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Research Progress in Oncology. Highlighting and Exploiting the Roles of Several Strategic Proteins in Understanding Cancer Biology

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Abstract: Although almost all biological processes are mediated by a variety of proteins, it is important to bring to spotlight recent experimental and clinical research advances that had their focus on highlighting and taking advantage of the roles of several strategic proteins in order to gain more understanding of cancer biology. Proteins have a major stake in the initiation, progression, sustenance and completion of cellular processes, and have also demonstrated their vital roles in cancer processes. The characteristic functions of proteins and modified proteins have been utilized in the understanding and treatment of cancer. Recent insights in such roles and applications include linker histone H1.2 in the compaction of chromatin and gene silencing *via* the recognition of H3K27me3; c-Jun with Fra-2/c-Fos in the promotion of aggressive tumour phenotypes in tongue cancer; the use of sodium channel-inhibiting agents targeting the transmembrane protein in breast, colon and prostate cancer; SET-mediated activities; protein interaction networks in glioma; Gpnmb significance as a biomarker; β-carbolines inhibition on Wnt/β-catenin signaling; p53 mutants co-opt chromatin pathways; Bone morphogenetic protein 4 as regulator of the behaviors of cancer cell; Brain-Expressed X-linked (BEX) proteins in human cancers; targeting CDK4/6 including protein kinases to make a reversal of multidrug resistance in sarcoma. In-depth knowledge of Proteomics will go a long way in helping us uncover a lot more strategies that will help us in the long fight against cancer.

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1 Introduction

Efforts made by researchers in biomedical and social research with a focus on cancer have been targeted at prevention, detection, diagnosis and treatment. While incidences of some infections such as polio have declined or been totally eradicated, cancer is classified as one of the diseases which incidences are projected to increase over time [1-3]. As of 2013, the American Association for Cancer Research (AACR) predicted that the incidence of cancer will increase from 12.8 million in 2008 to 22.2 million in 2030. Moreover, there is a directly proportional relationship between cancer incidence and technological advancements [4,5].

Cancer (malignant tumour or malignant neoplasm) continues to be one of the major causes of death globally [2], gaining more prominence in the developed world, which has prompted increased research into effective treatments toward a cure. Cancer is characterized by an abnormal phenotypic manifestation that results from unrepaired changes that occurred in the genetic make-up of an organism; a state where tissues are no longer fully responsive to the signals that regulate differentiation, survival, proliferation and death. This results in the accumulation of these cells within the tissue, leading to local damage and inflammation. Some of the causes are known while many remain unknown [3-5]. These alterations which could be scientifically referred to as mutations change certain protein components of a cell, fostering cancer initiation, development, and metastasis (a scientific description for spread–characteristic of cancer). Self-sufficiency (independence) in growth signals, resistance to growth inhibitory and regulatory signals, transgression of programmed cell death, unlimited

and uncontrolled replication capability, sustained ability for angiogenesis (to increase vascularization and oxygenation), invasion and metastasis (by altering cell adhesion and initiating epithelial-to-mesenchymal transition pathways) are all hallmarks of cancer, and are all initiated *via* oncogenesis. In molecular and translational cancer research, there is no doubt that prevention is key; and a good understanding of carcinogenesis will go a long way in helping to diagnose precancerous lesions and early stage cancers through the application of basic applied knowledge. Specifically, the knowledge of proteomics and biotechnology is fortifying researchers in understanding and manipulating human genetics towards unraveling the mysteries embedded in cancer processes.

Research efforts have highlighted and detailed extensive list of issues that include chromosomal and microsatellite genomic instability as it relates to defects in DNA repair pathways; growth factor (proto-oncogenes and their dysregulation) signalling in the progression of cell cycle; growth inhibitory signals in cell differentiation and dysregulating quiescence; tumour suppressors activation; telomere maintenance and immortality of the cell; sustenance of tumour growth through building a vascular system (angiogenesis); cell death by employing apoptosis; carcinogenesis (genetic and environmental triggers); prevention; epidemiology; strategies for reducing risk; gene interaction with environment; diagnosis and prognosis using molecular markers; defining tumour margins; diagnostic imaging; metastasis; new approaches to therapy *via* rational drug design; immunotherapy; gene therapy; combination therapies; [10,11] personalized treatment and combating drug resistance [8]; experimental systems and techniques comprising cell culture; genomic and proteomic approaches; studying cancer-associated signs and symptoms evident in the adverse effect of cancer treatment (such as hair loss, gastrointestinal disease, anaemia); psychosocial aspects of cancer; as well as other social, legal and ethical concerns surrounding cancer research. In the past decade, there has been rapid progress in the field of cancer treatment (including traditional therapies, chemotherapy, treatment with radiation and biotherapy employing interferon, super Interferon, gene therapy, p53 and liposome etc.) and in understanding what factors trigger carcinogenesis, ultimately aiding in the development of more effective prevention methods, and the ability to diagnose early-stage cancers accurately [1, 9-11].

Although almost all biological processes are mediated by a variety of proteins [12,13], it is important to bring to spotlight recent experimental and clinical research advances that had their focus on highlighting and taking advantage of the roles of several strategic proteins in order to gain more understanding of cancer biology. Emphasis regarding the role of several proteins in understanding cancer from recent studies will be discussed in this paper. The choice of proteins (few classes in this paper) is not an attempt to place proteins above every other biomolecule, but it is actually firstly, based on its fundamental role in almost all metabolic processes and its ease of modification to achieve the desired product and secondly, they are novel in utilizing them as targets in understanding cancer processes. Worthy of emphasis also is the fact that this class of proteins have been spotted in recent advances and represents a remarkable step forward in understanding cancer biology.

2 Some Strategic Proteins in Recent Cancer Biology Research

2.1 Histones

Deeper insights into the causes and consequences of histone modifications can largely help our understanding of cancer biology. Histones constitute the protein backbone of chromatin [15]. This octamer of small basic proteins called histones wrap the fundamental repeating unit of chromatin in the nucleosome core particle, composed of 147 base pairs of DNA [16]. Histones and their post-modifications play key roles in cancer processes [17], and there are quite a number of histone variants in human disease (as summarized in Table 1) [18]. Histones could act as damage-associated molecular markers when they are discharged into the extracellular compartment (Fig 1.), and could also be used for diagnosis or prognosis of cancer [17,19]**.** Evidence suggests that the dysregulation of the chromatin remodeling components by modifying enzymes and protein–protein interactions is the driving mechanism that determines gene activity underlying the growth and progression of tumours in humans [20]. Recent research has shown that histone deacetylases (HDACs) carry out an important role in cancer development by regulating the activity and expression of numerous proteins involved in cancer initiation as well as progression [19]. It is worth noting here that by removing acetyl groups from histones, HDACs are capable of creating a chromatin conformation that disallow the transcription of genes that code for particular proteins involved in tumour development (Fig. 1) acetylation and deacetylation are the basic mechanisms by which the activities of histones can be regulated. In characterizing a subtype of H1, H1.2 as a

Table 1. Histone variants in human disease.

Histone type	Cell-cycle stage	Number of gene copies	Mutation and expression pattern	Tumourigenic consequences
CENPA	RI	1	Over-expression; oncogene	Many types of cancers (including breast cancer, colorectal cancers, lung adenocarcinoma and hepatocellular carcinoma)
H2A.Z	RI	2	Over-expression; oncogene	Many types of cancers (including breast cancer, colorectal cancers, lung adenocarcinoma and hepatocellular carcinoma)
MacroH2A	Possibly RI	2	Reduced expression; tumour suppressor	Many types of cancers (including breast cancer, colorectal cancers, lung adenocarcinoma and hepatocellular carcinoma)
H2A.X	RI	1	Reduced expression	Increased cancer progression in p53 knockout

CENP-A, histone H3like centromeric protein A

RI - Replication Independent.

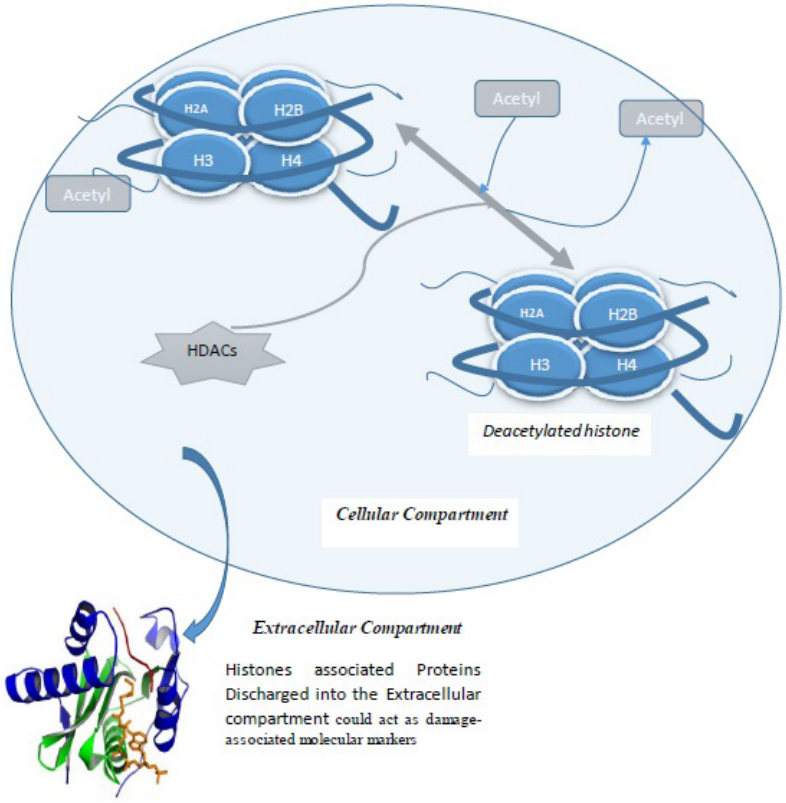

Figure 1. HDACs are capable of deacetylating histones by creating a chromatin conformation that disallow the transcription of genes that code for particular proteins involved in tumour development.

means of stimulating gene silencing through chromatin compaction *via* EZH2-mediated H3K27 trimethylation, as well as establishing the essentiality of the C-terminal tail of H1.2 in its binding to chromatin for transcription inactivation, research has buttressed the role of histone H1.2 in gene regulation; functioning as a linker that builds chromatin compactions as well as silencing genes *via* the identification of H3K27me3 [24]. Core histones which include H2A, H2B, H3 and H4 along with linker histones H1 and H5, play very important roles in compacting DNA strands and also in regulating transcription [22].

H1 is important in the formation of the 30 nm fibre of the chromatin [23], located at the point of entrance and exit of internucleosomal DNA and highly ordered chromatin; consisting of both N-terminal and C-terminal tails [24,25]. Multiple variants of H1 occur as a result of sequence heterogeneity in the N- and C-terminus. Genomic mapping establishes a relationship between H1 abundance and specific gene silencing by establishing the non-uniform distribution of H1 in specific regions [24]. H3K27me3 methyl-transferase EZH2 is upregulated in a number of cancers, including breast cancer, lympho-

mas and prostate cancer [19]. The polycomb repressive complex 2 (PRC2) which facilitates H3K27 trimethylation (H3K27me3) controls transcription at specific point, *via* its catalytic subunit – EZH2. This stimulates ubiquitylation of H2AK119 by inhibiting activation of RNA polymerase II (RNAPII), hence bringing about a repression in gene transcription *via* polycomb repressive complex 1 (PRC1). Experimental knockdown of H1.1 and EZH2 results in the activation of several growth suppressive genes which had been previously deactivated through EZH2-mediated H3K27 trimethylation [24]. A series of supporting experiments to corroborate these observations has been carried out. H3K27 (mono-, di-, and trimethylated) were immobilized on streptavidin-coated wells, and the binding of H1 subtypes (H1.1-H1.5) revealed that only H1.2 showed preferential interactions with H3K27me3 amongst other subtypes. *In vivo* studies with MCF7 breast cancer cells also revealed that suppressing the expression of EZH2 significantly reduced the concentration of H3K27 and consequent binding of H1.2 to the chromatin [24]. This further establishes the fact that the binding of H1.2 to the chromatin is H3K27 dependent [26]. This ascertains that, H1 subtypes differ in functional characteristics and each subtype regulate particular gene expression, and also that H3K27me3 is the determining factor for the localization of H1.2, usually at the promoter and protein coding regions. Ultimately, the localization of H1.2 at several growth suppressive gene regions occurs in an EZH2-dependent manner, responsible for chromatin compaction which turns off the expression of these genes, leading to a misregulation of such growth suppressive genes. This ultimately causes cancer in the breast, bladder and prostate glands [24]. Mutation in specific amino acids (V120, T126 and V132) at the C-terminal may lead to the formation of mutant H1.2 which has lost its ability to interact with H3K27me3, hence cannot properly localize and cause chromatin compaction. The role of H1.2 as a chromatin inactivator in the presence of H3K27me3 could be overturned in the absence of H3K27me3 by its interaction with CuL4A and PAF1 *via* RNA Polymerase II, serving as a transcriptional coactivator [26]. This could function as a potential therapeutic target for cancer treatment. Methyl-modifying and methyl-binding proteins [e.g., bromodomain protein 4 (BRD4): a chromatin-binding protein that functions as a histone acetyltransferase (HAT)] [27] or enzymes are thus potential pharmacological targets for cancer therapy [19]. This modification by an acetyl group on lysine residues, mediated by histone acetyltransferases (HATs) and deacetylases (HDACs) is a highly dynamic process that contributes to transcriptional activation and silencing [16].

MYC-induced nuclear antigen (MINA) is involved in glioblastoma carcinogenesis and reveals its probable mechanisms in cell-cycle control. It has also been found that cyclins and cyclindependent kinases are directly activated by MINA *via* the demethylation of H3K9me3 [28]. Understanding the functions of KATs (lysine acetyltransferases) in tumour development and progression is still limited. Studies however, show that KATs (lysine acetyltransferases) act as tumour suppressors, while others claim that they promote tumour progression, making available a rationale for the development of KAT inhibitors to act against cancer [29]. Deregulation of these histone modifying enzymes may result in the epigenetic silencing of tumour-suppressor genes by employment of DNA methyltransferases (for example, glioma cells). Diverse drugs which target histone-modulating enzymes, are in clinical trial stages, including suberoylanilide hydroxamic acid (vorinostat) - a highly potent inhibitor specific for HDAC, approved by the FDA for cutaneous T-cell lymphoma therapy [30].

2.2 Activator Protein-1

AP-1 proteins noted for their important roles as regulators of growth and invasion are involved in diverse functional metabolic processes in the cell, including differentiation, proliferation, and apoptosis, achieved through a dimeric complex consisting of a homodimer/heterodimer of Jun proteins or of Jun and Fos proteins in various combinations [31] as depicted in Figure 2. These complexes modulate AP-1 gene expression *via* binding to the AP-1 site on the AP-1 target genes [32] (Fig. 2). AP-1 family members such as Jun and Fos are differentially expressed in human cancers cells, allowing the AP-1 factor to mediate a wide variety of cellular functions and signal transduction pathways through several mitogenic signaling cascades. Other subfamilies of AP-1 proteins apart from Jun and Fos include Maf and ATF [33, 34]. AP-1 transcription factor has been regarded in binding to DNA in regulating gene expression to respond to a diverse array of stimuli [35]. For instance, research has shown that the AP-1 complex bound to the AP-1 binding site in DR4 promoter region is a heterodimer made up of c-Jun, JunB or JunD dimerized with Fos B or Fra-1 [36]. AP-1 is an important early activator of transcription in proliferation, cellular transformation and apoptosis under certain situations, including stress, cytoskeletal changes or withdrawal of growth factors [36]. Important growth factors in the form of extracellular stimuli including EGF, IGFs, retinoids and estrogen are noted for activating AP-1. In an experiment to demonstrate

the role of cFos in cellular processes including cancer, a cJun mutant (Tam67) capable of dimerizing with Jun or Fos proteins was developed that blocks AP-1 transcriptional activity and inhibits or suppresses cancer cell proliferation. This suggests that cFos proteins could be deactivated by targeting cJun in therapy to suppress cell proliferation. However, suppressing AP-1 activity does not necessarily suppress cancer cell growth as other mechanisms through which cancer can initiate and proliferate are available. It is therefore important to screen growth-suppressive anti-AP-1 agents using AP-1-dependent promoters such as c-Myc and cyclin D1 that are directly concerned with growth. Further investigation into the role of Fos family in the regulation of growth has shown that through knocking down of cJun or cFos mRNA and protein gene, cFos antisense suppresses cancer proliferation, but antisense cJun showed contrasting results [32]. Similarly, through a c-Fos and c-Jun gene knockout experiment in mice, AP-1 transcription factors c-Fos and c-Jun contributed to osteoclastogenesis [37]. Phosphorylated c-Jun affiliates with the Fos family when transcriptionally active to transactivate osteoclast-specific genes. The proteasome–ubiquitin system has also proven to mediate the metabolic regulation of transcriptional activity of AP-1 transcription factors as well as the stabilization of c-Fos and c-Jun, and inhibition therapies of proteasome–ubiquitin system have shown also to interaction with NF-kB and AP-1 pathways [37]. Complementary research shows that AP-1 blockade also contributes significantly to the reduction in the production of osteoclastic vascular endothelial

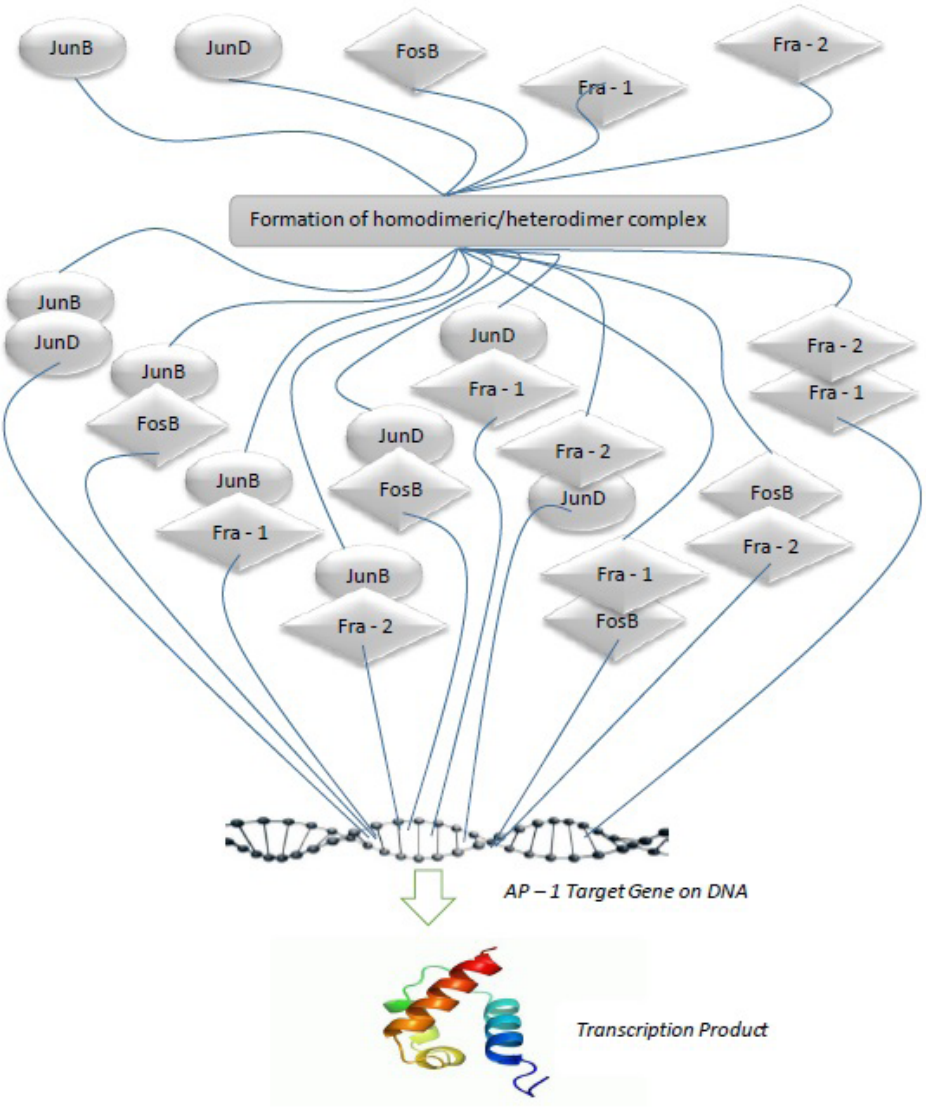

Figure 2. Homodimer/heterodimer complex of Jun and Fos proteins modulate AP-1 gene expression via binding to the AP-1 site on the AP-1 target genes.

growth factor. A transcriptional product of AP-1, vascular endothelial growth factor (VEGF) can promote tumour growth, osteoclastogenesis and angiogenesis, proving its adverse role in tumour cells processes [37]. Hence, inhibiting the osteoclastogenesis in an AP-1- dependent manner may inhibit tumour-induced lytic bone disease. c-Jun N-terminal kinase (JNK)-dependent activation of c-Jun has been shown in accordance with research to also play a significant role in OHT (4-hydroxytamoxifen)-induced cell death of ER-negative SkBr3 breast cancer cells [38]. Results suggest that oxidative stress, generated by NADPH activation, may be an initial OHT-dependent signal resulting in the activation of c-Jun N-terminal kinase (JNK)/c-Jun pathway, and finally apoptosis. OHT (4-hydroxytamoxifen) initiates two distinct signaling pathways converging to activation of the AP-1 complex. Induction of c-Fos expression coupled to c-Jun N-terminal phosphorylation however, is the most frequently encountered paradigm of AP-1 activation in mammalian cells [38]. It is also found that the OHT-induced AP-1 transactivation in an ERK and JNK-dependent manner suggests that AP-1 complex functions in OHT-induced apoptosis of cancer cells. In addition, OHT also proves to foster transcriptional induction of c-Fos expression. Also, it has been shown that active c-Jun is required for the expression of genes that increase mitochondrial outer membrane permeability [38]. The JNK/c-Jun pathway may also contribute to this intrinsic proapoptotic upregulation. Boosting of c-Jun N-terminal phosphorylation pharmacologically may serve as a viable method of sensitizing cancer cells *via* OHT-mediated cell death. Aggregate data demonstrate that AP-1 plays an important role in the pathogenesis of kinase-positive anaplastic large-cell lymphoma (ALK+ ALCL) by the binding of JUNB (JunB) and CJUN (cJun) at their binding sites on the AKT1 promoter. AKT1 promoter has been identified to contain putative AP-1 binding sites, and is a direct transcriptional target of JUNB and CJUN [33]. Research has significantly enlightened us on the posttranslational regulation of AKT and its kinase activity. Previous research shows that JUNB could suppress cell cycle progression *via* upregulation of the cyclin-dependent kinase inhibitor or by direct inhibition of cyclin D1 [33]. Recent research has also reported the repression of c-Fos to cause a decline in AP-1 activity *via* altering the ratio of AP-1 (the positive growth factor) and QM or Jif (both proteins serve as negative growth factor). QM interacts with c-Jun to suppress AP-1 activity [39].

Activator protein-1 has been proven to be a viable point of regulation by Desmoglein 3 (Dsg3), the pemphigus vulgaris antigen, in fostering cancer processes regulation. The cell adhesion protein Dsg3 (one of seven transmembrane desmosomal cadherins), an upstream cell surface activator for AP-1 which is upregulated in squamous cell carcinoma (SCC) is interestingly identified as a tumour-specific marker for head and neck SCC [40]. In addition to a marked increase in c-Jun, S63 phosphorylation is associated with Dsg3-overexpressing cells, where it regulates the activity of c-Jun/AP-1 which contributes to the motility, metastasis and invasion of cancer cells [40].

Epidermal growth factor receptor (EGFR), a 170 kDa single-pass transmembrane tyrosine kinase receptor plays a significant role in the development of many tumour types. Phorbol ester 12-O-tetradecanoyl-phorbol-13-acetate (TPA) and epidermal growth factor (EGF) are relevant ligands that bind to EGFR in a pathway mediated by the EGFR pathway to AP-1 activation [31]. EGF binding to EGFR results in dimerization and autophosphorlylation of EGFR towards activation of various downstream signaling processes [31]. EGFR is not only required for AP-1 induction, but also in the initiation of signaling for the activation of the process. The AP-1 induction by TPA is however, independent of EGFR tyrosine kinase and autophosphorylation of tyrosine [31]. The physiological functions of AP-1 in relation to the growth of cancer are seriously tied to the Fos and Jun family as evident in a lot of cancer types including colon, colorectal and breast cancers [41]. A key member of the tumour necrosis factor (TNF) receptor family, the human death receptor 4 (DR4), also called TRAIL-R1 has also be shown to be regulated by activator protein-1. It modulates the apoptotic pathway on binding to its tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) [42]. It has likewise been shown that some anticancer drugs such as DOX, VP16 and CD437 can increase AP-1 transcriptional activity of the DR4 promoter expression. Evidence suggests that genomic association between AP-1 and AP/TAZ/TEAD at enhancers fuels oncogenic growth [36]**.** YAP/TAZ (nuclear effectors of the Hippo pathway which regulates organ growth in healthy cells and in tumourigenesis) through TEAD factors that form a complex with AP-1, synergistically activating target genes involved in the control of S-phase entry as well as mitosis. Oncogenic growth induced by YAP/TAZ is strongly enhanced by an increased gain of AP-1, and they are potent inducers of cell proliferation and drivers of tumourigenesis [36]. However, AP-1-promoted skin tumourigenesis is observed to be prevented in the absence of YAP/TAZ [36]. Findings show that AP-1 factors are critical modulators of YAP/TAZ/TEAD-dependent gene expression [36]. AP-1 are found in quite a number of YAP/TAZ/TEAD-binding sites, forming a complex of transcription factor

that is bound to composite regulatory elements harboring both the TEAD and the AP-1 motifs [36].

JunD has been demonstrated to be involved in the antiproliferative effect of cannabinoids (the active components of marijuana and their derivatives) on human breast cancer cells by inhibition of cell cycle progression [43]. Experimentally, D9-tetrahydrocannabinol (THC) antiproliferative action in such cells was investigated, and the cannabinoid was shown to be involved in the modulation of JunD. THC activates JunD by upregulating gene expression as well as by translocating the protein into the nuclear compartment, accompanied by a decrease in cell proliferation [43]. Spectacularly, in human non-tumour mammary epithelial cells exposed to THC, there was no JunD activation, nor was there inhibition of proliferation. Similar investigations affirm that endocannabinoid anandamide inhibits human keratinocyte differentiation *via* decreasing AP-1 transcriptional activity and induces apoptosis of human non-tumour liver cells through overexpression of c-Jun and JunB, as well as stimulation of AP-1 DNA binding. JunD activation is thereby summarizezd to reduce the proliferation of cancer cells and plays a delicate role in cannabinoid antiproliferative action [42]**.** Investigations have shown that mitogen-activated protein kinase (MAPK) regulate the AP-1 dimer repertoire through the control of JunB transcription and Fra-2 protein stability [42]. MEKK1 activity could regulate AP-1 protein availability *via* post-translational mechanisms, and lead to the degradation of Fra-2. MEKKs could exert some level of control over gene expression through the regulation of the supply of the necessary transcriptional machinery [35]. Developing small molecular inhibitors of MEKK could serve as potential therapy for cancer types [35]**.** AP-1 has been documented as a key component in the direct regulation of inducible genes such as chemokines. Findings from using gastric epithelial AGS cells infected with H. pylori explains that Ras (the upstream activator for MAPK) and mitogen-activated protein kinase (MAPK) cascade could act as the upstream signaling for the activation of AP-1, which induces chemokine expression [44]**.** Likewise, AP-1 has been shown to regulate breast cancer cell growth through cyclins and E2F factors [45]. The role of cyclin D1 in cancer (breast cancer, in particular) has been well recorded. In the molecular mechanisms terms, inhibition of breast cancer cell growth *via* AP-1 blockade such as Tam67, has revealed that the suppression of cyclin D1 at the mRNA as well as protein levels has been shown to defined this downregulation of the E2F1 and E2F2 (transcriptional factors) which results in reduced binding of E2F protein to the E2F binding site. The blockade also suppresses the expression of the dimerizing partner of E2F, DP1, and results in the less formation of the complex E2F/DP1, which ends up in reduced availability [45]. The AP-1 factor and its binding site at the cyclin D1 promoter directly contribute to the basal promoter activity of the cyclin D1 gene as a fundamental mechanism [45]. The modification of the E2F1, E2F2 and DP1 expression by Tam67 brings into exposure a negative regulation of cyclin D1 expression through the E2F site in cyclin D1 promoter. This reinforces the fact that AP-1 plays a critical role in regulating cell proliferation.

Much hindrance is currently anticipated about managing tongue cancer, however, insight surfaces through assays [A HPV-type specific PCR and reverse line blot (RLB) analysis] designed to demonstrate the role of Activator Protein-1 (AP-1) proteins in the tumourigenesis of tongue cancer in the presence or absence of HPV [46]. Tongue squamous cell carcinoma (TSCC) is one of the most aggressive types of head and neck squamous cell carcinomas (HNSCC) with poor prognosis [47]. The outcome shows a selective participation of c-Jun with Fra-2/c-Fos to promote aggressive tumour phenotypes [48]. Down regulation of Fra-2 causes a decrease in the expression of Fos-2 and Jun-2, and silencing Fra-2 leads to a decrease in the expression of viral oncogenes E6/E7. Evidence shows that there is a decrease in the expression of the proinvasive factor MMP-9 which has been observed to be more pronounced in HPV^{+ve} cells than in HPV^{-ve} cells [48]. High DNA binding ability has also been observed with c-Fos, c-Jun and JunB during tumourigenesis of oral carcinomas [48].

2.3 Voltage-gated Na^+ channles (VGSCs)

In addition to the contributions of histones and activator proteins, the role of proteins in understanding cancer has also been extended to structural proteins such as membrane proteins. Voltage-gated Na^+ channels (a transmembrane proteins) [49], provide evidence of possessing a role in cancer processes through a population-based study. Voltage-gated Na^+ channels (VGSCs)-inhibiting drugs when taken before and during cancer diagnosis increased patient survival chances in those with carcinomas of the breast, bowel and prostate. VGSC-inhibiting drugs such as ranolazin and phenytoin reduce metastasis *in vivo* [50,51]. Also, carbamazepine, flecainide, phenytoin, riluzole, mexiletine and valproate are all VGSC inhibitors that reduced metastatic behaviours of cells. Some VGSC inhibitors such as phenytoin, valproate and carbamazepine could increase the risk of cancer in animal models [50].

2.4 Glycoprotein non-melanoma protein B (Gpnmb)

Different types of cancers have been approached therapeutically and experimentally by targeting the molecules (proteins in particular) that participate in the entire process. A good example is the benefits of Gpnmb (glycoprotein non-melanoma protein B) as well as its significance in non-alcoholic steatohepatitis as a biomarker. This has shed more light on metabolic factors that directly and indirectly affect the thriving of cancer [52]. Gpnmb is a type 1 membrane protein and secreted in its soluble form by ADAM 10-mediated cleavage. Soluble forms of Gpnmb have reportedly been found in various tumour cell lines, osteoblasts and dendritic cells. Gpnmb mRNA is shown to be enhanced during development of cirrhosis and hepatocellular carcinoma [53,54]. There is an outstanding expression of Gpnmb in stellate cells [55] and hepatic macrophages. There is also a direct interaction among Gpnmb and calnexin in hepatic macrophages [53,54].

GPNMB is a cell-surface proteoglycan expressed by melanoma and glioblastoma cells [56,57]. GPNMB [which could also be referred to as osteoactivin, dendritic cell-heparin integrin ligand (DC-HIL), or hematopoietic growth factor inducible neurokinin-1] is composed of three domains [56]. These domains are a single transmembrane domain; a long extracellular domain (ECD), as well as a relatively short cytoplasmic tail. In addition to the diverse roles GPNMB plays in normal cells. In T-cells activation as well as taking part in the specialization of osteoclasts and osteoblasts, GPNMB is strategic in the invasion and metastasis of many cancers types, including colorectal cancer, hepatocellular carcinoma, cutaneous melanoma and breast cancer [56]. Extracellular fragments of GnmpB has been shown to have neuroprotective effects and also possess the ability to activates the PI3K/Akt and MEK/ERK pathways through the Na^+/K^+-ATPase. Fragments of GPNMB found outside the cell bind a receptor/protein (Na^+/K^+-ATPase) on the plasma membrane, which finally activates the PI3K/Akt and MEK/ERK pathways [56]. GPNMB can be activated by a disintegrin and metalloproteases (ADAMs) by cleavage, leading to activation. Alpha subunits of Na^+/K^+-ATPase (NKA), which are the binding partners to the extracellular fragment of GPNMB are the major transporter of Na^+ and K^+ through the plasma membrane of many mammalian cells and are responsible for the homeostasis of high K^+ and low Na^+ concentrations inside the cytoplasm of the cell. This α subunit expression is significantly elevated in glioblastoma, melanoma, colorectal cancers, lung cancers, renal cell carcinoma and hepatocellular carcinomas [56]. GPNMB is critical to the invasion and metastasis of several cancers types, and the knowledge of NKA binding to the extracellular fragments of GPNMB may function as a novel therapeutic target for various cancers. Enhancing the expression of GPNMB pharmacologically has been shown to increase the sensitivity of melanoma cells to CR011-vcMMAE (antibody-drug conjugate) [57]. As stated earlier, GPNMB could be targeted by CR011-vcMMAE, which has been proven *via* previous studies to induce apoptosis in tumour cells expressing GPNMB. GPNMB is often exposed to a partial transcriptional repression within melanoma cells possessing an activated ERK pathway [57]. This could vividly explains the reason why the inhibitors of ERK pathway induce GPNMB expression in melanoma cell lines that harbor NRAS or BRAF mutations; however, this is not the same in a melanoma cell line that possesses a wild-type NRAS/BRAF [57]. From results of previous experiments, it could be suggested here that a synergizing combination of CR011-vcMMAE with compounds that target a different pathway like the ERK pathway may serve as a therapeutically beneficial strategy in growth-inhibitory activity. A long half-life of CR011-vcMMAE for metastatic malignant melanoma and glioblastoma therapy has also been spotted, which will ultimately affect dosage.

2.5 Wnt/β-catenin

With additional credit to proteins, colorectal cancer also receives signs of bailout as novel β-carbolines inhibit Wnt/β-catenin signaling [58,59]. Adult stem cells are maintained in a pluripotent state by Wnt/β-catenin signaling pathway. This pathway is involved in the maintenance of adult homeostasis as well [60]. Initiation and progression of colorectal cancer, caused by mutations in genes that encode adenomatosis polyposis coli, β-catenin and axin have been linked to Wnt/β-catenin pathway [60]. Recent studies on anti-tumour drug development are targeting Wnt/β-catenin pathway [58,60]. In colorectal cancers, Wnt/β-catenin signaling is activated frequently by mutated APC or β-catenin, and the expected ideal antagonist of this pathway would be the transcriptional complex of TCF and β-catenin in the nucleus. To antagonize the Wnt/β-catenin pathway, upstream components of the pathway can be targeted [59,60]. A novel Wnt/β-catenin signaling inhibitor belonging to the β-carboline structure-type compound has been identified and called Z86. Z86 inhibits expressions of endogenous Wnt/β-catenin signaling target genes. It also antagonizes the second axis formation of xenopus

embryos which are induced by Wnt. Z86 also inhibits GSK3β phosphorylation and leads to its over activation. Over activation encourages the phosphorylation and degradation of β-catenin. However, the mechanism Z86 uses to inhibit GSK3β phosphorylation still needs further investigation. Z86 inhibits the growth of colorectal cancer cells by arresting G1 phase of the cell cycle [58]. When Wnt/β-catenin signaling pathway is suppressed, there is inhibition of cell growth which may be achieved by decreased phosphorylation of GSK3β and increased phosphorylation of β-catenin.

2.6 SET (I2PP2A)

Through various studies, SET (also known as I2PP2A, an endogenous inhibitor of PP2A) has been shown to be a multi-regulator of pp2A, thereby marking it out as a target in MyC-driven, P13k/Akt-driven and AR-driven malignancies [61,62]. Therapeutic targeting of SET and P13k/Akt signaling pathway has been shown to be an effective means of suppressing Pten deficient prostate cancer lines [63-65]. Advanced prostate specimens have been found to contain SET expression both in its cystolic and nuclear microenvironment, whereas SET was found almost exclusively in the nuclear microenvironment of benign samples [64]. A study that investigated the expression profile of this phosphoprotein (SET) in prostate cancer progression through quantitative PCR (q-PCR) analysis of cDNA derived from mRNA prostate cancer samples isolated in a commercial array, shows that out of a total number of 40 prostate cancer samples analyzed, 19 samples (47.5%) showed greater than two-fold SET expression over normal cells [64]. The expression was observed to be highest in metastatic samples on further evaluation. Significant elevations in SET RNA expression was also observed in primary tumours and metastases when compared to normal prostate tissues [64]. SET inhibition has been shown to lead to diminished prostate tumourgenesis. Comparative assessment of the impact of SET knockdown and the non-coding shRNA control on human prostate cancer (PC3) cell tumourgenesis revealed that within 20 days of injection, tumour growth was observed in 100% of mice subcutaneously injected with control shRNA-PC3, whereas a single tumour in SET knockdown cohorts at 96 days post implantation was observed [64]. Suggestions of SET expression being critical in the progression of castration resistant prostate cancer are quite true as a study that therapeutically targeted SET using OP449 proved it to be highly efficient at preventing prostate cancer tumourgenesis [64]. Focusing on human prostate cancer cell lines (22RV1, PC3 and C42) that have weak enzalutamide response, the growth kinetics have also been evaluated [64].

2.7 p53 protein

The role of p53 in cancer development over the years cannot be over-emphasized. Aggressive cancer development and changes in gene activity exclusive of changes in DNA sequence (epigenetic) are linked to mutant p53 protein, which has implications for such difficult-to-treat cancers as those in the pancreas and breast [66]. p53 is highly respected as the cellular security of the genome, most especially because it protects cells from physiological stress by piloting the expression of genes that put into effect some of the vital cellular processes such as cycle arrest, apoptosis, and DNA repair and modifications (Figure 3) [70-72]. p53 is an important tumour suppressor protein that kills cancer/tumour cells *via* apoptosis and aging. In many cancer forms, p53 is mutated, leading to severe malignancy. Of all genes in human cancer, p53 has been identified as the most frequently (50%) mutated [70,71,73]. p53 accumulates during DNA damage resulting in cell death, necessitating the regulation of p53 *via* multiple pathways. It codes the blueprint for producing the p53 tumour protein which keeps cells from growing and dividing in an uncontrolled way. When DNA becomes damaged, p53 elicits a series of protective responses to repair the cell; if the damage is too severe, it causes cell suicide. In most cases, a mutant p53 protein is caused by a single mutation in one of DNA building blocks leading to a single amino acid substitution in the p53 protein [66]. In addition to the loss of the normal p53 original function, the substituted forms of p53 could also acquire functions that promote cancer development in a more aggressive way [66]. MicroRNAs (miRNAs) have been outlined as one of the effective regulators of p53 (fig. 3). miRNAs are endogenous, small, noncoding RNAs that are approximately 22 nucleotides in length and can modulate the expression of target genes *via* binding to target messenger RNA. p53 is obviously a major element in overcoming cancer and it is becoming clear to us that miRNAs are vital regulators of cancer-associated genes [70]. p53 activation mediated by the microRNA-29 (miR29) family (a tumour suppressor protein) has been described as one of the vital regulatory pathways in cancer therapy by inducing apoptosis of cancer cells *via* p53 stabilization. miR29 up-regulates p53 activity to induce apoptosis in cancer/tumour cells [70]. We cannot effectively introduce miR29 into cells because miRNA and siRNA have poor

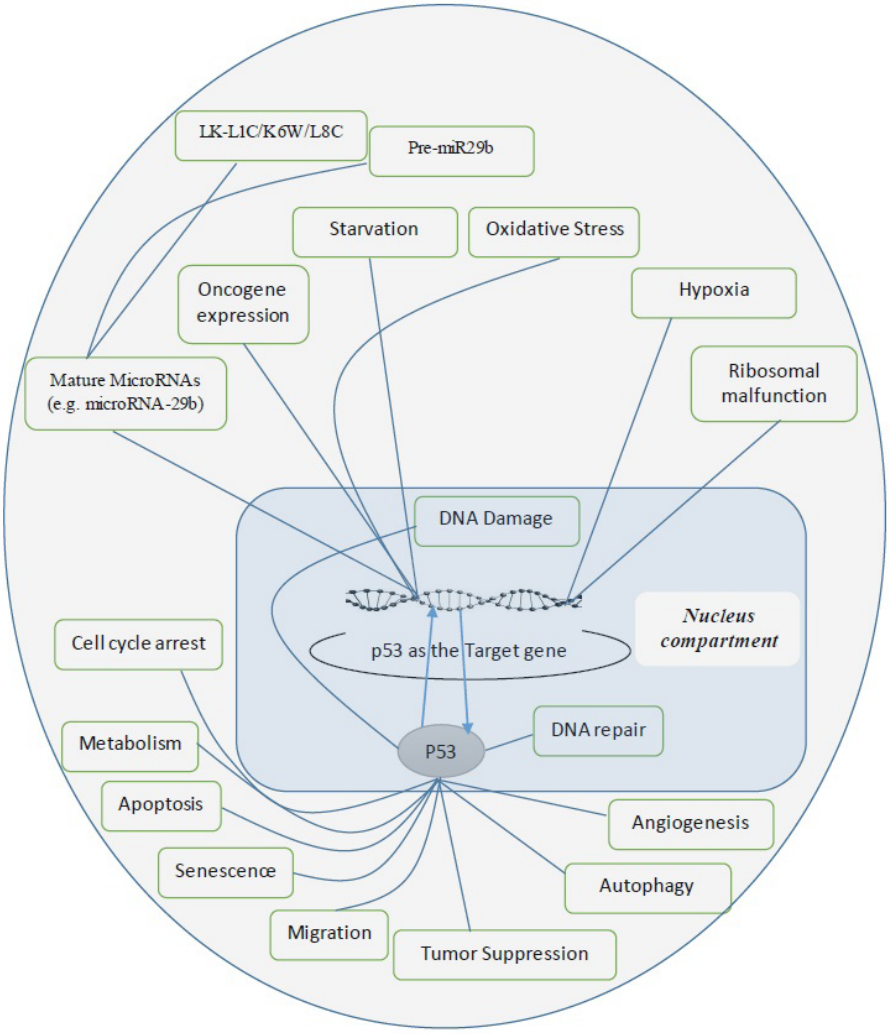

Figure 3. p53 is at the center of many cellular processes that oversee the survival of the cell.

penetration abilities into the cell [70]. As an alternative, amphiphilic peptides which have several benefits that can be easily modified for diverse applications have been used to enhance penetration into intracellular regions as a result of their cationic residues. Synthetic peptides bind to the terminal loop regions of pre-miRNAs, affecting their processing by Dicer. Research has proven LK-L1C/K6W/L8C peptide to be a directed modulator of miR29b-mediated p53 pathway [70]. LK-L1C/K6W/L8C would bind to pre-miR29b to promote its generation of mature miR29b by Dicer, facilitating apoptosis induction *via* improving p53 protein stability in tumour cells. We could opine at this point that LK-L1C/K6W/L8C affects miR29b-p53 pathway directly and it could possibly be a promising candidate for peptide-dependent antitumour drugs. Elevated levels of miR29b results in increased p53 activity that subsequently generates a higher rate of apoptosis in cancer cells.

LK-L1C/K6W/L8C is therefore, most likely to be a potent anticancer peptide and will certainly contribute to the development of novel therapeutic drugs. Leukaemia inhibitory factor (LIF), a cytokine that possesses multiple functions, depending on cell/tissue type, has also been shown to negatively regulate p53 through Stat3/ID1/MDM2 in colorectal cancers (CRC) *via* downregulation [70]. Leukaemia inhibitory factor (LIF) has been recently identified as a p53 target gene, which mediates the role of p53 in maternal implantation in normal physiological conditions [70]. In addition to the role of LIF being an important component of the p53 pathway [70], LIF mediates p53's role in embryonic implantation, induces differentiation of murine myeloid leukaemia cells, inhibits the differentiation of murine embryonic stem cells, and functions in autocrine and/or paracrine pathways. It has been shown that blocking the Stat3 pathway which is frequently activated in many types of cancers largely

abolishes the inhibitory effect of LIF on p53, crucial to the survival and growth of tumour cells. Stat3 can also upregulate MDM2, which is a key negative regulator of p53 protein [70]. Stat3 also induces ID1 transcriptionally to mediate its role in the regulation of p53. In summary, LIF is an important negative regulator of p53 by activating the Stat3/ID1/MDM2 pathway. This in turn fosters chemoresistance in CRC [70]. Therefore, through targeting of LIF, employing Stat3 and ID1 to reactivate p53 is a viable therapeutic strategy to enhance chemosensitivity in CRC, especially in cancers with LIF overexpression.

Lysine demethylase KDM3A in a dual role has been demonstrated to regulate breast cancer cell invasion as well as apoptosis by targeting histone and the non-histone protein p53 [70]. KDM3A, which proved to suppress pro-apoptotic functions of p53 by erasing p53-K372me1 is demonstrated to promote chemoresistance of cancer by demethylating p53. Depletion of KDM3A showed the capability of reactivating mutated p53 to induce the expression of pro-apoptotic genes in breast cancer that has mutant p53 [32]. This suggests that KDM3A might be a potential therapeutic agent for human breast cancer, as well as a prevention strategy. We have established that a good understanding of the actual mechanisms and the particular proteins involved in DNA repair is required to develop therapeutic approaches for cancer and some neurodegenerative disorders such as Alzheimer's disease (AD) (the most common type of dementia and age-related neurodegenerative disease) [71]. It has been shown that SIRT6 expression is decreased in the brains of patients with Alzheimer's disease. Interestingly, research also shows that p53-dependent SIRT6 expression could protect against Aβ42-induced DNA damage [71]. Aβ 42 decreases SIRT6 and p53 levels, which is related to the JNK signaling pathway [71]. Overexpression of SIRT6 is shown to prevent Aβ42-induced DNA damage, and the SIRT6 activators could serve as a novel therapeutic target for AD and cancers.

Phenethyl isothiocyanate (PEITC), a dietary-related compound, has been shown to function in the reactivation of mutant p53 to inhibit tumour growth. PEITC, which is abundantly present in vegetables, has been shown to exert cancer chemopreventive effects in animal models, as well as in humans as supported by epidemiological studies [55]. PEITC has moved through phase 1 and phase 2 clinical trials (http://www.clinicaltrials.gov/ct2/results?term=PEITC). Inhibition of cytochrome P450s has been proposed for PEITC as the mechanism of action. Reactivation of the transactivation functions of p53 mutants presents a promising strategy to target cancer cells selectively. The reactivation of p53 has been shown in mouse model; however, in p53-deficient cells, PEITC is shown to induce apoptosis *via* the activation of extracellular signal-regulated kinases (ERK1/2) [70]. The occurrence of p53 mutations before the ontogenesis of invasive breast cancer suggests the potential of PEITC in the prevention of breast cancer. These findings may bring to light practical, target-based strategies for cancer prevention and therapy.

The pro-tumourigenic/metastatic Six1 homeoprotein has also been reported to decrease p53 levels *via* a dual mechanism involving upregulation of microRNA-27a and downregulation of ribosomal protein L26 (RPL26), of which the latter binds to and inhibits miR-27a [69]. Six1 (a homeodomain containing transcription factor) is a developmental regulator controlling cell migration and invasion, as well as proliferation in progenitor cell populations [69]. In cancer cells such as ovarian, breast, colorectal and hepatocellular carcinoma, it promotes almost the same activities that it regulates during normal cellular development. These findings indicate that Six1 expression which leads to a marked resistance to therapies targeting the p53–MDM2 interaction with a proportional decrease in RPL26 across many types of tumours [69]. Importantly, it is observed that Six1 expression leads to a remarkable resistance to therapies that target the p53–MDM2 interaction. Investigations on cancer cell lines derived from patients tumours with different types of p53 GOF amino acid substitutions to identify what these mutants forms of p53 actually bind in the cancer genome showed, that mutant p53 binds to and activates the group of genes that comprises epigenetic signature, especially those related to histone acetylation and histone methylation [72]. In particular, GOF p53 mutated protein directly targets genes encoding strategic epigenetic enzymes, including MLL1, MLL2 and MOZ. Analysis of The Cancer Genome Atlas (TCGA) data has shown elevated expression of the epigenetic regulatory MLL1, MLL2 and MOZ genes in GOF patient p53 tumours, compared to tumours with normal p53 protein or tumours without the p53 protein [73]. Gene expression is regulated by chemical modifications (including methylation and acetylation) on chromatin groups of proteins called histones, that allow DNA to stretch open and others to tighten the chromatin [72]. These groups change how compact DNA is fashioned in certain regions of the genome, which in turn affects the genes that will be transcribed to RNA and eventually proteins, the first step in many processes including cell proliferation. Normally, as an epigenetic enzyme, MLL1 puts a methyl group on the histone at a place that encourages transcription and favors cellular growth [73,74]. Mutant p53 proteins tap into the MLL1 pathway, leading to genome-

wide histone methylation changes and therefore allowing for uncontrolled cell replication. Altered epigenetic pathways have been implicated in various aspects of cancer which might be a reasonable mechanism for explaining some of the uncontrolled cell replication. This provides the first evidence that GOF mutant p53 directly regulates key epigenetic factors [72]. Cancer cell proliferation is markedly lowered by genetic knockdown of MLL1 or by pharmacological inhibition of the MLL1 methyl transferase complex [73-75]. Interestingly, a new epigenetic mechanism is becoming apparent, studying the progression of tumours with gain-of-function p53 mutations and suggestions on new possibilities for designing combinational chromatin-based therapies in treating individual cancers propelled by prevalent GOF p53 mutation.

2.8 BMPs, BEX, CDK and Protein Kinases

Other prominent roles of proteins in understanding cancer are highlighted in BMPs, BEX, CDK and protein kinases. Bone morphogenetic protein (BMP) family members, such as BMP4 (which functions in suppressing cell growth *in vitro* and *in vivo* invasion, migration, epithelial–mesenchymal transition, mobility, control of cell proliferation, apoptosis, regulation of differentiation, and angiogenesis) seem to be both detrimental and beneficial to the cancer cells. It contributes to cancer pathogenesis as *BMP4* gene variants has been observed to predispose to colorectal cancer [76]. BMPs are extracellular signaling molecules belonging to the superfamily, transforming growth factor β (TGFβ) in vertebrate growth. The suppressive role of BMP4 has suggested it as a potential therapeutic target in cancer treatment [76]. BMP4 expression levels in sporadic cancer, most especially associated with patient prognosis in hepatocellular and ovarian cancer are commonly mutated in many tumour types. However, knowledge of the downstream mediators of BMP4 effects may allow a broader understanding of the different BMP4-induced phenotypes, tailoring specific targeted treatments.

The Brain-Expressed X-linked (BEX) family proteins (BEX1, BEX2, BEX3, BEX4 and BEX5), play a role in neuronal development and are expressed in a wide range of tissues. BEX1 and BEX3 function as tumour suppressors, while BEX2 appears to function as oncogene. BEX1 expression which controls cell surface receptor signaling and reestablishes imatinib response in resistant cells is lost in patients with acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) [77]. Certain subsets of breast cancer and gliomas are characterized by overexpression of BEX3 (acting as tumour promoter) of which increased expression lead to enhanced NF-κB signaling in addition to cell proliferation, and tumour formation, as evident in mouse xenograft models [77]. Efforts are still underway to better understand the role of BEX4 and BEX5.

In a number of cancer types, dysregulation (through a number of mechanisms including gene amplification or rearrangement, epigenetic alterations, loss of negative regulators, and point mutations) of the Cyclin D–cyclin dependent kinase (CDK) 4/6–inhibitor of CDK4 (INK4)–retinoblastoma (Rb) pathway alters the cell cycle processes *via* regulating the G1–S interface, resulting in decreased proliferation, proving its potential to serve as a candidate for cancer therapy [78]. Combining CDK4/6 chemotherapeutic inhibitors with other strategies may provide a breakthrough over-acquired as well as *de novo* therapy resistance. Some of these strategies include endocrine therapy (e.g., palbociclib's [PD-0332991] combination with letrozole); breast cancers phosphatidylinositol 3-kinase (PI3K) pathway regulators for hormone receptor-positive (HR+) cancer; and selective MEK and RAF inhibitors for cancer tumours with modified mitogen activated protein kinase (MAPK) pathway. Ribociclib [LEE011], and abemaciclib [LY2835219] are also approved, and are in late stages of development [78]. Similar to chemotherapeutics, certain protein kinases (found to be involved in the regulation of sarcoma cell progression, such as cell cycle, apoptosis, and survival) with aberrant expression/activity may be involved in sarcoma multidrug resistance (MDR). Targeting protein kinases along with inhibitory chemotherapeutics may be promising in overcoming MDR in sarcoma, by decreasing the proliferation as well as the growth of sarcoma cells, including reversing their resistance, thereby achieving a reduction in the doses of anticancer agents along with the associated side-effects [8]. Sarcomas are credited with approximately 1% of adult and 15% of pediatric cancers, and are commonly treated with surgical resection, chemotherapy and radiotherapy. However, acquired MDR is one of the common outcomes associated with sarcoma cells which attenuates the efficacy of therapy. Therefore, overcoming MDR by targeting protein kinases aimed at reversing the multidrug resistance is a necessity and could be generally applied in a wide variations of cancers towards an effective management. Over time, research in therapeutics aimed at treating cancer has also unintentionally produced byproducts of therapeutic strategies for other types of diseases such as HIV [8,79] and other viral infections that target the human genome.

2.9 Some Remarkable Protein-Protein Interactions (in Gliomas)

Though many of the processes in the cell actually involve a large category of protein-protein interaction, there is the need to point out some outstanding interactions that open a window for researchers to see them as viable targets for cancer therapy. In other words, though many protein-protein interaction exist, not all of such interactions are viable targets for cancer therapy. The discussion here is not pointing to a general protein-protein interaction, but as it relates to cancer development and progression. In cancers affecting the central nervous system, key targets in overcoming chemotherapy resistance in glioma has emerged through a topological robustness analysis of a network of protein-protein interaction [80]. Gliomas are tumours originating from the glial cells of the brain or spine [81], reported to possess a low survival rate even after surgery, chemotherapy and radiation treatments. Acquired resistance to drugs [temozolomide (broad-spectrum drug that shows promise for gliomas)] by gliomas has however, limited the clinical efficacy of the drug, posing as a major challenge to its use [82]. Functional network modules associated with drug resistance (e.g., temozolomide) were identified, which revealed protein-protein interactions within the network [82]. The modules are interrelated with growth factors NGF, PDGF and ErbB; interleukins IL-1, IL-2, IL-5 and IL-6; MAPK, TGF-β immunity related pathways and toll-like receptors. Temozolomide is a popular drug used in the treatment of glioma. Drug (temozolomide) resistant network has become evident to be capable of being distorted by the removal of nodes, with high degree of betweenness as it disrupts the entire protein-protein interactions network, and decreases cell proliferation in temozolomide-resistant cell lines, which can be made obvious upon knock-down of the central nodes. This reveals that these nodes are required for glioma cell viability. A good set of central nodes associated with glioma proliferation and invasion seen through network topology analysis are Map3k14, Mapk1, Hspa5, Atf2, Rac 1, Shc 1, Pik3ca, Akt1, Vim and Egr 1. Inhibition of Mapk1 enhances the effectiveness of temozolomide in brain implanted tumours and lowers the expression of E2f1 which reverses cisplatin resistance [80]. Hence, this reveals the potential therapeutic importance of these proteins in sensitizing glioma cells to drugs (e.g., temozolomide). Thus, investigating nodes with high degree and high betweenness could unravel novel drug targets and tackle chemotherapy resistance, prolonging the life of cancer patients. The roles of these proteins highlighted so far, could also be a means of providing breakthrough in other disease treatments.

3 Conclusion

Proteins occupy a central role in the metabolism of all living cells. As outlined in the central dogma of molecular biology, the genetic information encoded by the DNA is made functional to the cell after translation to proteins or RNA. This makes the protein a prime target for errors as well as for therapy either by direct targeting of the protein involve or by targeting the particular instruction that codes for it in the DNA. Though there is a long list of different forms, conformation and classes of protein that could be of interest, not all proteins have a part to play in cancer processes even though they are necessary for life. Out of the number and variety of proteins that could play a part in cancer biology, a few have been selected to be highlighted in this study. The choice of these proteins is not because they are of more importance than other proteins, but because recent advancement in their existing knowledge has surfaced, as a result of both laboratory and clinical research. These proteins include histones, activator protein – 1, Gnmpb, Wnt/β-catenin, *SET* (I2PP2A), BMPs, BEX, CDK, and Protein Kinases, and p53 protein. We are optimistic that other researchers will as well develop interest in other vital, candidate proteins that we have not highlighted here. Knowledge of these proteins, as demonstrated in this paper, suggests their potential as good targets for therapy either through inhibition or by other therapeutic strategies. Research on these proteins have identified them as viable tools that when fully employed puts us on our way closer to winning the global war against cancer.

List of Abbreviations Used

AACR - American Association for Cancer Research
BEX - Brain-Expressed X-linked
EZH2 - Enhancer of zeste homolog 2
H3K27 - Histone H3 lysine 27
H3K27me3 - Histone H3 trimethyl Lys27
H1, H1.2, H1.2, H1.2, H2A, H2B, H3, H4, and H5 - Main histone proteins involved in the structure of chromatin in eukaryotic cells
PRC2 - polycomb repressive complex 2
PRC1 - polycomb repressive complex 1
MCF-7 - Michigan Cancer Foundation-7
shRNA - short hairpin RNA
LD611 – a bladder cell lines
LNCaP - a prostate cell lines
FISH - Fluorescent *in situ* hybridization
PTGES, XAF1 and OR8S1 – Genes

AP-1 - Activator Protein-1
RLB reverse line blot
TSCC - Tongue squamous cell carcinoma
HNSCC - head and neck squamous cell carcinomas
VGSCs - Voltage-gated Na^+ channels
NAFLD - Non-alcoholic fatty liver disease
Gpnmb - glycoprotein non-melanoma protein B
OLETF - Otsuka Long-Evans Tokushima Fatty
HFHS - high fructose, high sucrose
APC - *adenomatous polyposis coli*
GSK-3β - glycogen synthase kinase-3 beta
SET - a Nuclear. *Phosphoprotein*
MLL1/MLL complex - a multiprotein complex
TGFβ - Transforming growth factor β
BEX - Brain-Expressed X-linked family proteins (BEX1, BEX2, BEX3, BEX4 and BEX5)
BMPs - Bone morphogenetic proteins
CDK - Cyclin D–cyclin dependent kinase
MAPK - mitogen activated protein kinase
MDR - multidrug resistance
AML - acute myeloid leukemia
CML - chronic myeloid leukemia
RNAPII - RNA polymerase II holoenzyme
MCF-7 cells - human breast adenocarcinoma cell line
LNCaP - prostate carcinoma cells
LD611 bladder carcinoma cells
PTGES- Prostaglandin E Synthase
XAF1- a gene in human that encodes the protein XIAP-associated factor 1
OR8S1- olfactory receptor family 8 subfamily S member 1
c-Jun- a protein that in humans is encoded by the *JUN* gene
NGF - Nerve growth factor
PDGF - Platelet-derived growth factor
WAT- white adipose tissue
HbA1c - Hemoglobin A1c -
wnt8 - a gene that encodes two *wnt8* proteins
pp2A - Protein phosphatase 2A
SET - a nuclear *phosphoprotein involved* in transcriptional activation of P450c17
GOF - Germline gain-of-function

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