Genetic and Epigenetic Control of CDKN1C Expression: Importance in Cell Commitment and Differentiation, Tissue Homeostasis and Human Diseases

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Abstract: The CDKN1C gene encodes the p57Kip2 protein which has been identified as the third member of the CIP/Kip family, also including p27Kip1 and p21Cip1. In analogy with these proteins, p57Kip2 is able to bind tightly and inhibit cyclin/cyclin-dependent kinase complexes and, in turn, modulate cell division cycle progression. For a long time, the main function of p57Kip2 has been associated only to correct embryogenesis, since CDKN1C-ablated mice are not vital. Accordingly, it has been demonstrated that CDKN1C alterations cause three human hereditary syndromes, characterized by altered growth rate. Subsequently, the p57Kip2 role in several cell phenotypes has been clearly assessed as well as its down-regulation in human cancers. CDKN1C lies in a genetic locus, 11p15.5, characterized by a remarkable regional imprinting that results in the transcription of only the maternal allele. The control of CDKN1C transcription is also linked to additional mechanisms, including DNA methylation and specific histone methylation/acylation. Finally, long non-coding RNAs and miRNAs appear to play important roles in controlling p57Kip2 levels. This review mostly represents an appraisal of the available data regarding the control of CDKN1C gene expression. In addition, the structure and function of p57Kip2 protein are briefly described and correlated to human physiology and diseases.

Keywords: p57Kip2; CDKN1C; epigenetics; disease; cell differentiation

1. Introduction

A well-orchestrated sequence of events allows the transition between the various phases of cell division cycle and the precise control of a perfect execution and accomplishment of each phase. Central actors in this process are heterodimers formed by cyclin/cyclin-dependent kinase complexes (CDK) whose activity is strictly regulated by a number of factors, including their amount, localization, and post-synthetic modifications (mainly phosphorylations). A further important modulation is due to the interaction with additional inhibitory proteins resulting in the formation of heterotrimers, generally lacking the kinase activity. These proteins are defined CDK inhibitors (CKI) or, alternatively, CDK regulator. One family of CKI, established on the basis of sequence homology and specificity of action,
is named CIP/Kip and includes three members, namely p21\textsuperscript{Cip1/WAF1}, p27\textsuperscript{Kip1} and p57\textsuperscript{Kip2}. Due to their broad inhibitory effect on cyclin-CDK complexes, CIP/Kip members have been mainly considered as antiproliferative proteins and their encoding genes as potential tumor suppressor genes. However, strong emerging pieces of evidence have demonstrated that the activities of CIP/Kip members are well beyond that of modulators of cell division [1]. Indeed, in function of their localization and interactors, CIP/Kip members might regulate a plethora of events including cell differentiation, cell movement, apoptosis, autophagy and all the major steps of carcinogenesis [1]. In addition, the tissue-specific functions of p57\textsuperscript{Kip2} cannot be substituted by other CIP/Kip family members, suggesting that each of them has peculiar roles in cell physiology.

In this brief review, we provide an appraisal of the published data on the p57\textsuperscript{Kip2} protein, that represents the least studied member within the CIP/Kip family. Our attention will be mainly focused on the regulation of \textit{CDKN1C} (the p57\textsuperscript{Kip2} encoding gene) expression and its relevance in human diseases, including overgrowth and undergrowth syndromes.

1.1. p57\textsuperscript{Kip2} Protein

Human \textit{CDKN1C} encodes a 316-amino-acid protein that migrates at 57 kDa by SDS-PAGE electrophoresis, hence the name p57\textsuperscript{Kip2}. p57\textsuperscript{Kip2} is the last identified member of the CIP/Kip family of the cyclin-dependent kinase inhibitors, also including p21\textsuperscript{Cip1/WAF1} and p27\textsuperscript{Kip1} [2,3]. The CIP/Kip proteins share structural similarity mainly related to the common activity of cell cycle regulators. The most characterized Cyclin/CDK inhibitory activity relies on two common features: a CDK binding/inhibitory domain (KID) located at the amino-term and the nuclear localization signal (NLS) at the carboxy terminal of the protein [4]. The KID includes three short peculiar motifs: a cyclin-binding domain, a CDK-binding site and a $\alpha$10 helix that, due to a specific pair of amino acids (phenylalanine-tyrosine), is able to mimic the adenine component of ATP, therefore blocking the catalytic site of CDKs [5]. Similarly to other CIP/Kip members, KID is necessary and sufficient to bind and inhibit CDK activity. Specifically, it has been reported that p57\textsuperscript{Kip2} inhibits the kinase activity of cyclin-CDK complexes in vitro, including cyclin E (A)/CDK2 and cyclin D1,2/CDK4 [2,3,6]. Besides CDKs, several other proteins have been reported to interact with the p57\textsuperscript{Kip2} amino-terminal domain. Particularly, known interactors of p57\textsuperscript{Kip2} at its N-terminal domain are the basic helix-loop-helix transcription factors, such as MyoD, Mash1, NeuroD, and Nex/Math2 [6–8]. Furthermore, p57\textsuperscript{Kip2} interacts, both in vivo and in vitro, with the transcription factor B-Myb, which plays an important role during early embryonic development. Particularly, B-Myb competes with cyclin A2 for binding to p57\textsuperscript{Kip2}, thus determining the release of active cyclin/CDK2 [9].

The carboxy-terminal region of p57Kip2 contains a QT box domain, rich in glutamine and threonine residues, which is homologous to the corresponding QT domain of p27\textsuperscript{Kip1} and can be responsible for further interactions of the protein. It has been reported that the QT box directly binds to c-Jun NH2-terminal kinase/stress-activated protein kinase, determining its inhibition [10,11]. In the QT domain, a consensus sequence for a putative nuclear localization signal (NLS) has been identified [2,3]. Proceeding towards the C-terminal, p57\textsuperscript{Kip2} presents, in homology with p21\textsuperscript{Cip1/WAF1}, a binding domain for the proliferating cell nuclear antigen (PCNA), a cofactor of DNA polymerase delta. Thus, it is able to bind and inhibit PCNA, even though with much lower affinity than p21\textsuperscript{Cip1/WAF1} [12].

Whereas the p57\textsuperscript{Kip2} amino- and carboxy-terminal domains are similar in sequence in mammals, the internal domain, consisting of proline/alanine-rich motifs, results as a peculiarity of human p57\textsuperscript{Kip2}: the PAPA region, a sort of hinge between the N- and the C-end of the protein. It is absent in p21\textsuperscript{Cip1/WAF1} and p27\textsuperscript{Kip1} and is responsible for the difference between the sequence-derived molecular weight and the SDS-PAGE observed molecular weight. The PAPA region is scarcely conserved in mouse and rat, where it is substituted by a proline-rich region followed by an acidic repeat in which glutamic or aspartic acid occur every four amino acids [3]. However, the functional meaning of the PAPA region is still unknown, even though some authors retain that it is important for protein interactions.
A peculiar characteristic of p57\textsuperscript{Kip2} protein is a limited degree of stable secondary and tertiary structures under physiological conditions. Specifically, the protein belongs to the so-called intrinsically unstructured proteins (IUPs), which can adopt different conformations upon binding to distinct and specific interactors. This property is shared with its siblings p21\textsuperscript{Cip1/WAF1} and p27\textsuperscript{Kip1}, and with numerous proteins involved in the control of cell proliferation. As a matter of fact, more than 70\% of human cancer-associated proteins are IUPs. This conformational flexibility allows a considerable versatility in terms of biomolecular interactors, expanding the range of their functions and, in turn, their involvement in numerous cellular processes [1]. On the other hand, post-synthetic changes of an IUP, like (but not only) phosphorylations, might play a fundamental role in guiding the protein towards specific interactions and specific functions. So far, only few phosphorylation sites have been identified in human p57\textsuperscript{Kip2} protein, such as threonine 310 (T310). Particularly, T310 phosphorylation has been suggested as being important for human protein degradation [1] and level control. Specifically, in analogy with p27\textsuperscript{Kip1} threonine 187 phosphorylation [13], the phosphorylation on T310 determines a phosphodegron which functions as a recognition site for the substrate recognition subunit (S-phase kinase-associated protein 2, Skp2) of the E3 ubiquitin ligase SCF complex (Skp1/Cul1/F-box protein). The Skp2-SCF complex guides target proteins to proteosomal degradation in a cell cycle-dependent manner (from late G1 to early M phase) and its activity appears strongly deregulated in human cancers [12]. Furthermore, besides the Skp2-SCF complex, the activity of the SCF-FBL12 complex, whose substrate recognition subunit (FBL12) is different from Skp2, has been reported to be involved in TGF\textbeta\textsuperscript{1}-induced p57\textsuperscript{Kip2} ubiquitin-dependent proteosomal degradation in osteoblast cells [14].

1.2. p57\textsuperscript{Kip2} in Embryonic and Adult Tissues

p57\textsuperscript{Kip2}, unlike the other two CKIs, shows a fine-tuned temporal and spatial expression from embryogenesis up to the adult life. p27\textsuperscript{Kip1} and p57\textsuperscript{Kip2} are widely expressed during embryogenesis. p27\textsuperscript{Kip1} is more abundant in ovary, testis, thymus, spleen, and developing retina, instead, p57\textsuperscript{Kip2} is mostly localized in cartilage, skeletal muscle, palate, pancreas, and intestine. Interestingly, the CKIs show a complementary expression pattern in several embryonic areas. Indeed, in the adrenal gland, p27\textsuperscript{Kip1} is only expressed in the medulla, while p57\textsuperscript{Kip2} is exclusively found in the cortex [2,3,15,16]. In contrast, p21\textsuperscript{Cip1/WAF1} is highly expressed in terminally differentiated cells of adult tissues rather than in embryonic cells [17,18], except for the embryonic carcass where there is an extensive muscle differentiation [18–20].

In adult tissues, p21\textsuperscript{Cip1/WAF1} and p27\textsuperscript{Kip1} are widely expressed, whereas p57\textsuperscript{Kip2} is detectable only in a restricted subset of mouse and human tissues/organisms, such as placenta, fat, kidney, ovary, adrenal gland, endometrium, lung, prostate, brain, kidney, pancreas, testis, heart, and skeletal muscle [2,3,16]. In most tissues, p57\textsuperscript{Kip2} is expressed at a low level. This may reflect the heterogeneity of some of these tissues where only certain cell types express the protein. The highest expression level is found in human placenta, particularly in the villus section of placenta, together with other genes involved in growth and tissue remodeling, like IGF2 and GPC3 [21]. In mice, during placental development, p57\textsuperscript{Kip2} is expressed in giant trophoblast cells. Therefore, p57\textsuperscript{Kip2} has been postulated to be involved in the allocation of maternal nutrients through the placenta [22,23]. Since human placenta lacks a cell type equivalent to the giant trophoblast cell, the function of p57\textsuperscript{Kip2} in human placenta might be different and further investigations appear necessary [24].

p57\textsuperscript{Kip2} level declines, in most organs, before birth, whereas p27\textsuperscript{Kip1} expression persists after birth and throughout adult life, suggesting that p57\textsuperscript{Kip2} is important during early organogenesis [15]. The crucial role of p57\textsuperscript{Kip2} in embryogenesis is corroborated by the finding that \textit{CDKN1C} knockout mice (p57\textsuperscript{KO}) die after birth with only less than 10\% of the mutant mice surviving until weaning. p57\textsuperscript{KO} mice show severe defects such as macroglossia, cleft palate, omphalocele, and gastrointestinal abnormalities, skeletal muscle and endochondral ossification defects, adrenocortical hyperplasia, lens cell hyperproliferation and apoptosis [25,26]. p57\textsuperscript{KO} mice also present several placental abnormalities, including trophoblastic dysplasia [27,28]. Conversely, p21\textsuperscript{KO} mice develop normally [29,30] and
p27\(^{\text{KO}}\) mice do not present gross developmental defects, even though the protein is expressed during embryogenesis and it is required for development. However, p27\(^{\text{KO}}\) mice display organ hyperplasia and tumorigenesis, consistent with the expected function of inhibitor of cell proliferation [31–33]. The importance of a proper control of p57\(^{\text{kip2}}\) dosage is also evident in mice that express a twofold level of p57\(^{\text{kip2}}\). They show an increase of embryonic lethality and a decreased body size [25,28]. Furthermore, the replacement of Cdkn1c with Cdkn1b (p57\(^{\text{KO}}\rightarrow\text{p27\(^{\text{KO}}\)}) cannot completely compensate for the specific role of p57\(^{\text{kip2}}\). In general, p27\(^{\text{kip1}}\) knock-in corrected many of the abnormalities observed in p57\(^{\text{KO}}\) mice, except for omphalocele, dysplasia of placenta and renal papilla [34]. This evidence supported the opinion that most of the functions performed by both p27\(^{\text{kip1}}\) and p57\(^{\text{kip2}}\) proteins during development are attributable to the CKI role through their conserved N-terminal KID domain. Thus, the phenotypic differences noticed in p27\(^{\text{kip1}}\) and p57\(^{\text{kip2}}\) mice most probably reflect both their different spatiotemporal expression patterns and the diverse cellular behavior towards an incomplete cell cycle inhibition [34]. However, it is also possible that the C-terminus domain of both CKIs plays similar functions or affects superimposable pathways. In addition, it should be taken into consideration that p57\(^{\text{KO}}\)→p27\(^{\text{KI}}\) mice express non-physiological levels of p27\(^{\text{kip1}}\).

In adult tissues, all the three CIP/Kip proteins are specifically expressed in terminally differentiated cells, but, of great interest, also in certain undifferentiated quiescent stem cells, probably because of their CKI activity. The finding that most p57\(^{\text{KO}}\) mice die soon after birth represented an obstacle for the characterization of p57\(^{\text{kip2}}\) function in adult tissues. This issue has been overcome by the generation of conditional KO mice. So far, the tissue-specific deletion of Cdkn1c has been performed only in adult hematopoietic stem cells (HSCs) and in neural stem cells (NSCs), evidencing the pivotal role of p57\(^{\text{kip2}}\) in the quiescence and maintenance of adult stem cells [35,36].

Among hematopoietic cell populations, p57\(^{\text{kip2}}\) is the only CKI to be prevalent in a pool of cells with long-term repopulating capability [37] and hematopoietic-specific ablation of p57\(^{\text{kip2}}\) in adult mice determines a clear depletion of the HSC population [35]. On the contrary, p21\(^{\text{Cip1/WAF1}}\) seems to be mainly important in regulating HSC cell cycle during stress condition when DNA is damaged [38,39]; instead, p27\(^{\text{kip1}}\) has limited activities, but becomes more effective in later committed progenitors [38]. In vitro experiments partially confirmed the in vivo observations. High p57\(^{\text{kip2}}\) mRNA and protein expression have been reported in the HSC side population, especially in c-kit(+)/Sca-1(+)/Lineage-SP cells and p57\(^{\text{kip2}}\) has been designated as responsible for the cell cycle blockage since its downregulation is required for S phase entry [37,40]. Moreover, RNA-sequencing analysis of HSC populations derived from a mouse model with a lacZ knock-in at Mds1 and Evi1 complex locus, which eliminates the ME domain, has revealed the silencing of p57\(^{\text{kip2}}\) expression and it is correlated with the reduction in the number of HSCs and a complete loss of long-term repopulation capacity [41]. Similar pieces of evidence have been obtained later by analyzing CKIs activities in NSCs. p21\(^{\text{KO}}\) and p27\(^{\text{KO}}\) mice show an increased proliferation of intermediate progenitor cells rather than of NSCs in the dentate gyrus of the hippocampus, where the two CKIs are barely expressed [42,43]. In contrast, p57\(^{\text{kip2}}\) is abundant in NSCs and its expression decreases when these cells become committed and proliferative. Conditional deletion of p57\(^{\text{kip2}}\) resulted initially in a transient recruitment of NSCs into the cell cycle, thus activating neurogenesis in brain of both young and aged mice, and later in an excessive depletion of the quiescent NSC population and impairment of hippocampal neurogenesis [36]. The new “disposable stem cell model” proposed recently by Encinas, might explain this phenomenon. During youth, the generation of new neurons is abundant in brain and progressively decreases with age. NSCs, upon activation, asymmetrically divide for limited rounds and then terminally differentiate into astrocytes, thus, dramatically reducing the pool of NSCs [44].

In vitro experiments reveal a dual role of p57\(^{\text{kip2}}\): one is related to the division capability of adult stem cells and the other one to differentiation. Indeed, p57\(^{\text{kip2}}\) mRNA and protein have been reported to be increased during differentiation of cerebral cortical precursor [45], oligodendrocytes [46], keratinocytes [47,48], podocytes [49] and skeletal myoblasts [50–52]. Skeletal muscle has a certain regenerative potential, given the presence of the satellite cells, which are muscle progenitor cells
that become activated following muscle injury, thus progressing through self-renewal, proliferation, differentiation, and fusion with pre-existing mature muscle fibers to replenish the lost muscle tissue [53]. In skeletal muscle cells, p57<sup>Kip2</sup> participates in the balancing of progenitor cell maintenance with muscle differentiation [54]. Indeed, Cdkn1c is upregulated in murine G<sub>0</sub> muscle satellite cells, and its inhibition is needed for satellite cell proliferation [55,56].

Data supporting a possible functional repair of the cardiac tissue have been accumulated over the last decades [57]. Indeed, this hypothesis relies also on the presence of cardiac progenitor cells, named cardiac stem cells (CSCs). The block of cell cycle progression in murine c-kit<sup>+</sup> CSCs is due to a complex signaling which involves also the upregulation of Cdkn1c [58]. Moreover, experimental evidence in mice demonstrated that cell cycle withdrawal in neonatal cardiomyocytes is associated with an increased expression of p57<sup>Kip2</sup>, p21<sup>Cip1/WAF1</sup>, and p27<sup>Kip1</sup> and that in adult cardiomyocytes, silencing CDK inhibitors, including p57<sup>Kip2</sup>, induces cell cycle re-entry [59–61]. In addition, studies in transgenic mouse reported a cardioprotective effect of ventricular-specific overexpression of p57<sup>Kip2</sup> with no side-effects on heart development [62]. Interestingly, also studies on zebrafish demonstrated that the repression of p57<sup>Kip2</sup> expression promotes heart regeneration [63].

Importantly, several pathways have been reported to modulate the expression of p57<sup>Kip2</sup> [64]. TGFβ/Smad signaling upregulates p57<sup>Kip2</sup> expression in HSCs, mediating the maintenance of hematopoietic stem cells [65], while it has been reported to induce p57<sup>Kip2</sup> degradation in osteoblasts [14]. On the contrary, Wnt/β-catenin and Notch/Hes pathways are reported to reduce p57<sup>Kip2</sup> expression in several cell types. For example, in midbrain dopaminergic neurons, Wnt1 downregulates p57<sup>Kip2</sup> [66], in lens epithelium [67] and in pancreas [68] Notch effectors suppress p57<sup>Kip2</sup> expression. However, the general picture is complex and difficult to understand due to the cross-talk and overlapping of different signal pathways.

1.3. CDKN1C Mapping and Structure

CDKN1C is localized, in humans, at the 11p15.5 locus and includes four exons and three introns (Figure 1). CDKN1C alternative splicing results in the formation of three mature mRNAs that have the same open reading frame, but different untranslated regions [69,70]. Human 11p15.5 locus contains numerous genes subjected to an imprinting modulation (Figure 1).
Figure 1. Structure of human 11p15.5 locus, CDKN1C gene, p57kip2 mRNA and p57kip2 protein. Panel (A) The panel shows the structure of the 11p15.5 locus with details of the KCNQ1 exon organization (in blue boxes). KCNQ1OT1 gene is included in the KCNQ1 gene and transcribed in a different direction. The ICR2 region is shown in orange; Panel (B) The figure shows the structure of CDKN1C gene and p57kip2 mRNA. In addition, at the bottom of the figure, it is represented the domain organization of p57kip2 protein and the sequence of the KID (kinase inhibitory domain).

Importantly, the homolog region in mouse (i.e., the distal region of chromosome 7) shows an equal cluster of linked genes, arguing for the significance of their coordinate regulation and for the presence of maintained regulatory mechanisms [71,72].

The human 11p15.5 gene cluster might be divided into two distinct domains, both presenting a specific “in cis” acting ICR (Imprinted Control Region). The centromeric domain of the cluster is 800 kb long and is controlled by ICR2. The domain includes, in addition to CDKN1C, KCNQ1 (KvLQT1 or potassium voltage-gated channel, KQT-like subfamily member 1), KCNQ1OT1 (also known as LIT1, KCNQ1-overlapping transcript 1 or long QT intronic transcript 1), PHLDA2 (Pleckstrin homology-like domain family A member 2) and SLC22A18 (Solute carrier family 22 member 18).

Structurally, ICR2 maps inside KCNQ1 intron 10 and is methylated on the maternal chromosome; it encompasses the promoter for the non-coding RNA Kcnq1ot1 (antisense to KCNQ1) (Figure 1) [73].

ICR1 is telomeric and regulates the imprinting of H19 (a gene for a long noncoding RNA) and IGF2 (encoding for insulin-like growth factor 2) by restricting the access to the enhancers (i.e., ICR1 is a chromatin insulator) [74]. Interestingly several of these genes have distinct imprinting. Indeed, IGF2 is paternally expressed, H19 is maternally transcribed, and CDKN1C is maternally expressed, even though a weak expression of the paternal allele has been demonstrated in some human tissues [75].

Two main promoter elements have been identified in mouse Cdkn1c that are similar in humans. First, a proximal promoter element (−165 to +15 from the transcriptional start site) contains several consensus sequences for Egr1 and Sp1 [52,76]. Intriguingly, both transcription factors are ubiquitously expressed and have been reported to regulate other members of the CIP/Kip family of CDK inhibitors [77,78]. Furthermore, a binding site for GATA2, a transcription factor playing a pivotal role in hematopoiesis, particularly in early and late stages of erythropoiesis, and in the TGF-β-response has also been described [79]. Finally, this promoter region also contains recognition sequences for the transcriptional repressors CTIP2/Bcl11b, implicated in the developmental process and carcinogenesis, and the T-box transcription factor TBX3, which is involved in the tissue patterning and differentiation during embryonic development and is up-regulated in a plethora of cancers [80]. Importantly, the accessibility of the reported transcriptional modulators to the CDKN1C promoter is strongly
influenced by the high presence of CpG islands, located upstream and downstream of the transcription start site, responsible for genomic imprinting and epigenetic gene silencing. This is achieved by CpG dinucleotide methylation and/or through chromatin remodeling by histone covalent modifications (histones H3 and H4 methylation and acetylation) [81]. More distal promoters have also been identified. They embrace E-boxes or E-box-like motifs for the interaction with basic-HLH proteins, including activators, like TCF4/E2-2 [82], E47 [83], Smad1/Atf2 complex [84], repressors, as Hes1 (a Notch effector) that, in intestinal crypt progenitor cells, inhibits Cdkn1c transcription by binding to a site located at −3300 [85], or Hes-related repressor protein Herp2 that acts as transcriptional repressor of CDKN1C in proliferating lens epithelial cells [67]. Furthermore, a glucocorticoid response element is located 5076 to 5062 bases upstream of the transcription start site of the human CDKN1C gene and is responsible for the glucocorticoid inducibility of the CDKN1C gene [86], thus explaining, at least in part, the antiproliferative effect of dexamethasone in human tumor cells such as Hela cell line [87].

In mouse, additional key elements of Cdkn1c transcription are located distantly from the gene. As a matter of facts, enhancers for its expression lie more than 25 kb downstream of the gene. Experiments with artificial chromosome also suggest the existence of enhancer(s) located very distantly from CDKN1C [88]. Accordingly, in humans, it has been suggested the presence of numerous CDKN1C enhancer elements localized in a region between 255–387 kb [89].

2. Control of CDKN1C Transcription

CDKN1C lies in humans and mice in a very complicated cluster of imprinted genes, controlled through superimposed cis-acting mechanisms. Genomic imprinting is an epigenetic process that results in parent-of-origin specific allelic expression [90]. A relatively small subset of genes within the mammalian genome (0.4%) is imprinted [91,92] showing a mono-allelic expression either in specific phenotypes of the whole organism or in peculiar tissues that favors the maternal (e.g., CDKN1C and UBE3A) or the paternal allele (e.g., DLK1 and NNDT) [93]. Imprinted expression is initially determined by differential DNA methylation that is established in the germline [94].

Regarding CDKN1C, its transcription is regulated by the imprinting center KvDMRI that acquires DNA methylation in the maternal germline [69,95,96]. This differentially methylated region spans the promoter of the paternally expressed long non-coding RNA Kcnq1ot1 required for continuous domain-wide imprinting. The CDKN1C promoter and gene body are also directly methylated on the paternal allele post-fertilization, after allelic silencing has been established [97].

Besides cis-acting mechanisms responsible for the imprinted silencing of the paternal allele (briefly summarized in the previous paragraph), trans-acting mechanisms participate in the epigenetic modulation of CDKN1C gene expression [98]. Indeed, a complex interplay among DNA methylation and post-translational modifications of histones contributes to the chromatin dynamics at the promoter and in CDKN1C gene body.

2.1. DNA CpG Island Methylation

CDKN1C gene is included in a CpG island extended about −600 bp from the transcriptional start site up into the gene body. This CpG island presents, in mice but not in humans, a differential methylation between the two inherited alleles, being the paternal one hypermethylated and the maternal one hypomethylated. This methylation pattern seems to be acquired successively to the ICR2-dependent DNA-modifications and is involved in the maintenance and reinforcement of the imprinted repression of the paternal allele. Several regulators have been involved in this process. One of them is Lsh (lymphoid-specific helicase) a protein belonging to the family of SNF2/helicases that act as chromatin remodeler and regulate DNA methylation. Lsh directly binds to CDKN1C promoter and allows the maintenance of hypermethylation of the paternal allele [99].

Complete biallelic hypermethylation occurs in human tumors and tumor cell lines [100,101], as well as in some undifferentiated tissues and cell types such as skeletal myoblasts. In this cell model,
the activation of the transcription factor MyoD drives DNA demethylation on the maternal allele, therefore allowing the Myo-D-dependent expression of p57<sup>Kip2</sup> [102].

Most interesting is also the role played by different members of the DNA methyltransferase (DNMT) family, the enzymes catalyzing the transfer of methyl groups to cytosines. Results from genetic ablation studies support the notion that not only DNMT1, mostly in charge of maintaining the methylation pattern of CpG islands during DNA replication, but also DNMT3a which is generally involved (together with DNMT3b) in de novo methylation of most imprinting control regions in the germline, are involved in CDKN1C promoter methylation. As matter of fact, both DNMT1 [56,103], and DNMT3a [56] have been found associated with CDKN1C promoter. Consistently with the importance of DNA methylation not only in paternal allele imprinting but also in p57<sup>Kip2</sup> expression modulation in specific cellular and cell cycle phase contexts, treatment of many human tumor cell lines with demethylating agents such as 5-azacytidine and 5-aza-2′-deoxycytidine results generally in p57<sup>Kip2</sup> expression activation [102,104].

2.2. Histone Marks

Histone modifications represent fundamental factors involved in chromatin plasticity, controlling gene promoter accessibility and gene expression activation [105,106]. Acetylation and methylation of core histone tails, in addition to DNA methylation, are key mechanisms for regulating CDKN1C transcription. Accordingly, the level of H3 and H4 acetylation directly correlates with the gene expression and, in turn, with several phenotypes including differentiation and carcinogenesis.

Specifically, a decrease of H3 lysine 4 dimethylation and histone H3 lysine 9 and 14 acetylation is observed on the paternal allele respect to the maternal one, facilitating its inactivation [107,108]. On the other hand, histone acetylation results to be increased on the paternal locus at the level of KvDMR1, following the expression of the long non-coding RNA and the corresponding CDKN1C inactivation [81].

Under various conditions, a direct correlation between CDKN1C expression and H3K9/K14 acetylation has been demonstrated. For example, cancer cells with low (or absent) p57<sup>Kip2</sup> present histone hypoacetylation and, vice versa, tumors with a high level of the CKI show hyperacetylation [109,110]. These findings are confirmed by the re-expression of p57<sup>Kip2</sup> after histone deacetylase (HDAC) inhibitor treatment [76]. Mechanistically, these changes involve the binding of HDACs, mostly HDAC1 and HDAC2, to the CDKN1C promoter region. We must underline that HDAC1 is highly expressed in many cancers including gastric [111], colorectal [112], hepatic [113], breast [114], and pancreatic cancer [115]. HDAC2 has been found mutated in colon cancer [116] and is overexpressed in esophageal [117], prostate [118], and gastrointestinal carcinomas [119].

An additional recognized histone epigenetic mark includes a lysine trimethylation, specifically H3K27me3 (trimethylation of lysine 27 of histone H3). Such a modification, also responsible for the paternal allele exclusion, is involved in the maturation of glial cells [120].

This histone trimethylation mark is due to the Polycomb repressive complex 2 (PRC2). The increase of H3K27me3 reduces CDKN1C expression, while its decrease, due to a reduction in the levels or activity of EZH, a specific promoter-binding PRC2 subunit, up-regulates gene transcription [121].

Di- and trimethylation of lysine 9 of the histone H3, an additional histone modification, also appears to control the expression of KvDMR1 on the maternal locus, while it is not present on the paternal allele, in accord with the imprinted silencing of the paternally-derived allele [107,108].

In the same context, it is important to stress the role of histone modifications in MyoD control of CDKN1C expression. As matter of fact, an altered accumulation of H3K9me2 on the maternal KvDMR1 allele results in the lack of response to MyoD in that it reduces the accessibility of the transcription factor to the DNA [102].
In brief, the regulation of \textit{KvDMR1} due to epigenetic factors (methylation of DNA, acetylation/methylation of histones) appears a key mechanism in the control of \textit{CDKN1C} expression. The last several years have identified the existence of a strict crosstalk between all the epigenetic modifications, including the binding of modifying enzymes to the specific sites of action. In this complex interplay, an important role for non-coding RNAs has emerged.

2.3. LncRNA Involvement in Epigenetic Regulation

As for many genes playing fundamental roles in development, \textit{CDKN1C} gene expression is controlled by lncRNAs, which act in strict crosstalk with signal pathway-induced transcription factors and chromatin modifiers, accounting for spatial- and temporal-specific gene activation during development or cell commitment and differentiation in adult life. Specifically, the macro lncRNA Kcnq1ot1, first discovered both in humans and mice as a \textit{KvDMR1}-associated RNA, has emerged as a critical regulator of the chromatin status of the gene, at least in relation to the imprinting control [122]. \textit{KCNQ1} and \textit{KCNQ1OT1} share a region of overlapping DNA and are transcribed in opposite directions. \textit{KCNQ1} encodes the potassium voltage-gated channel subfamily Q member 1, a protein required for the repolarization phase of the cardiac action potential. Differently from \textit{KCNQ1} that allows the synthesis of a protein, \textit{KCNQ1OT1} codifies a long-noncoding RNA that regulates the expression of several genes. Its promoter is normally hypermethylated in the maternal allele, thus hampering its expression. On the contrary, the paternal allele is normally transcribed, being hypomethylated [72,123]. When expressed, the long non-coding RNA remains in the nucleus where it is able to act on its own chromosome (i.e., it acts on \textit{chromatin in cis}). Mechanistically, it is able to interact with histone methyltransferase complexes (like G9a, Suz12, and Ezh2) causing the enrichment of repressive histone modifications. This activity results in the epigenetic inactivation of paternally inherited \textit{CDKN1C} [124]. Kcnq1ot1 is also able to bind DNMT1, allowing the hypermethylation of \textit{CDKN1C} promoter and therefore implementing the repression of gene expression [103].

Additional long non-coding RNAs, like Tug1 (taurine upregulated gene 1) [125], Linc00668 [126] and HEIH-coding RNA [127] have been reported to modulate \textit{CDKN1C} expression. Tug1 is a long non-coding RNA mostly occurring in the retina and in the brain. It has been proposed to control cell growth by epigenetically down-regulating \textit{CDKN1C}. In addition, Tug1 seems to predict a negative prognosis in gastric cancer [125]. These data indicate that lncRNAs regulate p57\textsuperscript{kip2} at the cellular level probably acting in a phenotype-specific manner.

3. \textit{CDKN1C} Expression and Human Diseases

Genetic and epigenetic disorders in the imprinted region 11p15 and \textit{CDKN1C} mutations can lead to embryonic abnormalities, such as those occurring in Beckwith-Wiedmann syndrome (BWS; OMIM 130650), IMAGe syndrome (OMIM 614732) and Russell–Silver syndrome (RSS-OMIM 180860) and acquired diseases such as cancer.

3.1. Human Developmental Disorders

BWS, IMAGe syndrome and RSS are genetic diseases with different features, belonging to the group of congenital imprinting disorders. BWS has a prevalence of 1–5:10,000 live births and is characterized by overgrowth, tumor predisposition, abdominal wall defects and congenital malformations such as macroglossia, hemihyperplasia, hyperinsulinemic hypoglycemia, ear anomalies, nephrogenic and capillary malformations and organomegaly [128]. Epigenetic and genetic alterations in the imprinting cluster on chromosome 11p15.5 are responsible for up to 80% of BWS cases.

They include epigenetic alterations such as methylation defects, specifically loss of methylation at IC2 regulatory region (IC2-LoM) and gain of methylation at IC1 (IC1-GoM), as well as genetic alterations including uniparental paternal disomy of the 11p15.5 locus (UPD), followed by a lower percentage of cases with microdeletion/duplications or point mutations involving either one of the two ICRs responsible for the locus imprinting region [129–131]. Of interest, in BWS patients without
methylation defects, CDKN1C gene mutations are frequently noticed [132], reaching the 50–70% in familial BWS cases. Although with a lower occurrence, CDKN1C mutations are also reported in sporadic BWS cases and they have been identified as the causative genetic alterations [128,133]. Missense/nonsense mutations are reported along the entire sequence of the gene, leading to increased proliferation and risk of cancer [134,135]. Interestingly, these (epi) genotypes have been associated with specific phenotypes which discriminate mainly between overgrowth in pre- or postnatal age (Figure 2) [129].

![Figure 2. CDKN1C gene alterations in hereditary syndromes and human cancers.](image)

Opposite to BWS, IMAGe (Intrauterine growth retardation, Metaphyseal dysplasia, congenital Adrenal hypoplasia, and Genital anomalies) syndrome is a rare condition (www.orpha.net) in which a cluster of CDKN1C missense mutations in the PCNA binding domain, result in growth inhibition) [136]. Interestingly, BWS and IMAGe, are characterized by loss of function and gain of function mutations of CDKN1C, respectively [136,137].
Imprinting alterations in the 11p15 region are also described in RSS, a disease (prevalence of 1–30:100,000 live birth) characterized by intrauterine growth retardation, very limited postnatal growth, skeletal abnormalities such as peculiar craniofacial characteristics and body asymmetry, and several minor malformations. Moreover, in RSS is also reported a maternal duplication in this region [138,139] and methylation alterations of imprinted genes on chromosome 7 [140]. Moreover, in one case of RSS a CDKN1C mutation affecting the PCNA binding domain has been found [141].

3.2. Human Cancers

Gene encoding cyclin-dependent inhibitors are frequently altered in human tumors. Among them, INK4 family represents the most clear paradigm [142,143]. The discovery of the involvement of p57Kip2 in BWS and in some human tumors suggests that p57Kip2, like p27Kip1, might also have a role in the process of carcinogenesis (Figure 2) [144]. Based on the roles played by the protein in the nuclear compartment, currently, it is considered a tumor suppressor; however, differently from p27Kip1 [143], somatic mutations have been rarely reported in tumors [145,146], underlining the importance of p57Kip2 expression control as the main cause of its altered levels in cancer. Particularly, a downregulation of CDKN1C is generally reported in cancer including gastric [147] and urothelial cancer [148,149], pancreatic adenocarcinomas [150], adrenocortical [151], lung [152], and breast cancer [153] as well as several leukemias [154]. Moreover, many authors have attributed to the p57Kip2 levels a value of prognostic marker since a decrease of its expression has been correlated to a poor prognosis [153,155]. As described above, different epigenetic and genetic mechanisms can modulate the expression of CDKN1C. Essentially, loss of imprinting, DNA methylation and post-translational modifications of histones in the promoter region as well microRNAs downregulate CDKN1C in human cancers. Among them, the main cause of reduction of p57Kip2 in cancers is generally the increased methylation of the large CpG islands localized in the CDKN1C promoter [81,150,153,156]. Particularly, the promoter methylation of CDKN1C has been found critical in hematological malignancies such as acute lymphoblastic leukemia [157,158] and large B cell lymphoma [104]. Recently, Zohny and colleagues have proposed as diagnostic markers of breast cancer the expression levels of p21CIP1/Waf1 and p57Kip2 combined with the promoter methylation of CDKN1C, since they found a silenced expression of the two CKIs and a hypermethylation of CDKN1C promoter in more than 50% of the breast cancer specimens analyzed, together with no hypermethylation at promoter of p21CIP1/Waf1-coding gene [159]. Moreover, several miRNAs have been reported to control p57Kip2 mRNA levels. miR21 downregulates CDKN1C in prostate cancer [160], miR25 in gastric cancer and glioma [161,162] and miR92b in brain tumors [163]. Furthermore, miR221/222 are reported to reduce p57Kip2 and p27Kip1 expression in hepatocarcinoma [164], in glioblastoma [165], in oral cancer [166], in colorectal cancer [167] and B-cell malignancies EBV-associated [168]. Experimental data confirmed, at least in ovarian cancers, the specific action of miR-221/222 on CDKN1C [169]. A further putative mechanism at the basis of CDKN1C down-regulation might be related to an increased rate of protein degradation, mainly due to the Skp2 overexpression, as frequently observed in human cancers. However, the relevance of Skp2-dependent degradation of p57Kip2 in carcinogenesis is still debated.

3.3. Other CDKN1C-Related Human Diseases

Gestational diseases, such as pre-eclampsia and intra-uterine growth restriction (IUGR), are also associated with altered p57Kip2 expression. Pre-eclampsia and IUGR are associated respectively with downregulation [170] and upregulation [171] of CDKN1C, underlining that a correct control of gene transcription is required for the proper development and progression of the pregnancy. p57Kip2, as reported above, is abundantly expressed in placental tissues, and, therefore, its dysregulated expression, in humans, is associated with placental mesenchymal and vascular proliferative disorders, such as placental mesenchymal dysplasia (PMD), and complete and partial hydatidiform moles [172,173].
Importantly, placentomegaly due to abnormal proliferation of extravillous trophoblasts, and accumulation of intervillous fibrinoid can be observed also in BWS syndrome [172,174].

PMD is a rare condition (0.02% pregnancies) associated with different fetal outcomes, ranging from structurally normal fetus/newborn (in most cases) to fetal and neonatal abnormalities, including those present in BWS, and mortality [175]. Indeed, PMD and BWS are associated in one-third of cases and paternal uniparental disomy at IGF2 and CDKN1C locus has been proposed as the genetic link between them [176–178].

The identification of p57Kip2 as an important player in these placental diseases has led to the development of diagnostic procedures based on immunohistochemistry using anti-p57Kip2 antibodies and histological analysis for the characterization of hydatidiform moles and PMD, and their differential diagnosis [179–181]. Although some human diseases may represent very different clinical entities, some common pathways may be identified in their etiopathogenesis. This could be the case for cancer, metabolic diseases and related cardiovascular disease [182–184]. Indeed, p57Kip2, among others, may provide a similar origin for neoplastic proliferation and metabolic disorders. p57Kip2 is specifically expressed in the endocrine portion of the pancreas and particularly in β-cells where it is paternally imprinted [185]. In focal hyperinsulinism of infancy, a syndrome characterized by hyperinsulinemic hypoglycemia, p57Kip2 is not expressed within the focal adenomatous hyperplastic lesions. This missing expression is caused by somatic loss of heterozygosity and associated with increased proliferation of β-cells [185]. On this basis, p57Kip2 negative human pancreatic islets restored proper glucose control when transplanted into hyperglycemic, immunodecient mice [186]. Interestingly, a gain-of-function mutant of p57Kip2 is associated with early-adulthood-onset diabetes, in addition to intrauterine growth restriction and short stature [187]. Not only glucose metabolism but also lipid metabolism could be affected by the genetic dosage of CDKN1C. In fact, a double dose of Cdkn1c promoted the brown adipose tissue development in a mouse model of the RSS [188]. Conversely, a loss-of-function mutation of p57Kip2, in the same model, hindered completely the formation of brown adipocytes [188].

The expression of p57Kip2 may also change according to genetic variations that do not pertain to CDKN1C, the p57Kip2-coding gene but are located in neighboring genomic sites. In particular, a mutation has been identified at the KCNQ1 locus that increases the expression of p57Kip2 in mouse pancreatic islets by epigenetically modifying Cdkn1c [189]. Differently from the maternally transmitted CDKN1C diseases, this mutation is effective only when inherited from the paternal allele and, no matter which is the mechanism increasing the levels of p57Kip2 in the endocrine pancreas, β-cell mass is reduced [189].

Thus, it is conceivable that altering p57Kip2 expression could be a promising therapeutic strategy also in humans with type 2 diabetes and/or obesity. Indeed, oral administration of FTY720, a sphingosine 1-phosphate receptor agonist, normalizes glycemia in diabetic db/db mice by downregulating islet p57Kip2 and promoting β-cell regeneration [190]. However, body weight significantly increased in treated animals. Probably, tissue-specific targeting of p57Kip2 should be pursued, in order to avoid undesired effect in either pancreatic or adipose tissue when trying to manipulate p57Kip2 in one of the two tissues.

4. Future Directions

It has been clearly established that p57Kip2 plays pivotal and specific roles in human physiology that cannot be replaced by the other two members of its protein family, i.e., p27Kip1 and p21Cip/WAF1. As a matter of fact, CDKN1C-deleted mice show a very high percentage of mortality demonstrating that the protein is necessary for correct embryogenesis. Accordingly, in humans, three important syndromes, all showing an altered growth, are due to CDKN1C alterations. Particularly, the BWS is characterized by signs of overgrowth with infants considerably larger than normal and the IMAGe and RSS are both characterized by slow growth before and after birth and growth retardation.
It is well known that adult stem cells settle specific niches in different tissues and organs, thus supporting their repair/regeneration [57,191–193]. In this regard, p57\textsuperscript{Kip2} has been discovered as a very important factor [36,56,61,63,194].

The molecular mechanisms by which p57\textsuperscript{Kip2} is so important for a normal growth and tissue differentiation, are still not well understood. They refer, only in part, to the capability of the protein to modulate cyclin/CDK activity, a function that is played approximately by the first 100 residues of p57\textsuperscript{Kip2} where the KID is localized. On the other hand, numerous activities of CKI have been associated with the C-end region that includes the PAPA domain and the QT domain. These protein domains seem to be involved in the control of cell movement and the organization of mitotic spindle (via interaction with the cytoskeleton). Numerous pieces of evidence also suggest that p57\textsuperscript{Kip2} C-terminus participates in endoreduplication, apoptosis, autophagy, and senescence. Altogether these observations point to the definite identification of p57\textsuperscript{Kip2} interactors as a pivotal issue in the studies on CKI. Unfortunately, the protein belongs to the family of IUP, namely, proteins lacking a tertiary structure that fold upon binding. This structural feature allows p57\textsuperscript{Kip2} to have a large degree of plasticity and to interact with several different proteins. Although this is certainly a great advantage in terms of function, it results in remarkable difficulties in the precise definition of the mechanism of p57\textsuperscript{Kip2} action. An additional important aspect of p57\textsuperscript{Kip2} studies is the knowledge of processes that regulate its level. CDKN1C is subject to an epigenetic control and only the maternal allele is expressed. The gene lies in a locus, 11p15.5, that represents a major example of regional imprinting and that is strongly regulated by mechanisms acting in cis (i.e., directly on DNA structure) as well as in trans (namely via DNA methylation and histone acetylation). An additional level of intracellular control of p57\textsuperscript{Kip2} amount could be related to the protein degradation that involves, a not completely clarified, ubiquitination/proteasomal mechanism.

In conclusion, while the important role of p57\textsuperscript{Kip2} is clear, the details of its regulation and interactors appear enigmatic and intensive research and the development of novel cellular and animal models are required. This is particularly relevant in view of the plethora of p57\textsuperscript{Kip2} functions played in different tissues and distinct phenotypes both in normal and pathological conditions. It is conceivable that the elucidation of these aspects will provide important directions for human physiologic research and for the development of novel strategies for targeted therapy of several relevant human diseases.

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**Abbreviations**

- **BWS** Beckwith-Wiedmann syndrome
- **CSC** Cardia stem cell
- **CDK** Cyclin-dependent kinase
- **CKI** CDK inhibitor
- **DNMT** DNA methyltransferase
- **HSC** Hematopoietic stem cell
- **ICR** Imprinted control region
- **IGF2** Insulin-like growth factor
- **HDAC** Histone deacetylase
- **IUGR** Intra-uterine growth restriction
- **IUP** Intrinsically unstructured protein
- **KID** CDK binding/inhibitory domain
- **LSH** Lymphoid-specific helicase
- **NLS** Nuclear localization signal
NSC  Neural stem cell
PCNA  Proliferating cell nuclear antigen
PMD  Placental mesenchymal dysplasia
PRC2  Polycomb repressive complex 2
p57KO  CDKN1C knockout
p57KO,p27KI  CDKN1C knockout + CDKN1B knockin
RSS  Russell-Silver syndrome
Skp2  S-phase kinase-associated protein 2
SCF  Skp1/Cul1/F-box
TUG  Taurine upregulated gene 1
T310  Threonin 310

References

1. Borriello, A.; Caldarelli, I.; Bencivenga, D.; Criscuolo, M.; Cucciolla, V.; Tramontano, A.; Oliva, A.; Perrotta, S.; Della Ragione, F. p57(Kip2) and cancer: Time for a critical appraisal. Mol. Cancer Res. 2011, 9, 1269–1284. [CrossRef] [PubMed]

2. Lee, M.H.; Reynisdottir, I.; Massague, J. Cloning of p57KIP2, a cyclin-dependent kinase inhibitor with unique domain structure and tissue distribution. Genes Dev. 1995, 9, 639–649. [CrossRef] [PubMed]

3. Matsuoka, S.; Edwards, M.C.; Bai, C.; Parker, S.; Zhang, P.; Baldini, A.; Harper, J.W.; Elledge, S.J. p57KIP2, a structurally distinct member of the p21CIP1 Cdk inhibitor family, is a candidate tumor suppressor gene. Genes Dev. 1995, 9, 650–662. [CrossRef] [PubMed]

4. Fotedar, R.; Fitzgerald, P.; Rousselle, T.; Cannella, D.; Doré, M.; Messier, H.; Fotedar, A. p21 contains independent binding sites for cyclin and cdk2: Both sites are required to inhibit cdk2 kinase activity. Oncogene 1996, 12, 2155–2164. [CrossRef] [PubMed]

5. Hashimoto, Y.; Kohri, K.; Kaneko, Y.; Morisaki, H.; Kato, T.; Ikeda, K.; Nakanishi, M. Critical role for the 310 helix region of p57(Kip2) in cyclin-dependent kinase 2 inhibition and growth suppression. J. Biol. Chem. 1998, 273, 16544–16550. [CrossRef] [PubMed]

6. Reynaud, E.G.; Guillier, M.; Leibovitch, M.P.; Leibovitch, S.A. Dimerization of the amino terminal domain of p57Kip2 inhibits cyclin D1-cdk4 kinase activity. Oncogene 2000, 19, 1147–1152. [CrossRef] [PubMed]

7. Vaccarello, G.; Figliola, R.; Cramerotti, S.; Novelli, F.; Maione, R. p57Kip2 is induced by MyoD through a p73-dependent pathway. J. Mol. Biol. 2006, 356, 578–588. [CrossRef] [PubMed]

8. Joseph, B.; Andersson, E.R.; Vlachos, P.; Södersten, E.; Liu, L.; Teixeira, A.I.; Hermanson, O. p57Kip2 is a repressor of Mash1 activity and neuronal differentiation in neural stem cells. Cell Death Differ. 2009, 16, 1256–1265. [CrossRef] [PubMed]

9. Joaquin, M.; Watson, R.J. The cell cycle-regulated B-Myb transcription factor overcomes cyclin-dependent kinase inhibitory activity of p57(Kip2) by interacting with its cyclin-binding domain. J. Biol. Chem. 2003, 278, 44255–44264. [CrossRef] [PubMed]

10. Chang, T.S.; Kim, M.J.; Ryoo, K.; Park, J.; Eom, S.J.; Shim, J.; Nakayama, K.I.; Nakayama, K.; Tomita, M.; Takahashi, K.; et al. p57KIP2 modulates stress-activated signaling by inhibiting c-Jun NH2-terminal kinase/stress-activated protein Kinase. J. Biol. Chem. 2003, 278, 48092–48098. [CrossRef] [PubMed]

11. Yamamoto, T.; Digumarti, H.; Aranbayeva, Z.; Wataha, J.; Lewis, J.; Messer, R.; Qin, H.; Dickinson, D.; Osaki, T.; Schuster, G.S.; et al. EGCG-targeted p57/KIP2 reduces tumorigenicity of oral carcinoma cells: Role of c-Jun N-terminal kinase. Toxicol. Appl. Pharmacol. 2007, 224, 318–325. [CrossRef] [PubMed]

12. Watanabe, H.; Pan, Z.Q.; Schreiber-Agus, N.; DePinho, R.A.; Hurwitz, J.; Xiong, Y. Suppression of cell transformation by the cyclin-dependent kinase inhibitor p57KIP2 requires binding to proliferating cell nuclear antigen. Proc. Natl. Acad. Sci. USA 1998, 95, 1392–1397. [CrossRef] [PubMed]

13. Borriello, A.; Cucciolla, V.; Criscuolo, M.; Indaco, S.; Oliva, A.; Giovane, A.; Bencivenga, D.; Iolascon, A.; Zappia, V.; Della Ragione, F. Retinoic acid induces p27Kip1 nuclear accumulation by modulating its phosphorylation. Cancer Res. 2006, 66, 4240–4248. [CrossRef] [PubMed]

14. Kim, M.; Nakamoto, T.; Nishimori, S.; Tanaka, K.; Chiba, T. A new ubiquitin ligase involved in p57KIP2 proteolysis regulates osteoblast cell differentiation. EMBO Rep. 2008, 9, 878–884. [CrossRef] [PubMed]
15. Nagahama, H.; Hatakeyama, S.; Nakayama, K.; Nagata, M.; Tomita, K.; Nakayama, K. Spatial and temporal expression patterns of the cyclin-dependent kinase (CDK) inhibitors p27Kip1 and p57Kip2 during mouse development. Anat. Embryol. 2001, 203, 77–87. [CrossRef] [PubMed]

16. Fagerberg, L.; Hallström, B.M.; Oksvold, P.; Kampf, C.; Djureinovic, D.; Odeberg, J.; Habuka, M.; Tomlinson, P.; Danielsson, A.; Edlund, K.; et al. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. Mol. Cell. Proteom. 2014, 13, 397–406. [CrossRef] [PubMed]

17. Macleod, K.; Sherry, N.; Hannon, G.; Beach, D.; Tokino, T.; Kinzler, K.; Vogelstein, B.; Jacks, T. p53-dependent and independent expression of p21 during cell growth, differentiation, and DNA damage. Genes Dev. 1995, 9, 935–944. [CrossRef] [PubMed]

18. Parker, S.B.; Eichele, G.; Zhang, P.; Rawls, A.; Sands, A.T.; Bradley, A.; Olson, E.N.; Harper, J.W.; Elledge, S.J. p53-independent expression of p21Cip1 in muscle and other terminally differentiating cells. Science 1995, 267, 1024–1027. [CrossRef] [PubMed]

19. Halevy, O.; Novitch, B.G.; Spicer, D.B.; Skapek, S.X.; Hannon, G.J.; Beach, D.; Lassar, A.B. Correlation of terminal cell cycle arrest of skeletal muscle with induction of p21 by MyoD. Science 1995, 267, 1018–1021. [CrossRef] [PubMed]

20. Fredersdorf, S.; Milne, A.W.; Hall, P.A.; Lu, X. Characterization of a panel of novel anti-p21Waf1/Cip1 monoclonal antibodies and immunohistochemical analysis of p21Waf1/Cip1 expression in normal human tissues. Am. J. Pathol. 1996, 148, 825–835. [CrossRef] [PubMed]

21. Sood, R.; Zehnder, J.L.; Druzin, M.L.; Brown, P.O. Gene expression patterns in human placenta. Proc. Natl. Acad. Sci. USA 2006, 103, 5478–5483. [CrossRef] [PubMed]

22. Tunster, S.J.; Van de Pette, M.; John, R.M. Fetal overgrowth in the Cdkn1c mouse model of Beckwith-Wiedemann syndrome. Dis. Models Mech. 2011, 4, 814–821. [CrossRef] [PubMed]

23. Tunster, S.J.; van de Pette, M.; John, R.M. Impact of genetic background on placental glycogen storage in mice. Placenta 2012, 33, 124–127. [CrossRef] [PubMed]

24. Enders, A.; Carter, A.M. What can comparative studies of placental structure tell us?—A review. Placenta 2004, 25 (Suppl. A), S3–S9. [CrossRef] [PubMed]

25. Yan, Y.; Frisen, J.; Lee, M.H.; Massagué, J.; Barbacid, M. Ablation of the CDK inhibitor p57Kip2 results in increased apoptosis and delayed differentiation during mouse development. Genes Dev. 1997, 11, 973–983. [CrossRef] [PubMed]

26. Zhang, P.; Liégeois, N.J.; Wong, C.; Finegold, M.; Hou, H.; Thompson, J.C.; Silverman, A.; Harper, J.W.; DePinho, R.A.; Elledge, S.J. Altered cell differentiation and proliferation in mice lacking p57KIP2 indicates a role in Beckwith-Wiedemann syndrome. Nature 1997, 387, 151–158. [CrossRef] [PubMed]

27. Zhang, P.; Wong, C.; DePinho, R.A.; Harper, J.W.; Elledge, S.J. Cooperation between the Cdk inhibitors p27(KIP1) and p57(KIP2) in the control of tissue growth and development. Genes Dev. 1998, 12, 3162–3167. [CrossRef] [PubMed]

28. Takahashi, K.; Nakayama, K.; Nakayama, K. Mice lacking a CDK inhibitor, p57Kip2, exhibit skeletal abnormalities and growth retardation. J. Biochem. 2000, 127, 73–83. [CrossRef] [PubMed]

29. Deng, C.; Zhang, P.; Harper, J.W.; Elledge, S.J.; Leder, P. Mice lacking p21CIP1/WAF1 undergo normal development, but are defective in G1 checkpoint control. Cell 1995, 82, 675–684. [CrossRef] [PubMed]

30. Brugarolas, J.; Chandrasekaran, C.; Gordon, J.I.; Beach, D.; Jacks, T.; Hannon, G.J. Radiation-induced cell cycle arrest compromised by p21 deficiency. Nature 1995, 377, 552–557. [CrossRef] [PubMed]

31. Fero, M.L.; Rivkin, M.; Tasch, M.; Porter, P.; Carow, C.E.; Firpo, E.; Polyak, K.; Tsai, L.H.; Broudys, V.; Perlmutter, R.M.; et al. A syndrome of multiorgan hyperplasia with features of gigantism, tumorsogenesis, and female sterility in p27(Kip1)-deficient mice. Cell 1996, 85, 733–744. [CrossRef]

32. Kiyokawa, H.; Kineman, R.D.; Manova-Todorova, K.O.; Soares, V.C.; Hoffman, E.S.; Ono, M.; Khanam, D.; Hayday, A.C.; Frohman, L.A.; Koff, A. Enhanced growth of mice lacking the cyclin-dependent kinase inhibitor function of p27(Kip1). Cell 1996, 85, 721–732. [CrossRef]

33. Nakayama, K.; Ishida, N.; Shirane, M.; Inomata, A.; Inoue, T.; Shishido, N.; Horii, I.; Loh, D.Y.; Nakayama, K. Mice lacking p27(Kip1) display increased body size, multiple organ hyperplasia, retinal dysplasia, and pituitary tumors. Cell 1996, 85, 707–720. [CrossRef]

34. Susaki, E.; Nakayama, K.I. Functional similarities and uniqueness of p27 and p57: Insight from a knock-in mouse model. Cell Cycle 2009, 8, 2497–2501. [CrossRef] [PubMed]
35. Matsumoto, A.; Takeishi, S.; Kanie, T.; Susaki, E.; Onoyama, I.; Tateishi, Y.; Nakayama, K.; Nakayama, K.I. p57 is required for quiescence and maintenance of adult hematopoietic stem cells. Cell Stem Cell 2011, 9, 262–271. [CrossRef] [PubMed]

36. Furutachi, S.; Matsumoto, A.; Nakayama, K.I.; Gotoh, Y. p57 controls adult neural stem cell quiescence and modulates the pace of lifelong neurogenesis. EMBO J. 2013, 32, 970–981. [CrossRef] [PubMed]

37. Yamazaki, S.; Iwama, A.; Takayanagi, S.; Morita, Y.; Eto, K.; Ema, H.; Nakamura, H. Cytokine signals modulated via lipid rafts mimic niche signals and induce hibernation in hematopoietic stem cells. EMBO J. 2006, 25, 3515–3523. [CrossRef] [PubMed]

38. Cheng, T.; Rodrigues, N.; Shen, H.; Yang, Y.; Dombrowski, D.; Sykes, M.; Scadden, D.T. Hematopoietic stem cell quiescence maintained by p21cip1/waf1. Science 2000, 287, 1804–1808. [CrossRef] [PubMed]

39. van Os, R.; Kammenga, L.M.; Ausema, A.; Bystrykh, L.V.; Draijer, D.P.; van Pelt, K.; Doutte, B.; de Haan, G. A Limited role for p21Cip1/Waf1 in maintaining normal hematopoietic stem cell function. Stem Cells 2007, 25, 836–843. [CrossRef] [PubMed]

40. Umemoto, T.; Yamato, M.; Nishida, K.; Yang, J.; Tano, Y.; Okano, T. p57Kip2 is expressed in quiescent mouse bone marrow side population cells. Biochem. Biophys. Res. Commun. 2005, 337, 14–21. [CrossRef] [PubMed]

41. Zhang, Y.; Stehling-Sun, S.; Lezon-Geyda, K.; Juneja, S.C.; Coillard, L.; Chatterjee, G.; Wuertzer, C.A.; Camargo, F.; Perkins, A.S. PR-domain-containing Msd1-Evi1 is critical for long-term hematopoietic stem cell function. Blood 2011, 118, 3853–3861. [CrossRef] [PubMed]

42. Pechnick, R.N.; Zonis, S.; Wawrowsky, K.; Pourmorady, J.; Chesnokova, V. p21Cip1 restricts neuronal proliferation in the subgranular zone of the dentate gyrus of the hippocampus. Proc. Natl. Acad. Sci. USA 2008, 105, 1358–1363. [CrossRef] [PubMed]

43. Qu, J.; Takagi, Y.; Harada, J.; Topalkara, K.; Wang, Y.; Sims, J.R.; Zheng, G.; Huang, P.; Ling, Y.; Scadden, D.T.; et al. p27Kip1 constrains proliferation of neural progenitor cells in adult brain under homeostatic and ischemic conditions. Stem Cells 2009, 27, 920–927. [CrossRef] [PubMed]

44. Encinas, J.M.; Michurina, T.V.; Peunova, N.; Park, J.H.; Tordo, J.; Peterson, D.A.; Fishell, G.; Koulakov, A.; Enikolopov, G. Division-coupled astrocytic differentiation and age-related depletion of neural stem cells in the adult hippocampus. Cell Stem Cell 2011, 8, 566–579. [CrossRef] [PubMed]

45. Tury, A.; Mairret-Coello, G.; DiCicco-Bloom, E. The cyclin-dependent kinase inhibitor p57Kip2 regulates cell cycle exit, differentiation, and migration of embryonic cerebral cortical precursors. Cereb. Cortex 2011, 21, 1840–1856. [CrossRef] [PubMed]

46. Dugas, J.C.; Ibrahim, A.; Barres, B.A. A crucial role for p57(Kip2) in the intracellular timer that controls oligodendrocyte differentiation. J. Neurosci. 2007, 27, 6185–6196. [CrossRef] [PubMed]

47. Martinez, L.A.; Chen, Y.; Fischer, S.M.; Conti, C.J. Coordinated changes in cell cycle machinery occur during keratinocyte terminal differentiation. Oncogene 1999, 18, 397–406. [CrossRef] [PubMed]

48. Gosselet, F.P.; Magnaldo, T.; Culerrier, R.M.; Sarasin, A.; Ehrhart, J.C. BMP2 and BMP6 control p57(Kip2) expression and cell growth arrest/terminal differentiation in normal primary human epidermal keratinocytes. Cell Signal. 2007, 19, 731–739. [CrossRef] [PubMed]

49. Hiromura, K.; Haseley, L.A.; Zhang, P; Monkawa, T.; Durvasula, R.; Petermann, A.T.; Alpers, C.E.; Mundel, P.; Shankland, S.J. Podocyte expression of the CDK-inhibitor p57 during development and disease. Kidney Int. 2001, 60, 2235–2246. [CrossRef] [PubMed]

50. Figliola, R.; Maione, R. MyoD induces the expression of p57Kip2 in cells lacking p21Cip1/Waf1: Overlapping and distinct functions of the two cdk inhibitors. J. Cell. Physiol. 2004, 200, 468–475. [CrossRef] [PubMed]

51. Reynaud, E.G.; Pelpel, K.; Guillier, M.; Leibovitch, M.P.; Leibovitch, S.A. p57(Kip2) stabilizes the MyoD protein by inhibiting cyclin E-Cdk2 kinase activity in growing myoblasts. Mol. Cell. Biol. 1999, 19, 7621–7629. [CrossRef] [PubMed]

52. Figliola, R.; Busanello, A.; Vaccarello, G.; Maione, R. Regulation of p57(KIP2) during muscle differentiation: Role of Egr1, Sp1 and DNA hypomethylation. J. Mol. Biol. 2008, 380, 265–277. [CrossRef] [PubMed]

53. Zullo, A.; Mancini, F.P.; Schleip, R.; Wearing, S.; Yahia, L.; Klingler, W. The interplay between fascia, skeletal muscle, nerves, adipose tissue, inflammation and mechanical stress in musculo-fascial regeneration. J. Gerontol. Geriatr. 2017, 65, 271–283.
54. Zalc, A.; Hayashi, S.; Auradé, F.; Bröhl, D.; Chang, T.; Mademtzoglou, D.; Mourikis, P.; Yao, Z.; Cao, Y.; Birchmeier, C. Antagonistic regulation of p57kip2 by Hes/Hey downstream of Notch signaling and muscle regulatory factors regulates skeletal muscle growth arrest. *Development* **2014**, *141*, 2780–2790. [CrossRef] [PubMed]

55. Fukada, S.; Uezumi, A.; Ikemoto, M.; Masuda, S.; Segawa, M.; Tanimura, N.; Yamamoto, H.; Miyagoe-Suzuki, Y.; Takeda, S. Molecular signature of quiescent satellite cells in adult skeletal muscle. *Stem Cells* **2007**, *25*, 2448–2459. [CrossRef] [PubMed]

56. Naito, M.; Morì, M.; Inagawa, M.; Miyata, K.; Hashimoto, N.; Tanaka, S.; Asahara, H. Dnmt3a Regulates Proliferation of Muscle Satellite Cells via p57Kip2. *PLoS Genet.* **2016**, *12*, e1006167. [CrossRef] [PubMed]

57. Sommese, L.; Zullo, A.; Schiano, C.; Mancini, F.P.; Napoli, C. Possible Muscle Repair in the Human Cardiovascular System. *Stem Cell Rev* **2017**, *13*, 170–191. [CrossRef] [PubMed]

58. Johnson, A.M.; Kartha, C.C. Proliferation of murine c-kit(pos) cardiac stem cells stimulated with IGF-1 is associated with Akt-1 mediated phosphorylation and nuclear export of FoxO3a and its effect on downstream cell cycle regulators. *Growth Factors* **2014**, *32*, 53–62. [CrossRef] [PubMed]

59. Zhang, Y.; Mignone, J.; MacLellan, W.R. Cardiac Regeneration and Stem Cells. *Physiol. Rev.* **2015**, *95*, 1189–1204. [CrossRef] [PubMed]

60. Evans-Anderson, H.J.; Alfieri, C.M.; Yutzey, K.E. Regulation of cardiomyocyte proliferation and myocardial growth during development by FOXO transcription factors. *Circ. Res.* **2008**, *102*, 686–694. [CrossRef] [PubMed]

61. Di Stefano, V.; Martelli, F. Removing the brakes to cardiomyocyte cell cycle. *Cell Cycle* **2011**, *10*, 1176–1177. [CrossRef] [PubMed]

62. Haley, S.A.; Zhao, T.; Zou, L.; Klysik, J.E.; Padbury, J.F.; Kochilas, L.K. Forced expression of the cell cycle inhibitor p57KIP2 in cardiomyocytes attenuates ischemia-reperfusion injury in the mouse heart. *BMC Physiol.* **2008**, *8*, 4. [CrossRef] [PubMed]

63. Xiao, C.; Gao, L.; Hou, Y.; Xu, C.; Chang, N.; Wang, F.; Hu, K.; He, A.; Luo, Y.; Wang, J.; et al. Chromatin-remodelling factor Brg1 regulates myocardial proliferation and regeneration in zebrafish. *Nat. Commun.* **2016**, *7*, 13787. [CrossRef] [PubMed]

64. Borriello, A.; Caldarelli, I.; Bencivenga, D.; Cucciolla, V.; Oliva, A.; Usala, E.; Danise, P.; Ronzoni, L.; Perrotta, S.; Della Ragione, F. p57Kip2 is a downstream effector of BCR-ABL kinase inhibitors in chronic myelogenous leukemia cells. *Mol. Cell. Biol.* **2006**, *26*, 53–62. [CrossRef] [PubMed]

65. Scandura, J.M.; Boccuni, P.; Massagué, J.; Nimer, S.D. Transforming growth factor beta-induced cell cycle arrest of human hematopoietic cells requires p57KIP2 up-regulation. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 15231–15236. [CrossRef] [PubMed]

66. Castelo-Branco, G.; Wagner, J.; Rodriguez, F.J.; Kele, J.; Sousa, K.; Rawal, N.; Pasolli, H.A.; Fuchs, E.; Kitajewski, J.; Arenas, E. Differential regulation of midbrain dopaminergic neuron development by Wnt-1, Wnt-3a, and Wnt-5a. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 12747–12752. [CrossRef] [PubMed]

67. Jia, J.; Lin, M.; Zhang, L.; York, J.P.; Zhang, P. The Notch signaling pathway controls the size of the ocular lens by directly suppressing p57Kip2 expression. *Mol. Cell. Biol.* **2007**, *27*, 7236–7247. [CrossRef] [PubMed]

68. Georgia, S.; Soliz, R.; Li, M.; Zhang, P.; Bhushan, A. p57 and Hes1 coordinate cell cycle exit with self-renewal of pancreatic progenitors. *Dev. Biol.* **2006**, *298*, 22–31. [CrossRef] [PubMed]

69. Hatada, I.; Mukai, T. Genomic imprinting of p57KIP2, a cyclin-dependent kinase inhibitor, in mouse. *Nat. Genet.* **1995**, *11*, 204–206. [CrossRef] [PubMed]

70. Potikha, T.; Kassem, S.; Haber, E.P.; Ariel, I.; Glaser, B. p57Kip2 (cdkn1c): Sequence, splice variants and unique temporal and spatial expression pattern in the rat pancreas. *Lab. Investig.* **2005**, *85*, 364–375. [CrossRef] [PubMed]

71. Lefebvre, L.; Mar, L.; Bogutz, A.; Oh-McGinnis, R.; Mandegar, M.A.; Paderova, J.; Gertsenstein, M.; Squire, J.A.; Nagy, A. The interval between Ins2 and Ascl2 is dispensable for imprinting centre function in the murine Beckwith-Wiedemann region. *Hum. Mol. Genet.* **2009**, *18*, 4255–4267. [CrossRef] [PubMed]

72. Mancini-DiNardo, D.; Steele, S.J.; Ingram, R.S.; Tilghman, S.M. A differentially methylated region within the gene Kcnq1 functions as an imprinted promoter and silencer. *Hum. Mol. Genet.* **2003**, *12*, 283–294. [CrossRef] [PubMed]

73. Smith, A.C.; Choufani, S.; Ferreira, J.C.; Weksberg, R. Growth regulation, imprinted genes, and chromosome 11p15.5. *Pediatr. Res.* **2007**, *61 Pt 2*, 43r–47r. [CrossRef] [PubMed]
74. Lee, M.P.; DeBaun, M.R.; Mitsuya, K.; Galonek, H.L.; Brandenburg, S.; Oshimura, M.; Feinberg, A.P. Loss of imprinting of a paternally expressed transcript, with antisense orientation to KVLQ1T, occurs frequently in Beckwith-Wiedemann syndrome and is independent of insulin-like growth factor II imprinting. *Proc. Natl. Acad. Sci. USA* 1999, 96, 5203–5208. [CrossRef] [PubMed]
75. Hark, A.T.; Schoenherr, C.J.; Katz, D.J.; Ingram, R.S.; Levorse, J.M.; Tilghman, S.M. CTCF mediates methylation-sensitive enhancer-blocking activity at the H19/IGf2 locus. *Nature* 2000, 405, 486–489. [CrossRef] [PubMed]
76. Pfurr, S.; Chu, Y.H.; Bohrer, C.; Greulich, F.; Beattie, R.; Mammadzada, K.; Hils, M.; Arnold, S.J.; Taylor, V.; et al. Inactivation of p57Kip2 by regional promoter hypermethylation and histone deacetylation frequently in Beckwith-Wiedemann syndrome and is independent of insulin-like growth factor II imprinting. *Proc. Natl. Acad. Sci. USA* 2001, 98, 1601–1609. [CrossRef] [PubMed]
77. Cucciolla, V.; Borriello, A.; Criscuolo, M.; Sinisi, A.A.; Bencivenga, D.; Tramontano, A.; Scudieri, A.C.; Edition, U.; Daniel, G.; Hoffmann, A.; Spengler, D. Zac1 regulates cell cycle arrest in neuronal progenitors via Tcf4. *J. Cell. Biol.* 2014, 104, 1020–1030. [CrossRef] [PubMed]
78. Billing, M.; Rörby, E.; May, G.; Tipping, A.J.; Soneji, S.; Brown, J.; Salminen, M.; Karlsson, G.; Enver, T.; Karlsson, S. A network including TGFbeta/Smad4, Gata2, and p57 regulates proliferation of mouse hematopoietic progenitor cells. *Exp. Hematol.* 2016, 44, 399–409. [CrossRef] [PubMed]
79. Lin, K.T.; Wang, L.H. New dimension of glucocorticoids in cancer treatment. *Carcinogenesis* 2003, 24, 359–368. [CrossRef] [PubMed]
80. Partemi, S.; Brugada, R.; et al. Mild Beckwith-Wiedemann and severe long-QT syndrome due to deletion of the mouse p57Kip2 (Cdkn1c) gene: Implications for the human disorder, Beckwith-Wiedemann syndrome. *J. Mol. Endocrinol.* 2003, 30, 359–368. [CrossRef] [PubMed]
81. Kim, T.H.; Shivdasani, R.A. Genetic evidence that intestinal Notch functions vary regionally and operate through a common mechanism of Math1 repression. *J. Biol. Chem.* 2011, 286, 11427–11433. [CrossRef] [PubMed]
82. Alheim, K.; Corness, J.; Samuelsson, M.K.; Bladh, L.G.; Murata, T.; Nilsson, T.; Okret, S. Identification of a functional glucocorticoid response element in the promoter of the cyclin-dependent kinase inhibitor p57Kip2. *J. Mol. Endocrinol.* 2003, 30, 359–368. [CrossRef] [PubMed]
83. Lin, K.T.; Wang, L.H. New dimension of glucocorticoids in cancer treatment. *Steroids* 2016, 111, 84–88. [CrossRef] [PubMed]
84. John, R.M.; Ainscough, J.F.; Barton, S.C.; Surani, M.A. Distant cis-elements regulate imprinted expression of the mouse p57(Kip2) (Cdkn1c) gene: Implications for the human disorder, Beckwith-Wiedemann syndrome. *Hum. Mol. Genet.* 2001, 10, 1601–1609. [CrossRef] [PubMed]
85. Gartel, A.L.; Goufman, E.; Najmabadi, F.; Tyner, A.L. Sp1 and Sp3 activate p21 (WAF1/CIP1) gene transcription in the Caco-2 colon adenocarcinoma cell line. *Oncogene* 2000, 19, 5182–5188. [CrossRef] [PubMed]
86. John, R.M.; Surani, M.A. Genomic imprinting, mammalian evolution, and the mystery of egg-laying mammals. *Cell* 2000, 101, 585–588. [CrossRef] [PubMed]
87. Yokota, T.; Matsuzaki, Y.; Miyazawa, K.; Zindy, F.; Roussel, M.F.; Sakai, T. Histone deacetylase inhibitors and histone deacetylation in human tumors. *Carcinogenesis* 2002, 21, 2741–2749. [CrossRef] [PubMed]
88. Gartel, A.L.; Goufman, E.; Najmabadi, F.; Tyner, A.L. Sp1 and Sp3 activate p57(KIP2) level by enhancing its expression through Sp1 transcription factor. *Carcinogenesis* 2008, 29, 560–567. [CrossRef] [PubMed]
89. Schmidt-Edelkraut, U.; Daniel, G.; Hoffmann, A.; Spengler, D. Zac1 regulates cell cycle arrest in neuronal progenitors via Tcf4. *Mol. Cell. Biol.* 2014, 34, 1020–1030. [CrossRef] [PubMed]
90. Alheim, K.; Corness, J.; Samuelsson, M.K.; Bladh, L.G.; Murata, T.; Nilsson, T.; Okret, S. Identification of a functional glucocorticoid response element in the promoter of the cyclin-dependent kinase inhibitor p57Kip2. *J. Mol. Endocrinol.* 2003, 30, 359–368. [CrossRef] [PubMed]
91. Surani, M.A.; Barton, S.C.; Norris, M.L. Development of reconstituted mouse eggs suggests imprinting of the genome during gametogenesis. *Nature* 1984, 308, 548–550. [CrossRef] [PubMed]
92. McGrath, J.; Solter, D. Completion of mouse embryogenesis requires both the maternal and paternal genomes. *Cell* 1984, 37, 179–183. [CrossRef]
93. Monk, D.; Sanches, R.; Arnaud, P.; Apostolidou, S.; Hills, F.A.; Abu-Amero, S.; Murrell, A.; Friess, H.; Reik, W.; Stanier, P.; et al. Imprinting of IGF2 P0 transcript and novel alternatively spliced INS-IGF2 isoforms show differences between mouse and human. *Hum. Mol. Genet.* 2006, 15, 1259–1269. [CrossRef] [PubMed]

94. Surani, M.A. Imprinting and the initiation of gene silencing in the germ line. *Cell* 1998, 93, 309–312. [CrossRef]

95. Hatada, I.; Inazawa, J.; Abe, T.; Nakayama, M.; Kaneko, Y.; Jinno, Y.; Niikawa, N.; Ohashi, H.; Fukushima, Y.; lida, K.; et al. Genomic imprinting of human p57KIP2 and its reduced expression in Wilms’ tumors. *Hum. Mol. Genet.* 1996, 5, 783–788. [CrossRef] [PubMed]

96. John, R.M.; Lefebvre, L. Developmental regulation of somatic imprints. *Differentiation* 2011, 81, 270–280. [CrossRef] [PubMed]

97. Bhogal, B.; Arnaudo, A.; Dymkowski, A.; Best, A.; Davis, T.L. Methylation at mouse Cdkn1c is acquired during postimplantation development and functions to maintain imprinted expression. *Genomics* 2004, 84, 961–970. [CrossRef] [PubMed]

98. Rossi, M.N.; Andresini, O.; Matteini, F.; Maione, R. Transcriptional regulation of p57(kip2) expression during development, differentiation and disease. *Front. Biosci.* 2018, 23, 83–108.

99. Fan, T.; Hagan, J.P.; Kozlov, S.V.; Stewart, C.L.; Muegge, K. Lsh controls silencing of the imprinted Cdkn1c gene. *Development* 2005, 132, 635–644. [CrossRef] [PubMed]

100. Riemenschneider, M.J.; Reifenberger, J.; Reifenberger, G. Frequent biallelic inactivation and transcriptional silencing of the DIRAS3 gene at 1p31 in oligodendroglial tumors with 1p loss. *Int. J. Cancer* 2008, 122, 2503–2510. [CrossRef] [PubMed]

101. Neumann, L.C.; Weinhäusel, A.; Thomas, S.; Horshemke, B.; Lohmann, D.R.; Zeschnigk, M. EFS shows biallelic methylation in uveal melanoma with poor prognosis as well as tissue-specific methylation. *BMC Cancer* 2011, 11, 380. [CrossRef] [PubMed]

102. Andresini, O.; Ciotti, A.; Rossi, M.N.; Battistelli, C.; Carbone, M.; Maione, R. A cross-talk between DNA methylation and H3 lysine 9 dimethylation at the KvDMR1 region controls the induction of Cdkn1c in muscle cells. *Epigenetics* 2016, 11, 791–803. [CrossRef] [PubMed]

103. Mohammad, F.; Mondal, T.; Guseva, N.; Pandey, G.K.; Kanduri, C. Kcnq1ot1 noncoding RNA mediates transcriptional gene silencing by interacting with Dnmt1. *Development* 2010, 137, 2493–2499. [CrossRef] [PubMed]

104. Li, Y.; Nagai, H.; Ohno, T.; Yuge, M.; Hatano, S.; Ito, E.; Mori, N.; Saito, H.; Kinoshita, T. Aberrant DNA methylation of p57(KIP2) gene in the promoter region in lymphoid malignancies of B-cell phenotype. *Blood* 2002, 100, 2572–2577. [CrossRef] [PubMed]

105. Li, C.; Choi, H.P.; Wang, X.; Wu, F.; Chen, X.; Lü, X.; Jing, R.; Ryu, H.; Wang, X.; Azadzoi, K.M.; et al. Post-Translational Modification of Human Histone by Wide Tolerance of Acetylation. *Cells* 2017, 6, E34. [CrossRef] [PubMed]

106. Faundes, V.; Newman, W.G.; Bernardini, L.; Canham, N.; Clayton-Smith, J.; Dallapiccola, B.; Davies, S.J.; Demos, M.K.; Goldman, A.; Gill, H.; et al. Histone Lysine Methylases and Demethylases in the Landscape of Human Developmental Disorders. *Am. J. Hum. Genet.* 2018, 102, 175–187. [CrossRef] [PubMed]

107. Umlauf, D.; Goto, Y.; Cao, R.; Cerqueira, F.; Wagscha, A.; Zhang, Y.; Feil, R. Imprinting along the Kcnq1 domain on mouse chromosome 7 involves repressive histone methylation and recruitment of Polycomb group complexes. *Nat. Genet.* 2004, 36, 1296–1300. [CrossRef] [PubMed]

108. Lewis, A.; Mitsuya, K.; Umlauf, D.; Smith, P.; Dean, W.; Walter, J.; Higgins, M.; Feil, R.; Reik, W. Imprinting on distal chromosome 7 in the placenta involves repressive histone methylation independent of DNA methylation. *Nat. Genet.* 2004, 36, 1291–1295. [CrossRef] [PubMed]

109. Algar, E.M.; Muscat, A.; Dagar, V.; Rickert, C.; Chow, C.W.; Biegel, J.A.; Ekert, P.G.; Saffery, R.; Craig, J.; Johnstone, R.W.; et al. Impprinted CDKN1C is a tumor suppressor in rhabdoid tumor and activated by restoration of SMARCB1 and histone deacetylase inhibitors. *PLoS ONE* 2009, 4, e4482. [CrossRef] [PubMed]

110. Attia, M.; Rachez, C.; De Pauw, A.; Avner, P.; Rogner, U.C. Nap1l2 promotes histone acetylation activity during neuronal differentiation. *Mol. Cell. Biol.* 2007, 27, 6093–6102. [CrossRef] [PubMed]

111. Cao, L.L.; Yue, Z.; Liu, L.; Pei, L.; Yin, Y.; Qin, L.; Zhao, J.; Liu, H.; Wang, H.; Jia, M. The expression of histone deacetylase HDAC1 correlates with the progression and prognosis of gastrointestinal malignancy. *Oncotarget* 2017, 8, 39241–39253. [CrossRef] [PubMed]
112. Jo, Y.K.; Park, N.Y.; Shin, J.H.; Jo, D.S.; Bae, J.E.; Choi, E.S.; Maeng, S.; Jeon, H.B.; Roh, S.A.; Chang, J.W.; et al. Up-regulation of UVRAG by HDAC1 Inhibition Attenuates 5FU-induced Cell Death in HCT116 Colorectal Cancer Cells. *Anticancer Res.* **2018**, *38*, 271–277. [PubMed]

113. Zhou, H.; Cai, Y.; Liu, D.; Li, M.; Sha, Y.; Zhang, W.; Wang, K.; Gong, J.; Tang, N.; Huang, A.; et al. Pharmacological or transcriptional inhibition of both HDAC1 and 2 leads to cell cycle blockage and apoptosis via p21(Waf1/Cip1) and p19(INK4d) upregulation in hepatocellular carcinoma. *Cell Prolif.* **2018**, *38*, 271–277. [PubMed]

114. Wakahara, M.; Sakabe, T.; Kubouchi, Y.; Hosoya, K.; Hirooka, Y.; Yurugi, Y.; Nosaka, K.; Shiomi, T.; Nakamura, H.; Umekita, Y. Subcellular Localization of maspin correlates with histone deacetylase 1 expression in human breast cancer. *Anticancer Res.* **2017**, *37*, 5071–5077. [PubMed]

115. Cai, M.H.; Xu, X.G.; Yan, S.L.; Sun, Z.; Ying, Y.; Wang, B.K.; Tu, Y.X. Depletion of HDAC1, 7 and 8 by histone deacetylase inhibition confers elimination of pancreatic cancer stem cells in combination with gemcitabine. *Sci. Rep.* **2018**, *8*, 1621. [CrossRef] [PubMed]

116. Ropero, S.; Ballestar, E.; Alaminos, M.; Arango, D.; Schwartz, S.Jr; Esteller, M. Transforming pathways unleashed by a HDAC2 mutation in human cancer. *Oncogene* **2008**, *27*, 4008–4012. [CrossRef] [PubMed]

117. Li, S.; Wang, F.; Qu, Y.; Chen, X.; Gao, M.; Yang, J.; Zhang, D.; Zhang, N.; Li, W.; Liu, H. HDAC2 regulates cell proliferation, cell cycle progression and cell apoptosis in esophageal squamous cell carcinoma EC9706 cells. *Oncol. Lett.* **2017**, *13*, 403–409. [CrossRef] [PubMed]

118. Hulsurkar, M.; Li, Z.; Zhang, Y.; Li, X.; Zheng, D.; Li, W. Beta-adrenergic signaling promotes tumor angiogenesis and prostate cancer progression through HDAC2-mediated suppression of thrombospondin-1. *Sci. Rep.* **2018**, *8*, 1621. [CrossRef] [PubMed]

119. Mitsuya, K.; Meguro, M.; Lee, M.P.; Katoh, M.; Schulz, T.C.; Kugoh, H.; Yoshida, M.A.; Nakauchi, H.; Furukawa, T.; Koseki, H.; Murakami, A.; Watanabe, S. Roles of histone H3K27 trimethylase Ezh2 in retinal proliferation and differentiation. *Dev. Neurobiol.* **2015**, *75*, 947–960. [CrossRef] [PubMed]

120. Heinen, A.; Tzekova, N.; Graffmann, N.; Torres, K.J.; Uhrberg, M.; Küry, P. Histone methyltransferase enhancer of zeste homolog 2 regulates Schwann cell differentiation. *Glia* **2012**, *60*, 1696–1708. [CrossRef] [PubMed]

121. Pandey, R.R.; Mondal, T.; Mohammad, F.; Enroth, S.; Redrup, L.; Komorowski, J.; Nagano, T.; Mancini-Dinardo, D.; Kanduri, C. Kcnq1ot1 antisense noncoding RNA mediates lineage-specific transcriptional silencing through chromatin-level regulation. *Mol. Cell* **2008**, *32*, 232–246. [CrossRef] [PubMed]

122. Zhang, E.; He, X.; Yin, D.; Han, L.; Qiu, M.; Xu, T.; Xia, R.; Xu, L.; Yin, R.; De, W. Increased expression of long noncoding RNA TUG1 predicts a poor prognosis of gastric cancer and regulates cell proliferation by epigenetically silencing of p57. *Cell Death Dis.* **2016**, *7*, e2109. [CrossRef] [PubMed]

123. Zhang, E.; Yin, D.; Han, L.; He, X.; Si, X.; Chen, W.; Xia, R.; Xu, T.; Gu, D.; De, W.; et al. E2F1-induced upregulation of long noncoding RNA LINC00668 predicts a poor prognosis of gastric cancer and promotes cell proliferation through epigenetically silencing of CKIs. *Oncotarget* **2016**, *7*, 23212–23226. [CrossRef] [PubMed]

124. Yang, F.; Zhang, L.; Huo, X.S.; Yuan, J.H.; Xu, D.; Yuan, S.X.; Zhu, N.; Zhou, W.P.; Yang, G.S.; Wang, Y.Z.; et al. Long noncoding RNA high expression in hepatocellular carcinoma facilitates tumor growth through enhancer of zeste homolog 2 in humans. *Hepatology* **2011**, *54*, 1679–1689. [CrossRef] [PubMed]
128. Brioude, F.; Kalish, J.M.; Mussa, A.; Foster, A.C.; Bliedt, J.; Ferrero, G.B.; Boonen, S.E.; Cole, T.; Baker, R.; Bertoletti, M.; et al. Expert consensus document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: An international consensus statement. *Nat. Rev. Endocrinol.* 2018, 14, 229–249. [CrossRef] [PubMed]

129. Mussa, A.; Russo, S.; De Crescenzo, A.; Freschi, A.; Calzari, L.; Maitz, S.; Macchiaiolo, M.; Molinatto, C.; Baldassarre, G.; Mariani, M.; et al. (Epi)genotype-phenotype correlations in Beckwith-Wiedemann syndrome. *Eur. J. Hum. Genet.* 2016, 24, 183–190. [CrossRef] [PubMed]

130. Heide, S.; Chantot-Bastaraud, S.; Keren, B.; Harbison, M.D.; Azzi, S.; Rossignol, S.; Michot, C.; Lackmy-Port Lys, M.; Demeer, B.; Heinrichs, C.; et al. Chromosomal rearrangements in the 11p15 imprinted region: 17 new 11p15.5 duplications with associated phenotypes and putative functional consequences. *J. Med. Genet.* 2018, 55, 205–213. [CrossRef] [PubMed]

131. Mussa, A.; Russo, S.; de Crescenzo, A.; Freschi, A.; Calzari, L.; Maitz, S.; Macchiaiolo, M.; Molinatto, C.; Baldassarre, G.; Mariani, M.; et al. Fetal growth patterns in Beckwith-Wiedemann syndrome. *Clin. Genet.* 2016, 90, 21–27. [CrossRef] [PubMed]

132. Cooper, W.N.; Schofield, P.N.; Reik, W.; Macdonald, F.; Maher, E.R. Molecular subtypes and phenotypic expression of Beckwith-Wiedemann syndrome. *Eur. J. Hum. Genet.* 2005, 13, 1025–1032. [CrossRef] [PubMed]

133. Brioude, F.; Luharia, A.; Evans, G.A.; Raza, H.; Haire, A.C.; Grundy, R.; Bowdin, S.C.; Riccio, A.; Sebastio, G.; Blied, J.; et al. Mutations of the Imprinted CDKN1C Gene as a Cause of the Overgrowth Beckwith-Wiedemann Syndrome: Clinical Spectrum and Functional Characterization. *Hum. Mutat.* 2015, 36, 894–902. [CrossRef] [PubMed]

134. Bourcigaux, N.; Gaston, V.; Logié, A.; Bertagna, X.; Le Bouc, Y.; Gicquel, C. High expression of cyclin E and G1 CDK and loss of function of p57KIP2 are involved in proliferation of malignant sporadic adrenocortical tumors. *J. Clin. Endocrinol. Metab.* 2000, 85, 322–330. [CrossRef] [PubMed]

135. Duquesnes, N.; Callot, C.; Jeannot, P.; Daburon, V.; Nakayama, K.I.; Manenti, S.; Davy, A.; Bessou, A. p57(Kip2) knock-in mouse reveals CDK-independent contribution in the development of Beckwith-Wiedemann syndrome. *J. Pathol.* 2016, 239, 250–261. [CrossRef] [PubMed]

136. Arboleda, V.A.; Lee, H.; Parraik, R.; Fleming, A.; Banerjee, A.; Ferraz-de-Souza, B.; Delot, E.C.; Rodriguez-Fernandez, I.A.; Braslavsky, D.; Bergadá, I.; et al. Mutations in the PCNA-binding domain of CDKN1C cause IMAGe syndrome. *Nat. Genet.* 2012, 44, 788–792. [CrossRef] [PubMed]

137. Dias, R.P.; Maher, E.R. An imprinted IMAGe: Insights into growth regulation through genomic analysis of a rare disease. *Genome Med.* 2012, 4, 60. [CrossRef] [PubMed]

138. Begemann, M.; Spengler, S.; Kanber, D.; Haake, A.; Baudis, M.; Leisten, I.; Binder, G.; Markus, S.; Rupprecht, T.; Segerer, H.; et al. Silver-Russell patients showing a broad range of ICR1 and ICR2 hypomethylation in different tissues. *Clin. Genet.* 2011, 80, 83–88. [CrossRef] [PubMed]

139. Eggermann, K.; Bliedt, J.; Brioude, F.; Algar, E.; Buiting, K.; Russo, S.; Türke, Z.; Monk, D.; Moore, G.; Antoniadi, T.; et al. EMQN best practice guidelines for the molecular genetic testing and reporting of chromosome 11p15 imprinting disorders: Silver-Russell and Beckwith-Wiedemann syndrome. *Eur. J. Hum. Genet.* 2016, 24, 1377–1387. [CrossRef] [PubMed]

140. Monk, D.; Wakeling, E.L.; Proud, V.; Hitchins, M.; Abu-Amero, S.N.; Stanier, P.; Preece, M.A.; Moore, G.E. Duplication of 7p11.2-p13, including GRB10, in Silver-Russell syndrome. *Am. J. Hum. Genet.* 2000, 66, 36–46. [CrossRef] [PubMed]

141. Brioude, F.; Oliver-Petit, I.; Blaise, A.; Praz, F.; Rossignol, S.; Le Jule, M.; Thibaud, N.; Faussat, A.M.; Tauber, M.; Le Bouc, Y.; et al. CDKN1C mutation affecting the PCNA-binding domain as a cause of familial Russell Silver syndrome. *J. Med. Genet.* 2013, 50, 823–830. [CrossRef] [PubMed]

142. Iolascon, A.; Giordani, L.; Moretti, A.; Basso, G.; Borriello, A.; Della Ragione, F. Analysis of CDKN2A, CDKN2B, CDKN2C, and cyclin Ds gene status in hepatoblastoma. *Hepatology* 1998, 27, 989–995. [CrossRef] [PubMed]

143. Iolascon, A.; Giordani, L.; Moretti, A.; Tonini, G.P.; Lo Cunsolo, C.; Mastropietro, S.; Borriello, A.; Della Ragione, F. Structural and functional analysis of cyclin-dependent kinase inhibitor genes (CDKN2A, CDKN2B, and CDKN2C) in neuroblastoma. *Pediatr. Res.* 1998, 43, 139–144. [CrossRef] [PubMed]

144. Pateras, I.S.; Apostolopoulou, K.; Niforou, K.; Kotsinas, A.; Gorgoulis, V.G. p57KIP2: “Kip”ing the cell under control. *Mol. Cancer Res.* 2009, 7, 1902–1919. [CrossRef] [PubMed]
145. Bencivenga, D.; Caldarelli, I.; Stampone, E.; Mancini, F.P.; Balestrieri, M.L.; Della Ragione, F.; Borriello, A. p27(Kip1) and human cancers: A reappraisal of a still enigmatic protein. *Cancer Lett.* 2017, 403, 354–365. [CrossRef] [PubMed]

146. Bonilla, F.; Orlow, I.; Cordon-Cardo, C. Mutational study of p16CDKN2/MTS1/INK4A and p57KIP2 genes in hepatocellular carcinoma. *Int. J. Oncol.* 1998, 12, 583–588. [CrossRef] [PubMed]

147. Shin, J.Y.; Kim, H.S.; Lee, K.S.; Kim, J.; Park, J.B.; Won, M.H.; Chae, S.W.; Choi, Y.H.; Choi, K.C.; Park, Y.E.; et al. Mutation and expression of the p27KIP1 and p57KIP2 genes in human gastric cancer. *Exp. Mol. Med.* 2000, 32, 79–83. [CrossRef] [PubMed]

148. Oya, M.; Schulz, W.A. Decreased expression of p57(KIP2)mRNA in human bladder cancer. *Br. J. Cancer* 2000, 83, 626–631. [CrossRef] [PubMed]

149. Hofmann, M.J.; Flor, A.R.; Seifert, H.H.; Schulz, W.A. Multiple mechanisms downregulate CDKN1C in human bladder cancer. *Int. J. Cancer* 2005, 114, 406–413. [CrossRef] [PubMed]

150. Sato, N.; Matsubayashi, H.; Abe, T.; Fukushima, N.; Goggins, M. Epigenetic down-regulation of CDKN1C/p57KIP2 in pancreatic ductal neoplasms identified by gene expression profiling. *Clin. Cancer Res.* 2005, 11, 4681–4688. [CrossRef]

151. Giovannoni, I.; Boldrini, R.; Benedetti, M.C.; Inserra, A.; De Pasquale, M.D.; Francalanci, P. Pediatric adenocortical neoplasms: Immunohistochemical expression of p57 identifies loss of heterozygoty and abnormal imprinting of the 11p15.5. *Pediatr. Res.* 2017, 81, 468–472. [CrossRef] [PubMed]

152. Sun, Y.; Jin, S.D.; Zhu, Q.; Han, L.; Feng, J.; Lu, X.Y.; Wang, W.; Wang, F.; Guo, R.H. Long non-coding RNA LUCAT1 is associated with poor prognosis in human non-small lung cancer and regulates cell proliferation via epigenetically repressing p21 and p57 expression. *Oncotarget* 2017, 8, 28297–28311. [CrossRef] [PubMed]

153. Qiu, Z.; Li, Y.; Zeng, B.; Guan, X.; Li, H. Downregulated CDKN1C/p57KIP2 drives tumorigenesis and associates with poor overall survival in breast cancer. *Biochem. Biophys. Res. Commun.* 2018, 497, 187–193. [CrossRef] [PubMed]

154. Radujkovic, A.; Dietrich, S.; Andrulis, M.; Benner, A.; Longerich, T.; Pellagatti, A.; Nanda, K.; Giese, T.; Germing, U.; Baldus, S.; et al. Expression of CDKN1C in the bone marrow of patients with myelodysplastic syndrome and secondary acute myeloid leukemia is associated with poor survival after conventional chemotherapy. *Int. J. Cancer* 2016, 139, 1402–1413. [CrossRef] [PubMed]

155. Guo, H.; Nan, K.; Hu, T.; Meng, J.; Hui, W.; Zhang, X.; Qin, H.; Sui, C. Prognostic significance of co-expression of nm23 and p57 protein in hepatocellular carcinoma. *Hepatol. Res.* 2010, 40, 1107–1116. [CrossRef] [PubMed]

156. Kobatake, T.; Yano, M.; Toyooka, S.; Tsukuda, K.; Dote, H.; Kikuchi, T.; Toyota, M.; Ouchi, M.; Aoe, M.; Date, H.; et al. Aberrant methylation of p57KIP2 gene in lung and breast cancers and malignant mesotheliomas. *Oncol. Rep.* 2004, 12, 1087–1092. [CrossRef] [PubMed]

157. Shen, L.; Toyota, M.; Kondo, Y.; Obata, T.; Daniel, S.; Pierce, S.; Imai, K.; Kantarjian, H.M.; Issa, J.P.; Garcia-Manero, G. Aberrant DNA methylation of p57KIP2 identifies a cell-cycle regulatory pathway with prognostic impact in adult acute lymphocytic leukemia. *Blood* 2003, 101, 4131–4136. [CrossRef] [PubMed]

158. Roman-Gomez, J.; Jimenez-Velasco, A.; Agirre, X.; Prosper, F.; Heiniger, A.; Torres, A. Lack of CpG island methylator phenotype defines a clinical subtype of T-cell acute lymphoblastic leukemia associated with good prognosis. *J. Clin. Oncol.* 2005, 23, 7043–7049. [CrossRef] [PubMed]

159. Zohny, S.F.; Baothman, O.A.; El-Shinawi, M.; Al-Malki, A.L.; Zamzami, M.A.; Choudhry, H. The KIP/CIP family members p21[Waf1/Cip1] and p57[Kip2] as diagnostic markers for breast cancer. *Cancer Biomark.* 2017, 18, 413–423. [CrossRef] [PubMed]

160. Mishra, S.; Lin, C.L.; Huang, T.H.; Bouamar, H.; Sun, L.Z. MicroRNA-21 inhibits p57Kip2 expression in prostate cancer. *Mol. Cancer* 2014, 13, 212. [CrossRef] [PubMed]

161. Kim, Y.K.; Yu, J.; Han, T.S.; Park, S.Y.; Namkoong, B.; Kim, D.H.; Hur, K.; Yoo, M.W.; Lee, H.J.; Yang, H.K.; et al. Functional links between clustered microRNAs: Suppression of cell-cycle inhibitors by microRNA clusters in gastric cancer. *Nucleic Acids Res.* 2009, 37, 1672–1681. [CrossRef] [PubMed]

162. Zhang, J.; Gong, X.; Tian, K.; Chen, D.; Sun, J.; Wang, G.; Guo, M. miR-25 promotes glioma cell proliferation by targeting CDKN1C. *Biomed. Pharmacother.* 2015, 71, 7–14. [CrossRef] [PubMed]

163. Nass, D.; Rosenwald, S.; Meiri, E.; Gilad, S.; Tabibian-Keissar, H.; Schlosberg, A.; Kuker, H.; Sion-Vardy, N.; Tober, A.; Kharenko, O.; et al. MiR-92b and miR-9/9* are specifically expressed in brain primary tumors and can be used to differentiate primary from metastatic brain tumors. *Brain Pathol.* 2009, 19, 375–383. [CrossRef] [PubMed]
164. Fornari, F.; Gramantieri, L.; Ferracin, M.; Veronese, A.; Sabbioni, S.; Calin, G.A.; Grazi, G.L.; Giovannini, C.; Croce, C.M.; Bolondi, L.; et al. MiR-221 controls CDKN1C/p57 and CDKN1B/p27 expression in human hepatocellular carcinoma. *Oncogene* **2008**, *27*, 5651–5661. [CrossRef] [PubMed]

165. Fu, X.; Wang, Q.; Chen, J.; Huang, X.; Chen, X.; Cao, L.; Tan, H.; Li, W.; Zhang, L.; Bi, J.; et al. Clinical significance of miR-221 and its inverse correlation with p27Kip1 in hepatocellular carcinoma. *Mol. Biol. Rep.* **2011**, *38*, 3029–3035. [CrossRef] [PubMed]

166. Yang, C.J.; Shen, W.G.; Liu, C.J.; Chen, Y.W.; Lu, H.H.; Tsai, M.M.; Lin, S.C. miR-221 and miR-222 expression increased the growth and tumorigenesis of oral carcinoma cells. *J. Oral Pathol. Med.* **2011**, *40*, 560–566. [CrossRef] [PubMed]

167. Sun, K.; Wang, W.; Zeng, J.J.; Wu, C.T.; Lei, S.T.; Li, G.X. MicroRNA-221 inhibits CDKN1C/p57 expression in hepatocellular carcinoma. *Int. J. Mol. Sci.* **2018**, *19*, 1055. [CrossRef] [PubMed]

168. Bazot, M.; Paschos, K.; Skalska, L.; Kalchschmidt, J.S.; Parker, G.A.; Allday, M.J. Epstein-Barr Virus Proteins EBNA3A and EBNA3C Together Induce Expression of the Oncogenic MicroRNA Cluster miR-221/miR-222 and Ablate Expression of Its Target p57KIP2. *PloS Pathog.* **2015**, *11*, e1005031. [CrossRef] [PubMed]

169. Wurz, K.; Garcia, R.L.; Goff, B.A.; Mitchell, P.S.; Lee, J.H.; Tewari, M.; Swisher, E.M. MiR-221 and MiR-222 alterations in sporadic ovarian carcinoma: Relationship to CDKN1B, CDKNIC and overall survival. *Genes Chromosomes Cancer* **2010**, *49*, 577–584. [CrossRef] [PubMed]

170. Unek, G.; Ozmen, A.; Mendilioglu, I.; Simsek, M.; Korgun, E.T. The expression of cell cycle related proteins PCNA, Ki67, p27 and p57 in normal and preeclamptic human placentas. *Tissue Cell* **2014**, *46*, 198–205. [CrossRef] [PubMed]

171. McMinn, J.; Wei, M.; Schupf, N.; Cusmai, J.; Johnson, E.B.; Smith, A.C.; Weksberg, R.; Thaker, H.M.; Tycko, B. Unbalanced placental expression of imprinted genes in human intrauterine growth restriction. *Placenta* **2006**, *27*, 540–549. [CrossRef] [PubMed]

172. Allias, F.; Lebreton, F.; Collardeau-Frachon, S.; Azziza, J.; Pasquier, C.J.; Arcin-Thoury, F.; Patrier, S.; Devouassous-Shisheboran, M. Immunohistochemical expression of p57 in placental vascular proliferative disorders of preterm and term placentas. *Fetal Pediatr. Pathol.* **2009**, *28*, 9–23. [CrossRef] [PubMed]

173. Fukunaga, M. Immunohistochemical characterization of p57(KIP2) expression in early hydatidiform moles. *Hum. Pathol.* **2002**, *33*, 1188–1192. [CrossRef] [PubMed]

174. McCowan, L.M.; Becroft, D.M. Beckwith-Wiedemann syndrome, placental abnormalities, and gestational proteinuric hypertension. *Obstet. Gynecol.* **1994**, *83* Pt 2, 813–817. [PubMed]

175. Linn, R.L.; Minturn, L.; Yee, L.M.; Maniar, K.; Zhang, Y.; Fritsch, M.K.; Kashireddy, P.; Kapur, R.; Ernst, L.M. Placental mesenchymal dysplasia without fetal development in a twin gestation: A case report and review of the spectrum of androgenetic biparental mosaicism. *Pediatr. Dev. Pathol.* **2010**, *13*, 187–192. [CrossRef] [PubMed]

176. H'Mida, D.; Gribaa, M.; Yacoubi, T.; Chaieb, A.; Adala, L.; Elghezal, H.; Saad, A. Placental mesenchymal dysplasia with beckwith-wiedemann syndrome fetus in the context of biparental and androgenic cell lines. *Placenta* **2008**, *29*, 454–460. [CrossRef] [PubMed]

177. Kaiser-Rogers, K.A.; McFadden, D.E.; Livasy, C.A.; Dansereau, J.; Jiang, R.; Knops, J.F.; Lefebvre, L.; Rao, K.W.; Robinson, W.P. Androgenetic/biparental mosaicism causes placental mesenchymal dysplasia. *J. Med. Genet.* **2006**, *43*, 187–192. [CrossRef] [PubMed]

178. Kalish, J.M.; Conlin, L.K.; Bhatti, T.R.; Dubbs, H.A.; Harris, M.C.; Izumi, K.; Mostoufi-Moab, S.; Mulchandani, S.; Saita, S.; States, L.J.; et al. Clinical features of three girls with mosaic genome-wide paternal uniparental isodisomy. *Am. J. Med. Genet. A* **2013**, *161a*, 1929–1939. [CrossRef] [PubMed]

179. Samadder, A.; Kar, R. Utility of p57 immunohistochemistry in differentiating between complete mole, partial mole & non-molar or hydropic abortus. *Indian J. Med. Res.* **2017**, *145*, 133–137. [PubMed]

180. Sasaki, S.; Sasaki, Y.; Kunimura, T.; Sekizawa, A.; Kojima, Y.; Iino, K. Clinical Usefulness of Immunohistochemical Staining of p57kip2 for the Differential Diagnosis of Complete Mole. *Biomed. Res. Int.* **2015**, *2015*, 905648. [CrossRef] [PubMed]

181. Castrillon, D.H.; Sun, D.; Weremowicz, S.; Fisher, R.A.; Crum, C.P.; Genest, D.R. Discrimination of complete hydatidiform mole from its mimics by immunohistochemistry of the paternally imprinted gene product p57KIP2. *Am. J. Surg. Pathol.* **2001**, *25*, 1225–1230. [CrossRef] [PubMed]

182. De Nigris, F.; Balestrieri, M.L.; Napoli, C. Targeting c-Myc, Ras and IGF cascade to treat cancer and vascular disorders. *Cell Cycle* **2006**, *5*, 1621–1628. [CrossRef] [PubMed]
183. Balestrieri, M.L.; Fiorito, C.; Crimi, E.; Felice, F.; Schiano, C.; Milone, L.; Casamassimi, A.; Giovane, A.; Grimaldi, V.; del Giudice, V.; et al. Effect of red wine antioxidants and minor polyphenolic constituents on endothelial progenitor cells after physical training in mice. *Int. J. Cardiol.* 2008, 126, 295–297. [CrossRef] [PubMed]

184. Vitiello, M.; Zullo, A.; Servillo, L.; Mancini, F.P.; Borriello, A.; Giovane, A.; Della Ragione, F.; D’Onofrio, N.; Balestrieri, M.L. Multiple pathways of SIRT6 at the crossroads in the control of longevity, cancer, and cardiovascular diseases. *Aging Res. Rev.* 2017, 35, 301–311. [CrossRef] [PubMed]

185. Kassem, S.A.; Ariel, I.; Thornton, P.S.; Hussain, K.; Smith, V.; Lindley, K.J.; Aynsley-Green, A.; Glaser, B. p57(KIP2) expression in normal islet cells and in hyperinsulinism of infancy. *Diabetes* 2001, 50, 2763–2769. [CrossRef] [PubMed]

186. Avrahami, D.; Li, C.; Yu, M.; Jiao, Y.; Zhang, J.; Naji, A.; Ziaie, S.; Glaser, B.; Kaestner, K.H. Targeting the cell cycle inhibitor p57Kip2 promotes adult human beta cell replication. *J. Clin. Investig.* 2014, 124, 670–674. [CrossRef] [PubMed]

187. Kerns, S.L.; Guevara-Aguirre, J.; Andrew, S.; Geng, J.; Guevara, C.; Guevara-Aguirre, M.; Guo, M.; Oddoux, C.; Shen, Y.; Zurita, A. A novel variant in CDKN1C is associated with intrauterine growth restriction, short stature, and early-adulthood-onset diabetes. *J. Clin. Endocrinol. Metab.* 2014, 99, E2117–E2122. [CrossRef] [PubMed]

188. Van De Pette, M.; Tunster, S.J.; McNamara, G.I.; Shelkovnikova, T.; Millership, S.; Benson, L.; Peirson, S.; Christian, M.; Vidal-Puig, A.; John, R.M. Cdkn1c Boosts the Development of Brown Adipose Tissue in a Murine Model of Silver Russell Syndrome. *PLoS Genet.* 2016, 12, e1005916. [CrossRef] [PubMed]

189. Asahara, S.; Etoh, H.; Inoue, H.; Teruyama, K.; Shibutani, Y.; Ihara, Y.; Kawada, Y.; Bartolome, A.; Hashimoto, N.; Matsuda, T. Paternal allelic mutation at the Kcnq1 locus reduces pancreatic beta-cell mass by epigenetic modification of Cdkn1c. *Proc. Natl. Acad. Sci. USA* 2015, 112, 8332–8337. [CrossRef] [PubMed]

190. Zhao, Z.; Choi, J.; Zhao, C.; Ma, Z.A. FTY720 normalizes hyperglycemia by stimulating beta-cell in vivo regeneration in db/db mice through regulation of cyclin D3 and p57(KIP2). *J. Biol. Chem.* 2012, 287, 5562–5573. [CrossRef] [PubMed]

191. Grimaldi, V.; Schiano, C.; Casamassimi, A.; Zullo, A.; Soricelli, A.; Mancini, F.P.; Napoli, C. Imaging Techniques to Evaluate Cell Therapy in Peripheral Artery Disease: State of the Art and Clinical Trials. *Clin. Physiol. Funct. Imaging* 2016, 36, 165–178. [CrossRef] [PubMed]

192. Nödl, M.-T.; Fossati, S.M.; Domingues, P.; Sánchez, F.J.; Zullo, L. The Making of an Octopus Arm. *Evodevo* 2015, 6, 19. [CrossRef] [PubMed]

193. Fossati, S.M.; Candiani, S.; Nödl, M.-T.; Maragliano, L.; Pennuto, M.; Domingues, P.; Benfenati, F.; Pestarino, M.; Zullo, L. Identification and Expression of Acetylcholinesterase in Octopus Vulgaris Arm Development and Regeneration: A Conserved Role for ACHE? *Mol. Neurobiol.* 2015, 52, 45–56. [CrossRef] [PubMed]

194. Zou, P.; Yoshihara, H.; Hosokawa, K.; Tai, I.; Shinmyozu, K.; Tsukahara, F.; Maru, Y.; Nakayama, K.; Nakayama, K.I.; Suda, T. p57Kip2 and p27Kip1 Cooperate to Maintain Hematopoietic Stem Cell Quiescence through Interactions with Hsc70. *Cell Stem Cell* 2011, 9, 247–261. [CrossRef] [PubMed]