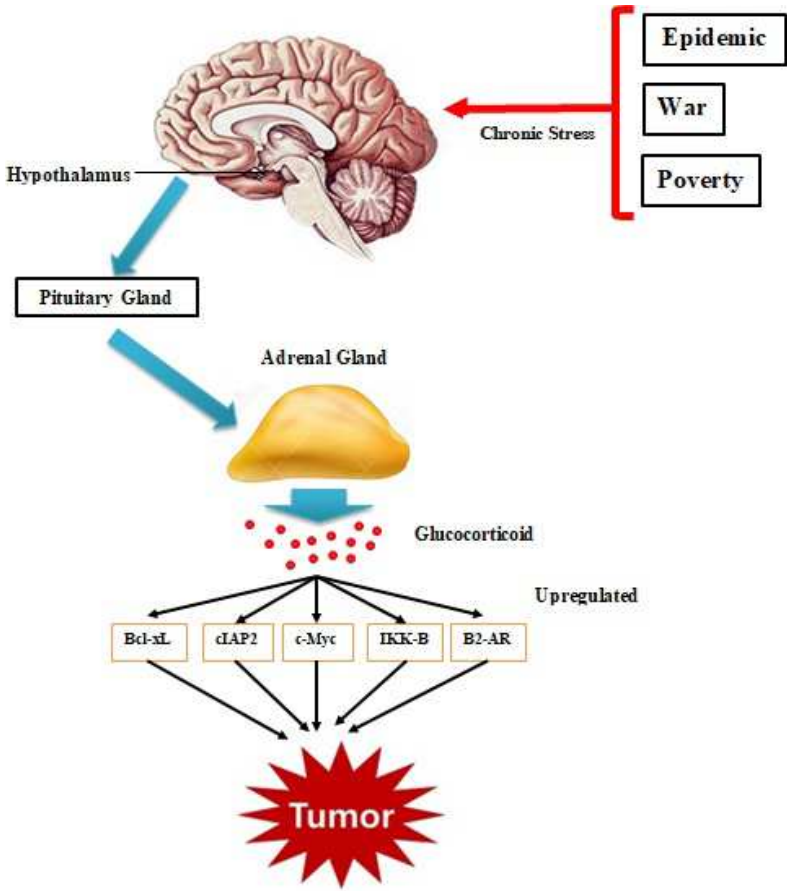

Figure 1. Chronic stress hormone in tumorigenesis.

3. Biology of miRNA

3.1. miRNA

According to central dogma of biology the unidirectional manner of genetic information is DNA-mRNA-protein. As a result, the vast majority of the research of previous time in molecular biology was highlighted the protein-coding genes and their transcripts, messenger RNAs (mRNAs). On the other hand, in the past two decades, noncoding RNAs (ncRNAs) have come to the light accomplishing significant roles in regulating diverse biological processes. In the whole

human genome, among transcribed DNA sequences only 2% encodes protein and rest 98% are ncRNA [28, 29]. In general, protein is produced through translation process from mRNA but noncoding RNA molecules are not translated into protein [30]. In eukaryotes, RNA interference (RNAi) is a mechanism of gene silencing at posttranscriptional period that is caused by tiny RNA molecules such as miRNA and single interfering RNA (siRNA) which are regarded as the novel classes of ncRNAs [31]. In spite of having the same in size (18-23 nt) and gene expression regulation mechanism they possess diversified origins and biogenesis process. In the genome, miRNAs are usually remaining on cluster manure in intronic as well as intergenic regions. Because of unknown function, these regions were known as "Junk DNA" [31, 32]. miRNAs are small, endogenous, evolutionary conserved, single stranded, non-coding RNA molecules that regulate gene expression by binding targeted mRNA through translational repression or degradation process [33, 34]. Therefore, miRNA plays a vital role in various cellular mechanisms i.e. development, cellular proliferation, differentiation, and apoptosis which in turn exhibit the promising indication of human diseases such as cancer and metabolic disorders [34].

3.2. miRNA Biogenesis

Nuclear processing and cytoplasmic maturation are two steps of human miRNA biogenesis which is accomplished by two ribonuclease III endonucleases, Drosha, and Dicer (Figure 2). In the nuclear processing of miRNA biogenesis pri-miRNA is generated for the transcription of miRNA gene with the help of RNA polymerase II or RNA polymerase III. Pri-miRNA possess a large stem-loop structure with single-stranded RNA extension at both ends such as polyadenylation and capping that helps in characterization of polymerase II [35]. The microprocessor complex formed by the RNaseIII enzyme Drosha and a double stranded RNA binding protein DGCR8 (DiGeorge critical region 8) also known as Parsha and pri-miRNA cleaved endonucleolytically by this nuclear microprocessor complex [8, 35]. Hairpin arms of pri-miRNA are cleaved at 5′ and 3′ position with two RNase domains of Drosha, whereas DGCR8 directly binds with pri-miRNA to determine accurate cleavage site. Drosha cleaves pri-miRNA co-transcriptionally and leads splicing of the miRNA containing protein coding or non-coding host RNA [36]. Drosha mediated cleavage is occurred by forming two diverse complexes, a small microprocessor complex with Drosha along with DGCR8, and a large complex with RNA helicase, double stranded RNA binding protein and heterogenous nuclear ribonucleo-proteins. In the processing of subset of pri-miRNA, RNA helicase p72 and p68 are plays a role as specificity factor. Therefore, microprocessor complex cleaves pri-miRNA to produce a hairpin shaped precursor with 65nt length that considered as pre-miRNA. At the last phase of nuclear processing, pre-miRNA is transhipped from nucleus to cytoplasm by the help of Exportin-5 with Ran-GTP complex [8, 37].

At the period of cytoplasmic maturation, the exported pre-miRNA binds with multi-protein complex named RISC loading complex (RLC) which is composed with RNase Dicer, the double stranded RNA binding domain protein TRBP (Tar RNA binding protein) and PACT (protein activator of PKR) and the central component Argonaute 2 (Ago2) [31, 35]. During the Dicer dependent cleavage, Ago2 cleaves the 3′ end of the arm to create a nick in the middle on the passenger stand by using slicer activity of Ago2 to generate Ago2 cleaved pre-miRNA or ac-pre-miRNA. The nicked ac-pre-miRNA is cleaved with RNase III Dicer to generate miRNA duplex with two nucleotides protruding at each 3′ end [9, 35]. After accomplishing Dicer dependent cleavage, miRNA duplex appears to be separated from the components of RLC i.e. Dicer, TRBP, PACT and ultimately form the gene silencing active RISC compound. The incorrect base pairing between double stands of miRNA duplex are responsible for the formation of thermodynamically less stable 5′ end that facilitates unwinding of miRNA duplex [9, 38]. As a result of unwinding, the guide stand and passenger stand are produced. Eventually the passenger stand is degraded and guide stand with core Ago2 protein turns into gene silencing RISC complex through binding targeted mRNA [39]. Mature miRNA with Ago protein binds with targeted mRNA which facilitates gene silencing through target recognition by miRNA with RISC complex. The target gene suppression mechanism relies deeply on level of complementarities between miRNA and its target [34, 39]. Inadequate complementarities in base pairing of miRNA and targeted mRNA occlude gene expression through translational repression process.

miRNA mediated gene expression regulation at post transcription level mainly emphasize on protein synthesis inhibition, target mRNA degradation, as well as targeted mRNA translocation into cytoplasmic processing bodies (p bodies). Translational repression is the first approach in inhibition of protein synthesis or silencing of gene expression method. Three general steps of translation are initiation, elongation, and termination [40]. The mRNA 5′ cap is recognized by the translation initiation complex through the cap binding component elF4E in eukaryotic cap dependent translation, which connected with the initiation complex elF4G. One more initiation factor elF3 links with elF4G to engage the 40S ribosome subunit to the end. The 40S subunit binds with 60S subunit on the 5′ UTR of mRNA at the start codon for translation elongation [40, 41]. elF4G also

connected with cytoplasmic polyadenylate binding protein C1 (PABPC1) that interacts mRNA poly (A) tail. Thus, the initiation complex facilitates ribosome recycling. However Ago2 protein binds with both 60S ribosomal subunit and elF6, which facilitates elF6 mediated prevention of 60S ribosomal subunit binding with 40S. Through this process Ago2 protein engage elF6 as a result 60S ribosomal subunit might not be able to bind with 40S subunit and cause translational repression of target mRNA [41, 42]. miRNA mediated translational repression of target mRNA happens in cytoplasmic processing bodies or P bodies. miRNA and target mRNA dependent manure facilitate the accumulation of Ago protein in P bodies that is the first functional link between miRNA and P bodies. Through physical interaction between GW182 as well as Ago turns to the translocation of mRNA into P bodies, which end result consequent degradation of mRNA [39, 43]. Deadenylation and decapping are two mRNA degradation processes which are served by molecular machineries of P bodies.

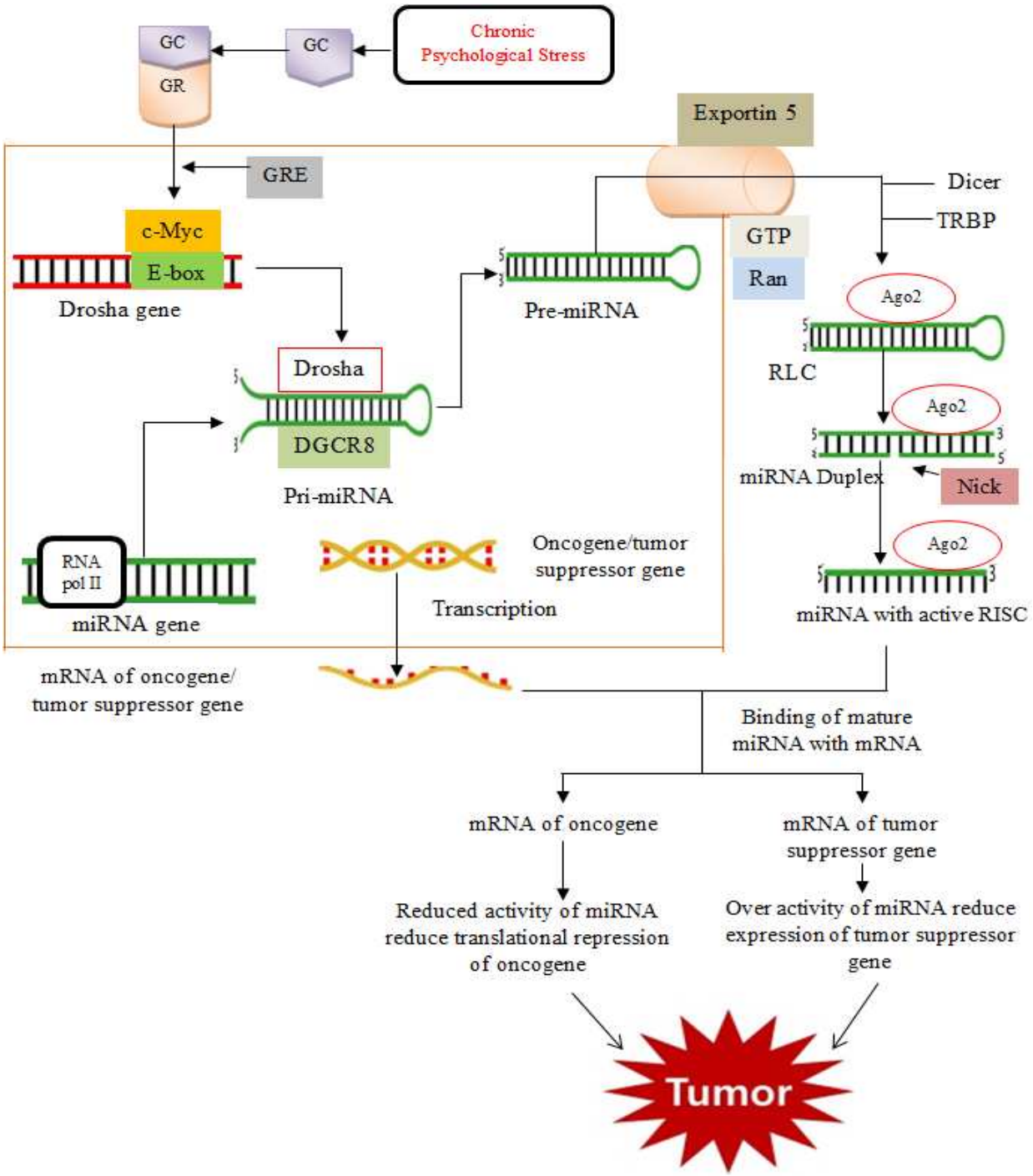

Figure 2. Stress hormone in miRNA processing and tumorigenesis.

In deadenylation process CCR4-NOT are key players for mRNA degradation by 3′->5′ decay as well as in decapping process DCP1/2 and XRN1 are also plays as key apparatus for mRNA degradation by 5′->3′ decay. As a result, miRNA repress translation of target mRNA through P bodies [43].

3.3. miRNA in Cancer Development

By up-regulating the expression of oncogene and constraining the expression of tumour suppressor gene miRNA may participate in tumorigenesis. When the target of miRNA is tumour suppressor gene responsible for apoptosis, over activity of abundant amount of miRNA repress tumour suppressor protein; as a result, miRNA perform as an oncogene. Conversely, when the target of miRNA is oncogene, reduced amount of miRNA over express oncoprotein through reducing translational repression; thus, miRNA act as tumour suppressor [9, 44].

3.4. GCs in regulation of miRNA Production

GCs act upon binding with GR that translocate from cytoplasm to nucleus to bind with GRE within the glucocorticoid responsive gene at promoter region and the intensity of transcriptional response are influenced for the location of GRE. Subsequently, GR regulates the transcription of gene by activating the transcription factors c-Myc that influences the cellular proliferation and tumorigenesis through directly up-regulating miRNA expression [16, 45]. Previous evidence described that Drosha, Dicer and DGCR8 are the significant factors involved in miRNA processing. Drosha is the target gene of transcription factor c-Myc which binds directly to the E-box of drosha promoter to activate drosha mRNA expression, thus up-regulating the drosha protein level as a significant factor of miRNA processing, drosha leads the formation of mature miRNA [17]. Therefore, we can propose a mechanism that stress hormone GCs stimulate miRNA formation by activating the oncogenic transcription factor c-Myc that transactivate drosha mRNA and protein expression. Consequently, mature miRNA regulate oncogenes and tumour suppressor genes to lead tumorigenesis.

4. miRNA in Signal Transduction Pathways of Cancer Formation

4.1. IGF1 Signalling Pathways

Cellular complex signalling systems involved with external stimuli as well as intrinsic factors which usually regulate cellular growth and proliferation (Figure 3). A signalling system which is consisted with insulin like growth factors (IGFs) and their receptors required for G_1-S phage cell cycle progression and cell division. IGF system contains three ligands i.e. IGF1, IGF2 and insulin, interact with type 1 insulin like growth factor receptor (IGF1R), IGF2R as well as the insulin receptor [46]. Binding of ligands with receptors are upregulated by mir-20a, mir-20b, mir-105, mir-134, mir-152, and mir-154 [47]. Ligand binding with IGF1R influences to the autophosphorylation of tyrosine kinase domain on the intracellular portion of β subunit, comprising juxtamembrane tyrosines and carboxyl-terminal serines phosphorylation. Consequently, the phosphorylation of juxtamembrane tyrosine provides a binding site for docking proteins comprising insulin receptor substrates 1-4 (IRS1-IRS4), and Src homology/collagen domain protein (SHC) this substrates facilitate transmission of IGF1R signal [46, 48]. P 85 regulatory subunit of Phosphatidylinositol 3-kinase (PI-3K) is activated by IRS1 which phosphorylates the phosphoinositides by increasing PIP3 and PIP2 concentration at plasma membrane. PI3 kinase activity is inhibited by a lipid 3 phosphatase PTEN which is most ordinary tumour suppressor that converts PIP3 back to PIP2. Expression of PTEN can be repressed by a range of miRNAs including the mir-17~92 cluster [49], mir-106b~25 [50], mir-21 [51], mir-26a [52], mir-29b [53], mir-214 [54], mir-216a and mir-217 [55], mir-212 [56], mir-221, mir-222 [57], mir-32 [58], mir-425 [59], mir-144 [60], mir-205 [61], and mir-183 [62]. Therefore, PDK1 is activated by PIP3 at the plasma membrane which leads to the AKT phosphorylation on Thr308. Meanwhile, AKT is also phosphorylated on Ser 473 by mTOR2, and Thr308 as well as Ser 473 mediated phosphorylation leads to full activation of AKT. Activation of AKT is also influenced by miRNAs i.e. mir-144 [60], mir-21 [51], and mir-101 [63].

4.2. AKT Signalling Pathway

AKT activation precedes the phosphorylation of a wide spectrum of substrates of numerous cellular process i.e. cell growth, cell proliferation, cell differentiation, cell survival, cell cycle progression, and cellular metabolism. Activated AKT prevents cells from death by directly phosphorylating some apoptotic components i.e. pro-apoptotic factor BAD is a part of BCL2 family of protein. Correspondingly, activated AKT also inhibits the conformational change and mitochondrial translocation of another pro-apoptotic member BAX as well as catalytic activity of pro-death protease caspase-9 [11]. The transcription factor NF-κB promotes cell survival in response to several apoptotic stimuli. IκB kinase (IKK), the inhibitor of NF-κB, is phosphorylated and

degraded by AKT which leads to nuclear translocation of NF-κB as well as activation of target genes. Cancer cell proliferation or tumorigenesis is also influenced by AKT mediated regulation of diverse signalling molecules engaged in cell cycle regulation. Tumour suppressor p 21 is a cell cycle inhibitor, Nuclear localization of p 21 is prevented by AKT mediated phosphorylation thus p 21 is going to be separated from its cyclin dependent kinase targets [64]. p 21 is also repressed by mir-17~92 [65, 66], mir-106b, mir-17-5 p [66]. In the same way, AKT phosphorylates p27 which up-regulates cytoplasmic retention of this cell cycle inhibitor and scaffold protein 14.3.3 mediated sequestration. Phosphorylation of MDM2 facilitates its translocation into nucleus which leads to down regulation of p53 activity [11]. Mir-221, mir-222 [65, 66] and mir-196a are responsible for inhibition of another cell cycle component p27 [67] as well as mir-25, mir-30d, mir-125b, mir-504, mir-214, mir-380 [68], and 380-5p [69] also facilitates suppression of apoptotic activity of p53. FOXOs hinder cellular proliferation through blocking distinct phases of cell cycle. By upregulating cell cycle inhibitor, FOXOs block S phase as well as causes G1 cell cycle arrest and FOXOs also leads to G2/M cell cycle arrest. By regulating the expression of numerous pro-apoptotic proteins i.e. FasL, TRAIL as well as Bim, FOXOs lead to stimulate the apoptosis [11]. Activated AKT occludes the expression and function of growth inhibiting factors FOXO and FasL by phosphorylation. An enormous number of miRNA facilitate the repression of apoptotic activity such as mir-27a, mir-96 [70], mir-1 [71], mir-155 [72], mir-135b, mir-182, mir-708 [65], mir-221, mir-222 [66], mir-29 responsible for FOXO, mir-221, mir-222 also responsible for Puma and mir-17-92, mir-25, mir-106, mir-93, mir-26a, mir-106a-263 responsible for repression of Bim expression [65].

4.3. MAPK Signalling Pathway

Mitogen activated protein kinases (MAPKs) consists of a kinases family that leads to enhance tumour growth and metastasis. MAPKs have three subfamilies: the c-Jun N-terminal kinases (JNKs), the extracellular-signal regulated kinases (ERKs), and p38 MAPKs. Corresponding to PI3K mediated signalling, the growth factor receptor bound protein 2 (Grb2)/SOS are phosphorylated by SHC which leads to IGF signal transmission [73]. Subsequently, the GDP in the Ras G-protein exchanged to a GTP by SOS protein. Activation of Ras GTP is happened by the stimulation of mir-31 [74]. The Ras GTP complex can activates the RAF kinase as well as subsequently phosphorylates and activates the next components MEK and ERK. Through phosphorylation of nuclear transcription factors i.e. c-Fos and Ets-like transcription factor-1 (Elk-1) activated ERK stimulates cell proliferation [75].

4.4. WNT Signalling Pathway

A large set of soluble proteins is contained by WNT family that leads to the embryonic developmental processes such as cell differentiation, proliferation, and epithelial-mesenchymal interactions as well as deregulations of WNT pathway also influences cancer formation [13]. miRNA mediated down regulation of numerous Wnt signalling inhibitors such as mir-410, mir-433 [76], mir-31 by targeting Frizzled related protein (FRP), mir-31 [77], mir-374a by targeting Wnt-inhibitory factor-1 (WIF1) [78], mir-290, mir-335-5p by targeting Dickkopf (DKK) [76] which facilitates Wnt ligand binding to its receptors i.e. Frizzled (FZD) and LDL receptor-related protein-5 or 6 (LRP5 or LRP6) generally initiates canonical WNT signalling pathway. Therefore, Phosphorylation of cytoplasmic protein Disheveled (Dvl) influences dissociation of β-catenin with the adenomatous polyposis coli (APC), Axin, casein kinase 1α (CK1α), and glycogen synthase kinase 3β (GSK3β) composted destruction complex [13]. β-catenin activity is increased by mir-499 mediated phosphorylation of Dsh protein [79] and miRNA regulated repression of each components of destruction complex i.e. mir-27, mir-135a, mir-135b, mir-106b, mir-155 for APC [80], Let-7 [81], mir-315 for AXIN [82], mir-26a, mir-9 for GSK3β [83], mir-155 for CK1α [84] and mir-9 also influences the stabilization of β-catenin [83]. The stabilized β-catenin initiates accumulation in the cytoplasm which influence translocation into the cell nucleus, as a result initiates β-catenin–LEF/TCF transcriptional complex formation that induce transcription of c-Myc, Cyclin D1, c-Jun, MMP7, and VEGF that facilitates cellular growth, differentiation, proliferation, metastasis as well as angiogenesis. Three Wnt signaling inhibitors runt related transcription factor-3 (RUNX3), Nemo-like kinase (NLK), sex-determining region Y-box (SOX) bind with TCF/LEF and β-catenin which finally leads to the inhibition of Wnt signaling [82]. mir-130a downregulates RUNX3 mediated complex formation [85], mir-92b involves with NLK [86] and mir-141, mir-499 also repress SOX mediated complex [79], therefore mir-9 stabilize β-catenin and finally stimulate tumorigenesis through Wnt signaling [83]. Due to the absence of miRNA mediated down regulation of Wnt signal inhibitors, sFRP, WIF-1, and Cerberus bind directly with Wnt molecules and the DKK binds with the LRP5/LRP6 component of the Wnt receptor complex to inhibit Wnt signalling. As a result, β-catenin turns to associates with cytoplasmic destruction complex which enhance phosphorylation of β-catenin and interaction with β-TRCP (Beta transducing repeat containing protein), finally promote ubiquitination of β-catenin and proteosome mediated degradation [87].

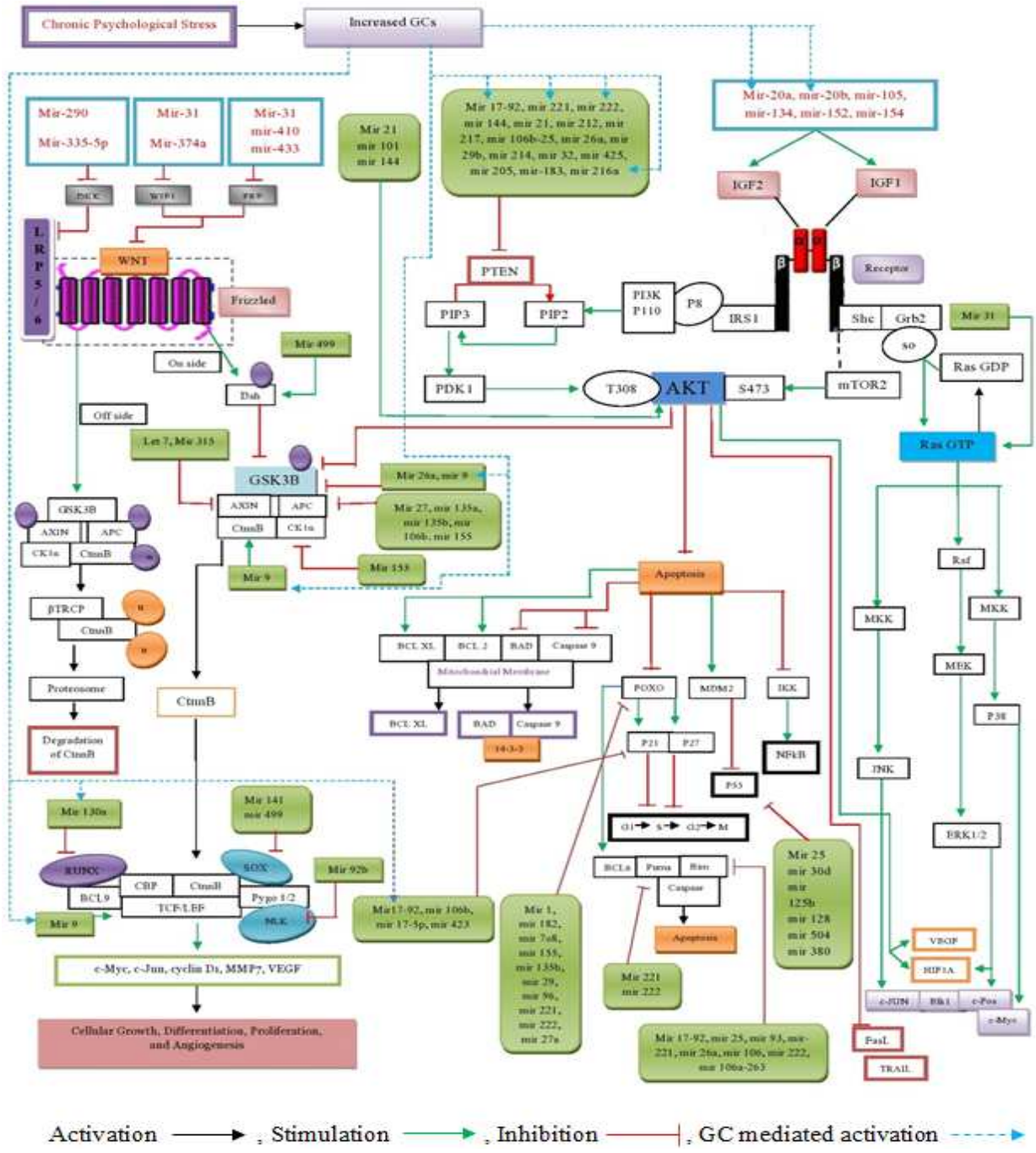

Figure 3. GCs regulated signal transduction pathways during cancer.

4.5. GCs in miRNA Regulated Signal Transductions

Previous findings depict that mature miRNA is produced through stress hormone GCs mediated activation of transcription factor c-Myc, that up-regulates drosha protein expression. A large number of miRNA is identified that are stimulated by GCs and capable to regulate different oncogenic and apoptotic protein expression of numerous signal transductions during cancer [16, 17]. According to the finding evidence, GCs stimulate the activation of mir-214, mir-216a, mir-17-92 cluster, mir-221, mir-222, mir-9, mir-130a, mir-17-5p, mir-27a, mir-106-263 cluster [66, 88-90] that are up-regulated by c-Myc and play significant role in tumorigenesis.

5. Conclusion

Chronic psychological stress is intimately allied with cancer progression. The effects of chronic stressor are conveyed via SNS and the HPA axis, augmented by the unchecked

secretion of stress-related mediators like GCs and altered behaviours. All these mediators functions as immunosuppressors or mitogens in the tumour microenvironment. The converging effects of psychological stress on cancer cells are operated through the regulation of proliferative and migratory pathways by mature miRNA. Stress hormone GCs up-regulate oncogenic transcription factor c-Myc that play a role as the activator of Drosha to produce mature miRNA. Even though, c-Myc has been revealed to act as negative regulator of miRNA expression [91], several important miRNAs are discovered those are activated by c-Myc [83, 92]. Previous studies provide evidence that c-Myc function as a coordinator of miRNA expression by controlling Drosha levels via the transactivation of Drosha expression. However, recent evidence demonstrated that c-Myc does not appear to regulate DGCR8 directly rather affects DGCR8 mRNA via Drosha and that c-Myc-Drosha-DGCR8 axis maintains the microprocessor activity for processing pri-miRNA to pre-miRNA [17]. The transactivation of Drosha by c-Myc and DGCR8 may augment another layer of complexity to c-Myc mediated miRNA regulation which is activated by stress hormone GCs. Furthermore, GCs up-regulate a large number of miRNA by targeting c-Myc which enhance tumorigenesis and inhibit apoptosis through IGF, AKT and WNT signalling pathways. Overall, the work describes a possible new approach on how GCs operated c-Myc and miRNA processing plays role in tumorigenesis and it might be a hallmark in the designing of new cancer treatment strategies.

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