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It's Getting Complicated—A Fresh Look at p53-MDM2-ARF Triangle in Tumorigenesis and Cancer Therapy

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Anti-tumorigenic mechanisms mediated by the tumor suppressor p53, upon oncogenic stresses, are our bodies' greatest weapons to battle against cancer onset and development. Consequently, factors that possess significant p53-regulating activities have been subjects of serious interest from the cancer research community. Among them, MDM2 and ARF are considered the most influential p53 regulators due to their abilities to inhibit and activate p53 functions, respectively. MDM2 inhibits p53 by promoting ubiquitination and proteasome-mediated degradation of p53, while ARF activates p53 by physically interacting with MDM2 to block its access to p53. This conventional understanding of p53-MDM2-ARF functional triangle have guided the direction of p53 research, as well as the development of p53-based therapeutic strategies for the last 30 years. Our increasing knowledge of this triangle during this time, especially through identification of p53-independent functions of MDM2 and ARF, have uncovered many under-appreciated molecular mechanisms connecting these three proteins. Through recognizing both antagonizing and synergizing relationships among them, our consideration for harnessing these relationships to develop effective cancer therapies needs an update accordingly. In this review, we will re-visit the conventional wisdom regarding p53-MDM2-ARF tumor-regulating mechanisms, highlight impactful studies contributing to the modern look of their relationships, and summarize ongoing efforts to target this pathway for effective cancer treatments. A refreshed appreciation of p53-MDM2-ARF network can bring innovative approaches to develop new generations of genetically-informed and clinically-effective cancer therapies.

Keywords: p53, MDM2, p14ARF, ARF, *CDKN2A*, tumor suppressor, oncogene, cancer therapy

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INTRODUCTION

Discovered more than 40 years ago, tumor-suppressor p53 (encoded by *TP53* in human and *Trp53* in mouse) has become the most popular gene due to the fact that it is the most frequently altered gene in cancers (Vogelstein et al., 2010; Dolgin, 2017). Functioning as guardian of the genome, p53 responds to oncogenic stresses by inducing mechanisms like cell cycle arrest, senescence and programmed cell death (apoptosis) to allow damaged cells to either undergo necessary repairs or be eradicated from the environment before permanent transformation leading to malignant cancer progression (Kastenhuber and Lowe, 2017).

Decades of extensive studies have revealed tremendous complexity of the p53 universe. A master regulator of systemic homeostasis, p53 regulates pathogenesis of many diseases other than cancer, including neurodegeneration, cardiovascular diseases, metabolic disorders, autoimmune and infectious diseases (Takatori et al., 2014; Siegl and Rudel, 2015; Kung and Murphy, 2016; Szybinska and Lesniak, 2017; Aloni-Grinstein et al., 2018; Maor-Nof et al., 2021; Men et al., 2021). As if we need a further reminder about p53's significance in human health, the culprit of the global COVID-19 pandemic, SARS-CoV-2, also targets p53 for its full pathogenic effects (Cardozo and Hainaut, 2021). Connections between p53 and these diverse physiological conditions led to expanded knowledge of many biological processes downstream of p53, such as metabolism, autophagy, translational control and epigenetic regulation, among others (Levine, 2019; Boutelle and Attardi, 2021).

Equally complicated is the network of mechanisms regulating p53 functions. Regulation of p53 is dictated by many factors, including mutation status and post-translational modification of p53, composition of response elements (REs) of p53 target genes, interaction between p53 and cofactors, and the heterogeneity in spatial and temporal dynamics of p53 activity (Hafner et al., 2019; Farkas et al., 2021). It is a highly choreographed process to control cell fate through the huge number (>3,500 by estimation) of p53 target genes and other p53-controlled mechanisms (Fischer, 2017; Sammons et al., 2020).

Amidst the tremendous complexity surrounding p53, one constant is the central hub formed by p53 and its key regulator, mouse double minute 2 (MDM2). The relationship between p53 and MDM2 is considered the final gatekeeper for majority of stress-induced signaling pathways whose main objective is to unlock the power of p53-mediated activities (Levine, 2020). The importance of p53-MDM2 hub also signifies the critical roles of direct MDM2 regulators, chief among them alternate open reading frame (ARF), in controlling p53 functions. We will herein summarize the conventional understanding of p53-MDM2-ARF relationships, unconventional and unique perspectives provided by recent studies, and implications for cancer therapeutics as our knowledge of this powerful triangle continues to evolve.

THE SIMPLE TRIANGLE CONNECTING P53, MDM2 AND ARF

Conventional Wisdom for p53-MDM2-ARF Relationship

To deploy anti-tumorigenic functions, wild type (WT) p53 stands ready to be activated in short orders, while maintaining in the background of cellular machineries to prevent unnecessary damages. This fast-deployment system requires a simple mechanism for on and off switches, controlled mainly by a single protein, MDM2. Initially recognized as an oncogene overexpressed in transformed mouse cells, MDM2 was quickly found to promote tumorigenesis by inhibiting p53's transcriptional activity (Fakharzadeh et al., 1991; Cahilly-Snyder et al., 1987; Oliner et al., 1993). The structure of MDM2 contains a main N-terminal p53-binding domain, a C-terminal RING domain and sequence motifs facilitating its localizations in (NLS: nuclear localization signal; NoLS: nucleolar localization signal) and out (NES: nuclear export signal) of nucleus (**Figures 1A,B**). The interaction between MDM2 and p53 is made particularly strong by p53's ability to bind MDM2 through multiple interfaces (Chi et al., 2005; Yu et al., 2006; Poyurovsky et al., 2010). Functioning as a E3 ubiquitin ligase, MDM2 serves as a constant quencher of p53 activity by mediating ubiquitination of p53 on its C-terminus to promote proteasome-mediated degradation (Haupt et al., 1997; Midgley and Lane, 1997). To release the strong clamp of MDM2, stress-induced signaling pathways use a variety of mechanisms to probe and prod between p53 and MDM2 to free p53. These mechanisms mainly lead to post-translational modifications (PTM) of p53, such as phosphorylation at serine 15/20/37/106 and threonine 18 to weaken p53-MDM2 interaction, and acetylation at C-terminal domain (CTD) lysine residues to prevent MDM2-mediated ubiquitination (Shieh et al., 1997; Unger et al., 1999; Nakamura et al., 2000; Rodriguez et al., 2000; Sakaguchi et al., 2000; Li et al., 2002; Hsueh et al., 2013). The relative significance of these PTM events has been a subject of debates. For example, lysine-to-arginine (KR) substitutions at multiple CTD acetylation sites significantly altered expression of p53 target genes but resulted in few abnormal phenotypes in mouse models (Krummel et al., 2005; Tang et al., 2008). A nonsense mutation at serine 15 was found to reduce p53-mediated transactivation but have little effect on p53's interaction with MDM2 and its stability (Dumaz and Meek, 1999). These discrepancies can be attributed to functional regulation of individual PTM sites, crosstalk between PTM sites, other MDM2-mediated p53 PTM such as neddylation, and complexity surrounding p53-MDM2 hub to calibrate p53 activities (Lambert et al., 1998; Xirodimas et al., 2004; Laptenko et al., 2015). To ensure that p53 functions are only activated in a transient manner, MDM2 is transcriptionally induced by WT p53 to form a regulatory feedback loop (Barak et al., 1993). p53-mediated regulation of MDM2 likely contributes to a system capable of fine-tuning p53 functions.

Another way to activate p53 functions is through direct inhibition of MDM2. Among pathways reported to date, ARF-mediated MDM2 inhibition is the most well studied mechanism. ARF (or p14 in human and p19 in mouse) is encoded by the *CDKN2A* locus, which also encodes another tumor suppressor, p16INK4A (**Figure 1C**). ARF and p16INK4A are transcribed from two partially overlapped open reading frames and translated to two unrelated proteins. ARF activates p53 by directly interacting with MDM2 to inhibit its functions (Kamijo et al., 1998; Pomerantz et al., 1998). Mechanistically, two arginine rich domains (amino acids, or aa 1–14 and 82–101) of ARF predispose its localization to the nucleolus (Zhang and Xiong, 1999; Rizos et al., 2000). The N-terminal 1–14 motif interacts with the central region of MDM2, exposing its NoLS motif to sequester ARF-MDM2 complex in the nucleolus (Weber et al., 1999; Weber et al., 2000a; Lohrum et al., 2000). This phenomenon prevents MDM2 from exporting p53 into the cytoplasm for degradation, thus preserving p53 functions

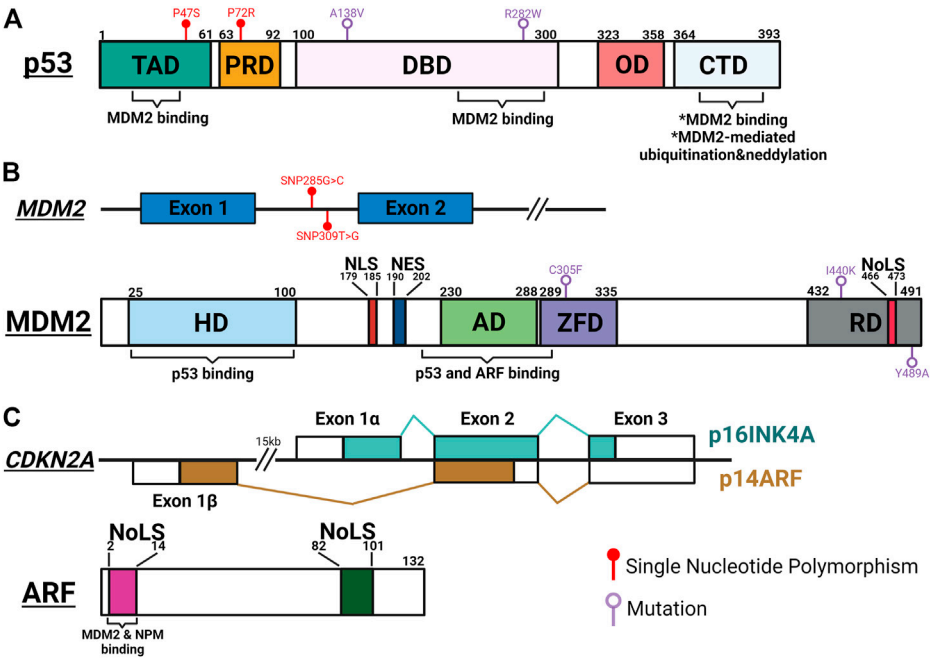

FIGURE 1 | Schematic summary of important genetic and protein features of p53, MDM2 and ARF. **(A)** p53 interacts with MDM2 through its transactivation domain (TAD), DNA binding domain (DBD) and carboxy-terminal domain (CTD). MDM2-mediated post-translational modifications occur at the CTD, leading to inactivation and degradation of p53. Single nucleotide polymorphisms (SNP) in TAD (P47S; rs1800371) and proline-rich domain (PRD) (P72R; rs1042522) modulate p53's ability to suppress tumorigenesis and regulate metabolic fitness. Temperature sensitive mutations of p53 in DBD (A138V and R282W) result in resistance to MDM2-mediated degradation. OD, oligomerization domain. **(B)** Upper panel: SNPs of *MDM2* regulate the functional oscillation between p53 and MDM2. SNP309T>G (rs2279744) results in higher MDM2 expression and inhibits p53-MDM2 oscillation. SNP285G>C (rs117039649) contributes to lower MDM2 expression and is associated with reduced risks for female reproductive cancers. Lower panel: MDM2 interacts with p53 through its N-terminal hydrophobic domain (HD) and acid domain (AD), and with ARF through AD. Interaction with ARF exposes the NoLS motif in the RING domain (RD) to sequester the ARF-MDM2 complex in the nucleolus. A cancer-associated single mutation, C305F, in the zinc finger domain (ZFD) mediates interaction between MDM2 and ribosomal proteins (RP) to regulate p53 function in response to metabolic stress. Two mutations in RD (I440K and Y489A) reduce MDM2-mediated p53 degradation but still limit p53 activity in response to DNA damage. **(C)** Upper panel: The *p16INK4A/p14ARF* locus. Each transcript utilizing a unique first exon, *p16INK4A* (Exon 1α) and *p14ARF* (Exon 1β) splice into common exon 2 and 3 in alternate reading frames to produce two distinctive amino acid sequences, resulting in two unrelated proteins. Lower panel: ARF interacts with MDM2 and NPM through its conserved N-terminal motif between amino acids 1 and 14. Both 1–14 and 82–101 arginine rich NoLS motifs are important for ARF's ability to translocate to the nucleolus and activate p53. The figure was created with BioRender.com and not drawn to scale.

(Tao and Levine, 1999; Weber et al., 1999). In addition to the spatial restriction, ARF also stabilizes p53 through inhibiting MDM2's ubiquitin-ligase activity (Honda and Yasuda, 1999; Midgley et al., 2000). Interestingly, several studies have demonstrated disconnections between nucleolar localization of ARF-MDM2 complex, p53 stabilization, and p53-mediated functions, implicating additional complexity surrounding this linear relationship between ARF, MDM2 and p53 (Llanos et al., 2001; Korgaonkar et al., 2002). Mirroring the feed-back mechanism between MDM2 and p53, WT p53 recruits histone deacetylases (HDAC) and polycomb group (PcG) proteins to repress ARF expression (Zeng et al., 2011).

Factors Known to Function Through p53-MDM2-ARF Triangle

Mechanisms regulating the expression and function of ARF, MDM2 and p53 have been extensively studied (See reviews by Maggi et al., 2014; Hafner et al., 2019; Klein et al., 2021). In the vast pool of regulators, a few unique players function through all three to control cancer development, such as cell proliferation factor mammalian target of rapamycin (mTOR) and oncogene c-Myc (**Figure 2**). In response to cellular stresses, p53 inhibits mTOR activity either by activating mTOR inhibitor the tuberous sclerosis (TSC)1/TSC2 complex through AMP-activated kinase (AMPK) and sestrin-1/2, or inducing transcription of phosphatase and tensin homolog (PTEN) to inhibit mTOR activator AKT (Stambolic et al., 2001; Feng et al., 2005; Budanov and Karin, 2008). A recent study demonstrated, using an acetylation-defective *p53-4KR* mouse model, that p53's ability to suppress mTOR function is linked to distinctive tumor-suppressive activities independent of cell cycle arrest, senescence, and apoptosis (Kon et al., 2021). The ability of p53 to fine-tune mTOR activity has implications beyond tumor suppression. Recent studies showed that p53-regulated mTOR functions affect cells' metabolic fitness during early development and dictate evolutionary advantages/disadvantages in our ancestors (Bowling et al., 2018; Gnanapradeepan et al., 2020).

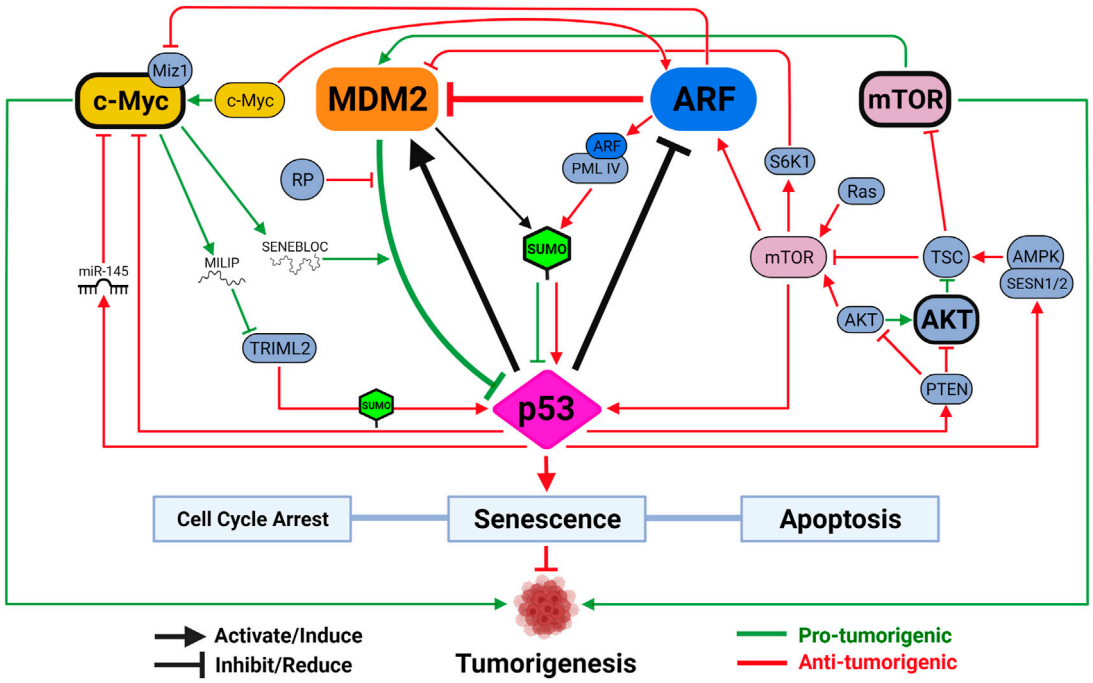

FIGURE 2 | The functional triangle between p53, MDM2 and ARF. The MDM2-p53 duplex is considered the central hub controlling p53-mediated tumor-suppressive activities. Mechanisms disrupting MDM2-p53 interaction lead to p53 activation, which induces MDM2 expression through a negative feedback loop. ARF promotes p53 activation by inhibiting MDM2. Activated p53 reduces ARF expression through HDAC and PcG transcriptional repressors, and loss of p53 often leads to ARF induction. mTOR and c-Myc are two versatile signaling factors that mediate tumor-regulating mechanisms by engaging with all three members of the triangle. Both mTOR and c-Myc (unbolded) induce p53 activation when initially encountering DNA damage stress but are both capable of, upon overexpression or sustained activation (bolded), promoting tumorigenesis by inhibiting p53 activity. Created with BioRender.com.

As a negative feedback mechanism to integrate DNA damage response into cellular metabolism, mTOR activation increases p53 activity. In the event of PTEN loss, mTOR directly binds and phosphorylates p53 to promote senescence, a phenomenon previously known to be regulated by mTOR to counter DNA damage (Korotchkina et al., 2010; Jung et al., 2019). Miceli et al. (2012) showed that, in response to oncogenic Ras signaling or loss of TSC function, activated mTOR enhances translation of existing *ARF* mRNA to promote p53 activity and tumor suppression. In cases with loss of TSC function, mTOR also induces p53 activity by activating S6 kinase 1 (S6K1) to phosphorylate MDM2 and compromise its ability to move to the nucleolus (Lee et al., 2007; Lai et al., 2010). It is worth noting, however, that excessive activation of AKT/mTOR signaling results in p53 inhibition to promote tumorigenesis in some cancers due to AKT-mediated stimulation of MDM2 (Mayo and Donner, 2001). Combined inhibition of AKT/mTOR and MDM2 in these cancers, therefore, showed some promise as a therapeutic strategy (Kojima et al., 2008; Daniele et al., 2015). A novel pro-tumorigenic activity induced by mTOR-MDM2 pathway was recently described in tumor microenvironment (TME). Kamer et al. (2020) showed that lung cancer cells induce mTOR-dependent MDM2 translation in stromal cells, establishing a positive feedback loop to promote neighboring cancer cells' metastatic potential. This mechanism was shown to be independent of stromal-p53, representing another dimension of mTOR's tumor-promoting activity.

Endogenous c-Myc induces ARF expression and p53-dependent apoptotic programs upon initial response to DNA damage, but ultimately selects for spontaneous inactivation of ARF-MDM2-p53 pathway leading to tumorigenesis (Zindy et al., 1998; Eischen et al., 1999; Nieminen et al., 2013; Phesse et al., 2014). To suppress c-Myc-induced tumorigenesis, p53 can transcriptionally repress c-Myc directly through promoting histone deacetylation or indirectly through induction of microRNA (miR)-145 (Ho et al., 2005; Sachdeva et al., 2009). ARF directly interacts with c-Myc or its transcriptional cofactor Miz1 to inactivate pro-tumorigenic transcriptional programs and induce growth arrest and cell death even in the absence of p53 (Datta et al., 2004; Qi et al., 2004; Herkert et al., 2010). Two parallel pathways through MDM2 have also been described to sustain p53 activity to counter c-Myc's pro-tumorigenic functions. In addition to ARF-MDM2 interaction, ribosomal protein (RP)-MDM2 interaction is also required to maximize p53 activity to inhibit c-Myc-induced tumorigenesis (Macias et al., 2010; Meng et al., 2015). Two recent studies demonstrated how c-Myc targets p53-MDM2-ARF tumor-suppressive axis by regulating two separate long noncoding RNAs (lncRNAs). Xu et al. (2020) identified SENEBLOC, a c-Myc-induced lncRNA involved in evasion of senescence by acting as a scaffold to increase association between p53 and MDM2, thus promoting p53 degradation. Another c-Myc

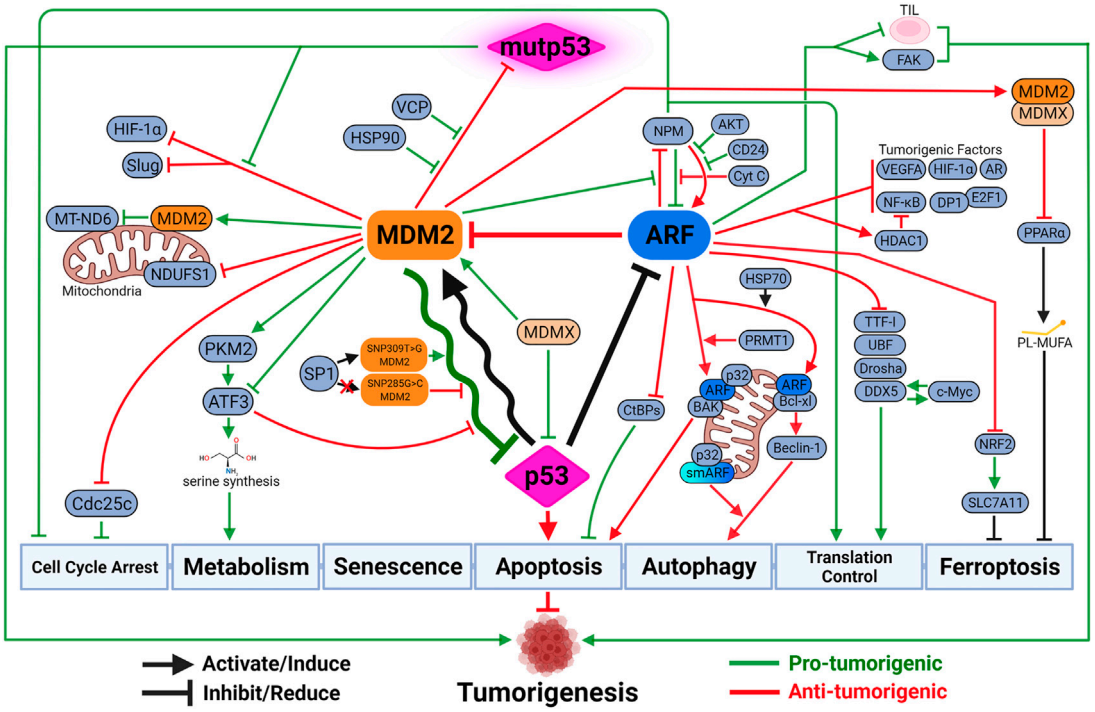

FIGURE 3 | The updated look at the p53-MDM2-ARF functional complex. Both MDM2 and ARF mediate a variety of p53-independent functions to regulate tumorigenesis. These functions can be either synergistic with or antagonizing against p53-medaited tumor-suppressive activities. Due to the negative feedback loop, the oscillatory relationship between MDM2 and p53 dictates the intensity and duration of p53-mediated tumor-suppressive activities. The outcome of the oscillation depends on their respective expression and activity levels, which are influenced by genetic alterations such as SNP and mutations. Paradoxically, MDM2 sometimes exhibits anti-tumorigenic activity by inhibiting mutant p53 (mutp53) functions, inhibiting pro-tumorigenic factors upon p53 activation, or inducing other tumor-suppressive mechanisms like ferroptosis. ARF also possesses tumor-promoting capabilities when protecting cancer cells against specific types of cell death like anoikis, or exhausting functions of tumor-infiltrating lymphocytes (TIL) to promote cancer progression. Created with BioRender.com.

responsive lncRNA, c-Myc-Inducible Long noncoding RNA Inactivating p53 (MILIP), was found to promote p53 turnover by reducing p53 SUMOylation through inhibiting tripartite-motif family-like 2 (TRIML2) (Feng et al., 2020). As TRIML2 has been found to influence cell fate decisions based on duration of p53-mediated response, the exact dynamic between c-Myc and p53 could dictate outcomes of c-Myc-induced tumorigenesis, including response to different therapies (Kung et al., 2015).

Interestingly, SUMOylation of p53 has been shown as a significant PTM mechanism through which MDM2 and ARF regulate p53 functions. Both MDM2 and ARF can mediate small ubiquitin-like modifier (SUMO)-1-mediated SUMOylation of p53 through their ability to target p53 to the nucleolus (Chen and Chen, 2003). Mechanistically, ARF interacts with a specific spliced variant of promyelocytic leukemia protein (PML), PML IV, to stabilize SUMO1-conjugating enzyme UBC9 in nuclear bodies (NB) to promote p53 SUMOylation and activation (Ivanschitz et al., 2015). ARF also mediates p53-independent functions by inducing SUMOylations of other targets, including NPM and MDM2 (Xirodimas et al., 2002; Tago et al., 2005). In human cells, MDM2-ARF complex, independent of their ability to relocate to nucleolus, also promotes SUMO-2/3-mediated SUMOylation of p53 to modulate its transcriptional activity (Stindt et al., 2011). As SUMOylation is emerging as a promising therapeutic target in cancer, its interaction with p53-MDM2-ARF pathway will be under increasing scrutiny (Kroonen and Vertegaal, 2021).

THE CURIOUS CASE BETWEEN MDM2 AND P53

Evolutionarily, structural and functional features between MDM2 and p53 are highly conserved from multi-cellular eukaryotic organisms to mammals like mouse and human (Lane et al., 2010). It suggests a critical role of p53-MDM2 hub in consolidating diverse stress signaling pathways to determine cell fates. It is posited that one of the advantages of a biological central-hub like p53-MDM2 is ability to build functional complexity, including redundant, compensatory and feedback pathways, around it as needed (Levine, 2020). For example, DNA damage sensor activating transcription factor 3 (ATF3) activates p53 by preventing its degradation by MDM2, which in turn mediates ubiquitination and

degradation of ATF3 to inactivate p53 (Yan et al., 2005; Mo et al., 2010) (**Figure 3**).

Tug-of-War Oscillatory Relationship Between p53 and MDM2

Part of this complexity can be attributed to oscillatory relationship between MDM2 and p53. The regulatory feedback loop, which allows p53 to upregulate its own inhibitor MDM2, is meant to suppress lethal p53 activity in normal cells and during development (de Oca Luna et al., 1995; Jones et al., 1995; Ringshausen et al., 2006). As the result, the mutual relationship between p53 and MDM2 can dictate physiological homeostasis outside the context of cancer development. For example, normal aging process relies on a balanced p53-MDM2 signaling network, of which dysregulations lead to premature aging or pathological conditions (Wu and Prives, 2018). Interestingly, it has been shown that p53 oscillates faster in mouse and rat cells than in cells from human, monkey, or dog. It is suggested that faster p53 oscillations in mouse might be due to subtle changes in p53 RE of mouse MDM2, leading to altered expression of MDM2 and a stronger feedback loop signal (Stewart-Ornstein et al., 2017). These variations could have significant consequences, due to the connected nature between p53-MDM2 oscillations and transcriptional regulations of p53 target genes (Hafner et al., 2017). In cancer cells, it is suggested that oscillatory p53-MDM2 activity is dictated by the intensity of stress signals, as well as expression level of p53 and MDM2 upon encountering stresses (Lev Bar-Or et al., 2000; Lahav et al., 2004; Ma et al., 2005). This hypothesis was demonstrated in cells with a single nucleotide polymorphism (SNP) of *MDM2* (SNP309T>G; rs2279744) that results in higher level of MDM2 and inhibition of coordinated p53-MDM2 oscillation (Hu et al., 2007). Higher expression of SNP309T>G *MDM2* is due to increased affinity of its transcriptional activator Sp1, which preferentially responds to estrogen signaling (Phelps et al., 2003; Bond et al., 2004). As the result, SNP309T>G *MDM2* is found to associate with accelerated tumor formation in a gender-specific and hormone-dependent manner (Bond et al., 2006; Post et al., 2010). In contrast, another *MDM2* SNP that is only 24 base pairs upstream of SNP309, SNP285G>C (rs117039649), disrupts an Sp1-binding site to decrease MDM2 expression. SNP285G>C is exclusively found in Caucasians and, when coexisting with SNP309T>G, associates with reduced risks for female reproductive cancers (Knappskog et al., 2011). Interestingly, increased longevity was observed in females with SNP309T>G *MDM2* if they didn't suffer from cancer diagnoses (Gross et al., 2014). This phenomenon could be attributed to higher MDM2 expression leading to suppressed p53 stress response in stem cell populations. Similar paradoxical regulations between cancer susceptibility and metabolic fitness have been linked to other SNPs in p53-MDM2 pathway, including Proline72Arginine (P72R; rs1042522) and Proline47Serine (P47S; rs1800371) of p53 (Kung et al., 2015; Jennis et al., 2016; Kung et al., 2016; Kung et al., 2017; Gnanapradeepan et al., 2020). It remains to be seen if these SNPs also impact the fine balance separating tumorigenesis and homeostasis through regulating oscillatory activity between p53 and MDM2.

Tumor-Suppressive Functions of MDM2

Negative feedback activity is not the only outcome for p53-mediated MDM2 induction. For example, in non-small-cell lung cancer (NSCLC), WT p53 suppresses cancer metastasis by facilitating MDM2-mediated degradation of metastatic promoter Slug (Wang et al., 2009). More recently, p53-induced MDM2 was found to slow down cell cycle progression by promoting degradation of mitosis-promoting factor Cdc25C, which is also a transcriptionally-repressed target of p53 (Clair et al., 2004; Giono et al., 2017). Considering that MDM2 can potentially reach many targets through its E3 ligase activity, the consequence of p53-induced MDM2 expression could be tumor-promoting or tumor-suppressing depending on the cell type and surrounding factors. Hypoxia-inducible factor 1-alpha (HIF-1α) is another pro-tumorigenic factor that can be degraded by MDM2 in a p53-dependent manner (Ravi et al., 2000). Interestingly, mutant p53 (mutp53) was found to exert its tumor-promoting activity by dissociating HIF-1α from MDM2, leading to HIF-1α upregulation (Kamat et al., 2007). The aforementioned metastatic promoter Slug can also be stabilized in the presence of mutp53, which represses MDM2 through inhibiting p73-mediated MDM2 transactivation (Wang et al., 2009). MDM2 can also mediate the degradation of mutp53 and keep it at basal levels in cancer cells (Haupt et al., 1997; Terzian et al., 2008). Since mutp53 is incapable of inducing MDM2 expression to complete the feedback loop, it can be stabilized through interacting with factors disrupting mutp53-MDM2 complex, such as heat shock protein (HSP) chaperones HSP90 and valosin-containing protein (VCP), to execute pro-tumorigenic activities (Midgley and Lane, 1997; Peng et al., 2001; Li et al., 2011a; Wang et al., 2021). The recent finding demonstrating functional plasticity of mutp53 between tumor-suppressor and tumor-promoter revealed new dimension in p53 biology, including MDM2's potential role in regulating mutp53 activities (Kadosh et al., 2020).

MDM2 Functions Antagonizing Against or Synergizing With p53 Activity

Not surprisingly, functional complexity evolving around MDM2 has drawn increasing attention in recent years (Klein et al., 2021). Many MDM2-mediated functions have been shown to operate independent of p53 but demonstrate capacities to synergize or antagonize p53-mediated pathways. It is well established that mitochondria p53 confers important biological functions, both in mediating mitochondria-based apoptosis and regulating mitochondrial respiration to control cancer development (Leu et al., 2004; Murphy et al., 2004; Matoba et al., 2006). It has been shown that upon oxygen deprivation, a fraction of MDM2 localizes to the mitochondria in p53-independent manner, inhibits mitochondrial respiration by reducing complex I subunit NADH-dehydrogenase 6 (MT-ND6), enhances

reactive oxygen species (ROS) production, and promotes cancer cell migration and invasion (Arena et al., 2018). Interestingly, however, a more recent study showed that cytosolic MDM2, by sequestering mitochondria stabilizer NADH:ubiquinone oxidoreductase 75 kDa Fe-S protein 1 (NDUFS1), induces ROS to promote apoptosis (Elkholi et al., 2019). It remains to be seen what regulatory mechanisms differentiate MDM2's ability to promote or inhibit tumorigenesis through regulating mitochondria functions.

Under metabolic stress, p53 can support cancer cell proliferation and survival by mediating metabolic reprogramming. One such mechanism manifests in the event of serine deprivation, during which p53 activates the synthesis of serine and glutathione, preserving anti-oxidant activity to reduce oxidative stress (Maddocks et al., 2013). MDM2 is also capable of triggering serine synthesis pathway upon serine starvation, independent of p53, through PKM2 (pyruvate kinase 2)-mediated recruitment to chromatin to facilitate a ATF3/4-mediated transcriptional program (Riscal et al., 2016). It will be interesting to dissect the regulatory mechanisms distinguishing this pathway and aforementioned p53-MDM2-ATF3 feedback loop upon DNA damage. In contrast to the pro-tumorigenic functions in response to serine depletion, MDM2 and p53 can also converge on anti-tumorigenic pathways, such as an iron-dependent form of nonapoptotic cell death, ferroptosis (Stockwell et al., 2017). Jiang et al. (2015) first showed that ferroptosis is a critical mechanism for p53-mediated tumor suppression. Their argument relies on the fact that an acetylation-defective p53 mutant, p53(3KR), retains ferroptosis-inducing and tumor-suppressing capabilities despite failing to promote cell-cycle arrest, senescence and apoptosis. This is supported by the discovery that a African-centric, cancer-predisposing p53 polymorphism P47S has impaired ability to promote ferroptosis by inducing levels of antioxidants coenzyme A (CoA) and glutathione (GSH) (Jennis et al., 2016; Leu et al., 2019). Interestingly, Liu et al. (2017a) showed that mutp53 can sensitize some cancer cells to ferroptosis by inhibiting the cystine/glutamate antiporter and glutathione biosynthesis, providing another mechanistic basis for p53 reactivation therapy. A recent finding by Venkatesh and colleagues showed that MDM2, working in a complex with Murine Double Minute X (MDMX), facilitates ferroptosis through altering cellular lipid profiles and preventing anti-oxidant responses (Venkatesh et al., 2020). Interestingly, MDM2's positive regulation of ferroptosis may not be entirely p53-independent. It was shown in some cancer cells, stabilization of p53 by MDM2 inhibitor Nutlin-3 delays ferroptosis induced by cystine deprivation (Tarangelo et al., 2018). This phenomenon was found to depend on the p53 target gene p21, but the underlying mechanism is still unclear. Whether this effect is dictated by the p53-MDM2 relationship and sensitive to other forms of MDM2 regulations requires more extensive studies.

MDMX Regulates MDM2-p53 Functions

Despite the recent discovery of its role collaborating with MDM2 to promote ferroptosis, MDMX (also known as MDM4) is mostly considered a pro-tumorigenic factor like MDM2 (Ramos et al., 2001). Similar to MDM2, MDMX can directly inhibit p53 functions through binding between their N-terminal domains (Shvarts et al., 1996; Danovi et al., 2004). The functional significance of MDMX-mediated p53 inhibition was demonstrated in a transgenic mouse model where loss of *Trp53* rescues embryonic lethality caused by *Mdm4* deletion (Parant et al., 2001).

In addition to inhibiting p53 functions directly, MDMX's contribution to tumorigenesis could also be attributed to its ability to enhance MDM2 activity. Although MDMX does not possess intrinsic E3 ligase activity, early investigations showed that it can form heterodimers with MDM2 to increase MDM2 stability and promote MDM2-mediated ubiquitination and degradation of p53 (Sharp et al., 1999; Gu et al., 2002; Linares et al., 2003). Subsequent studies revealed that the C terminus of MDMX not only is required for the formation of MDM2/MDMX heterodimer, but also is able to rescue E3 ligase activity lost in MDM2 containing E3-defective C-terminal mutations (Singh et al., 2007; Uldrijan et al., 2007). Moreover, it was later shown that MDM2/MDMX heterodimer is a more efficient E3 ligase of p53 compared to MDM2 homodimer, suggesting that it could be the predominant form in cells regulating p53 functions (Kawai et al., 2007; Huang et al., 2011; Leslie et al., 2015). The functional relationship between p53, MDM2 and MDMX is evolutionarily conserved, highlighting their importance in maintaining physiological homeostasis (Momand et al., 2011; Dolezelova et al., 2012; Coffill et al., 2016). Interestingly, MDMX's E3 ligase activity was found to be retained in some invertebrates and can be restored in the human ortholog by substituting a few amino acids (Iyappan et al., 2010; Coffill et al., 2016). It suggests that functions of MDMX have evolved to adapt to increasing environmental complexities, potentially through its interactions with MDM2 and p53 (Tan et al., 2017).

THE EXPANDING UNIVERSE BETWEEN ARF AND P53

The importance of ARF in tumor suppression was readily demonstrated in mouse models. Transgenic mice homozygous for *Arf* loss ($p19Arf^{null}$) succumb to spontaneously-developed tumors of a wide spectrum, including sarcomas, lymphomas, carcinomas and nervous system cancers, within a year (Kamijo et al., 1997; Kamijo et al., 1999). Functional distinctions between Arf and p16Ink4a were also evident in mice, in which loss of both tumor suppressors results in significantly more severe phenotypes (Sharpless et al., 2004). The picture of ARF's functional significance in human cancers is murkier. Despite the loss of *CDKN2A* being the most frequent genetic event second only to p53 mutations, it is difficult to dissect the respective contributions of p14ARF and p16INK4A to tumor suppressions in human. Despite the limitations, ARF-specific alterations, both proteogenomic and epigenetic, have been found in a wide variety of human cancers including central nervous system, bladder, colon, breast, prostate, ovarian, liver,

gastric, lung, head and neck, as well as hematologic cancers. It unequivocally suggests that ARF plays a critical role in tumor suppression (Maggi et al., 2014; Inoue and Fry, 2018).

ARF Mediates p53-independent Tumor Suppression

The first indication that ARF possesses p53-independent functions was revealed when *Arf*/*Trp53* double-knockout and *Arf*/*Trp53*/*Mdm2* triple-knockout mice developed tumors of distinctive origins compared to Arf^{null} or $Trp53^{null}$ mice (Weber et al., 2000b). A similar conclusion has been reached in human cancers through demonstrations that 1) ARF is capable of suppressing tumor progression in the absence of active p53; and 2) loss of ARF often synergizes with dysregulated p53 to promote tumorigenesis (Eymin et al., 2003; Sandoval et al., 2004; Muniz et al., 2011; Forys et al., 2014). Moreover, high prevalence of *TP53* and *CDKN2A* co-inactivation has been identified in a variety of cancers, including glioblastoma, hepatocellular carcinoma, lung cancer, pancreatic cancer, bladder cancer, and triple-negative breast cancer (TNBC) among others (Cerami et al., 2012; Gao et al., 2013). It further implicates ARF's p53-independent tumor-suppressive functions, although more studies are needed to define ARF's roles apart from those of p16INK4A in each cancer type.

ARF and NPM

Several p53-independent mechanisms have been associated with ARF-mediated tumor suppression. In response to hyperproliferative signals, ARF sequesters pro-tumorigenic nucleophosmin (NPM) in nucleolus to promote cell cycle arrest (Brady et al., 2004). The relationship between ARF and NPM appears to be mutual, but the impact of NPM on ARF function is context dependent. The interaction between ARF and NPM can preserve ARF function by preventing its degradation, while overexpressed NPM or cancer-associated NPM mutants have been shown to inhibit ARF functions by restricting its ability to translocate between nucleolus and cytoplasm (Bertwistle et al., 2004; Kuo et al., 2004; Korgaonkar et al., 2005; Colombo et al., 2006; Moulin et al., 2008). This unique relationship between ARF and NPM not only can be disrupted by MDM2, but is also sensitive to other factors, including AKT, cytochrome c, and CD24 to regulate p53-dependent and -independent functions of ARF (Brady et al., 2004; Hamilton et al., 2014; Wang et al., 2015; González-Arzola et al., 2020). ARF-NPM interaction also regulates ARF's ability to promote apoptosis independent of p53 (Hemmati et al., 2002; Eymin et al., 2003).

ARF Functions at the Mitochondria

ARF-mediated apoptosis relies on ARF's ability to localize to mitochondria, and is regulated by the interaction between ARF and mitochondrial protein p32 (Itahana and Zhang, 2008). A recent study elucidated the underlying mechanism by showing that, under genotoxic stresses, PRMT1 (protein arginine methyltransferase 1) methylates arginine residues within the NLS/NoLS of ARF, resulting in the release of ARF from NPM and increased interaction between ARF and p32 (Repenning et al., 2021). Mitochondria-bound ARF induces apoptosis by activating BAK instead of BAX, suggesting a tightly-regulated process controlling ARF-mediated apoptosis in the absence of p53 (Müer et al., 2012).

BAK-dependent apoptosis is not the only anti-tumorigenic mechanism that ARF induces once reaching mitochondria. With the help of heat shock protein 70 (HSP70), ARF travels to mitochondria, interacts with Bcl-xl, disrupts the Bcl-xl/Beclin-1 complex to release autophagic factor Beclin-1 to induce autophagy (Abida and Gu, 2008; Pimkina et al., 2009; Pimkina and Murphy, 2011). This ability to induce autophagic cell death from mitochondria is interestingly shared by the full-length ARF and a shorter isoform of ARF, smARF (short mitochondrial ARF) (Reef et al., 2006; Budina-Kolomets et al., 2013). The contribution of smARF to tumor suppression remains controversial due to its low abundance and unstable nature, but its physiological function has been clearly demonstrated in a mouse model where expression of smArf significantly rescued developmental defects of *Arf*-null mice (van Oosterwijk et al., 2017). Interestingly, p32 was also found to interact with and stabilize smARF, raising the question that if p32 serves as an arbitrator at mitochondria to regulate both apoptosis and autophagy triggered by ARF and smARF (Reef et al., 2007). Both mitochondrial p32 and ARF have been shown to control metabolic programming between oxidative phosphorylation and glycolysis (Fogal et al., 2010; Christensen et al., 2014; Gotoh et al., 2018; Koss et al., 2020). Since the metabolic state of mitochondria is important in regulating both cancer cell-intrinsic and -extrinsic mechanisms, ARF's influence on tumor metabolism independent of p53 warrants further investigation (Xiao et al., 2019; Yao et al., 2019).

ARF and Translational Control

By virtue of being an nucleolar protein, ARF exerts p53-independent tumor suppression through regulating ribosome biogenesis, ribosomal RNA (rRNA) processing and translation (Sugimoto et al., 2003; Cottrell et al., 2020). ARF-mediated regulation of NPM is also involved in this process, as ARF reduces function and stability of NPM required for ribosome biogenesis (Itahana et al., 2003; Apicelli et al., 2008; Maggi et al., 2008). ARF has been shown to regulate ribosomal functions and translation through many other mechanisms, such as directly interacting with rRNA promoter, blocking nucleolar import of RNA polymerase I transcription termination factor (TTF-I), inactivating rRNA transcriptional factor upstream binding factor (UBF), downregulating rRNA-processing enzyme Drosha, and limiting nucleolar localization of RNA helicase DDX5 (Ayrault et al., 2004; Lessard et al., 2010; Saporita et al., 2011; Kuchenreuther and Weber, 2014). Interestingly, ARF's ability to interact with DDX5 also prevents interaction between DDX5 and c-Myc, disrupting a oncogenic positive feedback loop that increases c-Myc-mediated transcription and cell transformation (Tago et al., 2015).

Other p53-independent Tumor-Suppressive Functions of ARF

The reach of ARF's p53-independent, tumor-suppressive functions extends to many other cancer-related pathways. To

inhibit pro-tumorigenic machineries, ARF blocks E2F1's transcriptional activity by interacting with E2F1 and E2F1 cofactor DP1; inhibits HIF-1α-mediated transcription by sequestering HIF-1α in nucleolus; attenuates NF-κB functions by recruiting transcriptional repressor histone deacetylase 1 (HDAC1) to NF-κB subunit RelA/p65; interacts with androgen receptor to repress its transactivation activity; and suppresses translation of tumor angiogenic factor vascular endothelial growth factor A (VEGFA) (Eymin et al., 2001; Fatyol and Szalay, 2001; Martelli et al., 2001; Datta et al., 2002; Rocha et al., 2003; Datta et al., 2005; Kawagishi et al., 2010; Lu et al., 2013). ARF also interacts directly with anti-apoptotic transcriptional corepressor C-terminal binding protein 1 (CtBP1) and 2 (CtBP2), leading to their degradation and p53-independent apoptosis (Paliwal et al., 2006; Kovi et al., 2010).

ARF also promotes other anti-tumorigenic mechanisms. In response to DNA damage, ARF induces both p53-dependent and -independent senescent response, the later through ATM/ATR/CHK signaling pathway (Eymin et al., 2006; Carlos et al., 2013; Monasor et al., 2013). Another binding partner of ARF is nuclear factor erythroid 2-related factor 2 (NRF2), which transcriptionally activates *SLC7A11*, a component of the cystine/glutamate antiporter complex. By importing cystine, SLC7A11 promotes biosynthesis of antioxidant glutathione (GSH), resulting in reduction of ROS and lipid peroxides (DeNicola et al., 2011; Ye et al., 2014). By interacting with NRF2, ARF inhibits SLC7A11 expression to promote lipid peroxidation and trigger ferroptosis (Chen et al., 2017). With the list of regulated cell death mechanisms ever-increasing, more p53-independent tumor-suppressive pathways induced by ARF could be discovered in the very near future (Tang et al., 2019).

Co-Inactivation of p53 and ARF

Considering the plethora of p53-independent pathways described for ARF-mediated tumor suppression, there is surprisingly few mechanistic studies conducted in cancers with co-inactivation of p53 and ARF. Forys et al. used both mouse embryonic fibroblast (MEF) and human TNBC cell lines to show that co-inactivation of p53 and ARF induces an pro-tumorigenic signaling signature that includes induction of interferon-β (IFN-β) and activation of signal transducer and activator of transcription 1 (STAT1) (Forys et al., 2014). In a Eμ-Myc-driven lymphoma mouse model recapitulating late-stage p53 inactivation, Klimovich et al. (2019) showed that loss of ARF confers resistance to p53 restoration in established lymphoma. This result suggests that co-inactivation of p53 and ARF not only exacerbates tumorigenesis, but also compromises efficacy of p53 reactivation therapy. On the other hand, evidence is emerging to link co-inactivation of p53 and ARF to novel therapeutic opportunities. Co-deletion of *TP53* and *CDKN2A* was recently linked to gastric premalignancy and cancer progression mediated by dietary carcinogens (Sethi et al., 2020). Despite being a malignancy-driving event, co-deletion of *CDKN2A* following p53 inactivation also induces replication stress and sensitizes cancer cells to DNA damage response inhibitors. Since deletion of *CDKN2A* in this study didn't distinguish between p16INK4A and ARF, the exact contribution of ARF needs to be further studied. The same caveat is applied to the same group's another study in esophageal squamous cell carcinoma, where they found that *Trp53*/*Cdkn2a* loss synergizes with transcription factor Sox2 to promote chromatin remodeling, enhance Stat3 functions, activate endogenous retroviruses, and induce double-stranded RNA expression and dependence of RNA editing enzyme ADAR1 (Wu et al., 2021). Implication of this study could inform new strategies to develop therapies against cancers that display similar characteristics (p53/ARF co-inactivation and ADAR1 dependency), such as TNBC (Forys et al., 2014; Kung et al., 2021).

Tumor-Promoting Functions of ARF

It is worth noting that ARF's p53-independent functions have been suggested to promote cancer progression under certain circumstances. Overexpression of ARF in cancer has been mostly considered a byproduct of p53 mutation due to the previously mentioned negative feedback loop, and generally correlated with better prognosis (Kamijo et al., 1998; Silva et al., 2001; Song et al., 2014). Several studies, however, have provided mechanistic insights regarding how ARF's presence might promote progression of some cancers. Humbey et al. (2008) first described, in a mouse model, that overexpression of ARF protects Eμ-Myc-driven lymphoma by inducing autophagy in response to nutrient starvation. Their data suggests that ARF, in a tumor-type specific manner, controls the switch between cyto-toxic and cyto-protective effects of autophagy in response to metabolic stress. Another cell-intrinsic pro-survival function of ARF was shown in spreading cancer cells in which ARF interacts with focal adhesion kinase (FAK) to stabilize cytoskeleton structure and protect cells from anoikis, a form of programmed cell death during cell detachment (Vivo et al., 2017). A recent study also shed some light on a cell-extrinsic mechanism through which ARF behaves as a tumor promoter. Koss et al. showed that during cancer development, tumor-induced metabolic stress suppresses function of epigenetic modifier enhancer of zeste homolog 2 (EZH2), leading to upregulation of ARF. Without affecting p53 function, ARF promotes mitochondrial dysfunction and metabolic exhaustion of tumor-infiltrating lymphocytes (TIL), resulting in cancer progression (Koss et al., 2020). More ARF-mediated pathways, p53-dependent and -independent, are expected to be identified in regulating TME functions.

THERAPEUTIC OPPORTUNITIES TO TARGET P53-MDM2-ARF TRIANGLE

Potential therapies to activate p53 command the most attention in development of drugs targeting p53-MDM2-ARF network. Direct restoration of WT p53 expression using intra-tumoral injection of p53-delivering adenovirus has been used to treat cancers in China since 2003 (Xia et al., 2020). Extreme cautiousness towards gene therapy in general and p53-targeting gene therapy in particular casts a cloud over when this treatment will become clinically available worldwide. In contrast, tremendous amount of efforts have been devoted to develop pharmacological activators of p53, including activators of

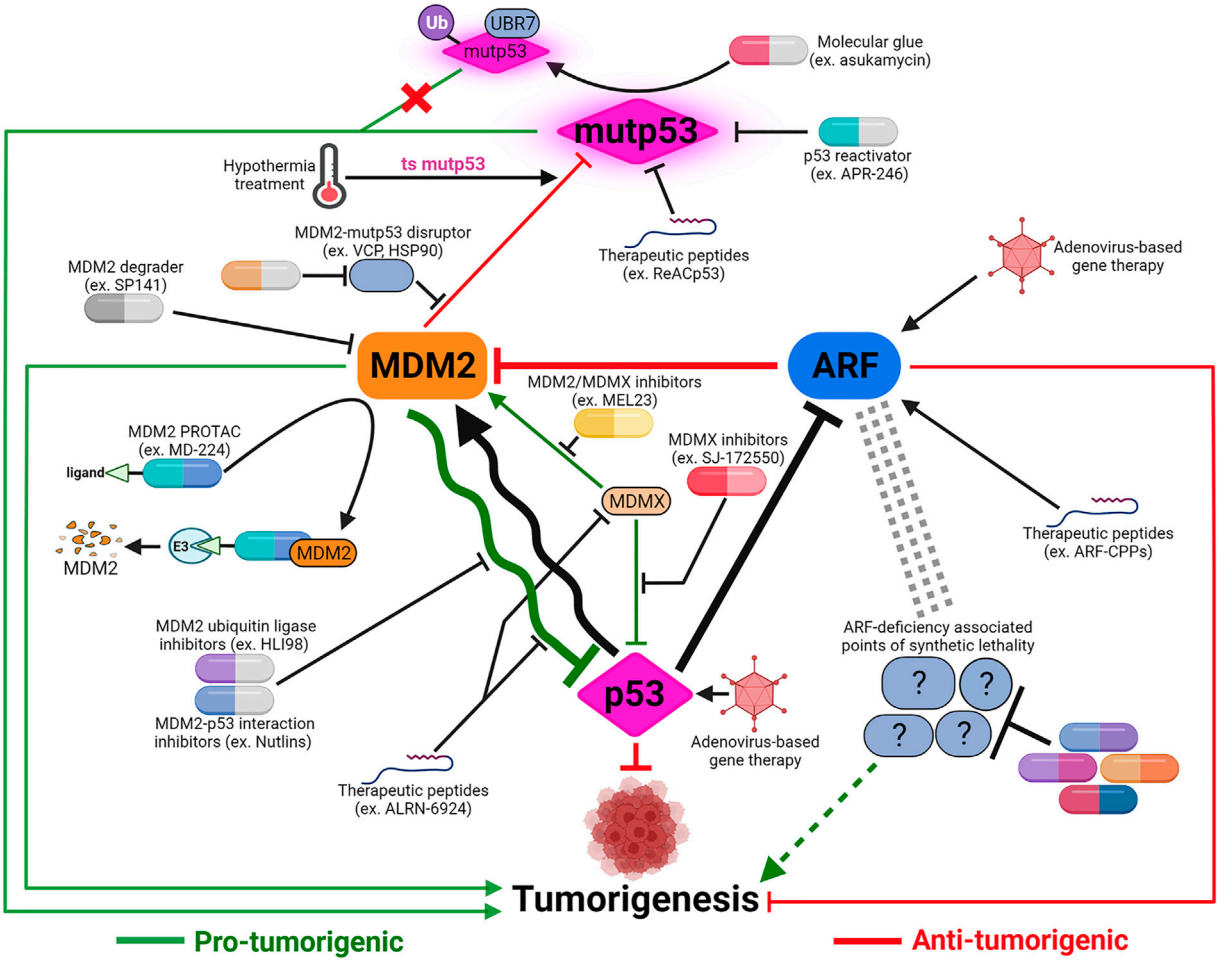

FIGURE 4 | Cancer therapeutic strategies targeting the p53-MDM2-ARF signaling axis. The majority of p53-based therapeutic strategies are designed to reactivate mutant p53 or inhibit MDM2-p53 and MDM2/MDMX-p53 interactions using small molecules. Development of alternative strategies, such as applying hypothermal therapy to induce MDM2-mediated degradation of temperature-sensitive mutp53, or utilizing pan-MDM2 inhibitors, are meant to maximize anti-tumor potency depending on the context of MDM2-p53 relationship. In addition to small molecules, other modalities including therapeutic peptides and proteolysis targeting chimera (PROTAC) are also being explored to target both MDM2's p53-dependent and -independent functions. The realization of ARF's many p53-independent functions and the functional significance of p53-ARF co-inactivation in cancers necessitates development of ARF-based therapies. Virus-mediated gene therapy and therapeutic peptides are potential ways to restore ARF functions. Identification of synthetic lethality associated with ARF deficiency can uncover novel therapeutic targets to compensate for ARF loss and potentially synergize with p53-targeting treatments. Created with BioRender.com.

WT p53 and re-activators of mutp53 to restore p53 functions (Nguyen et al., 2017). Other than PRIMA-1^{MET} (also called APR-246), a small-molecule mutp53 re-activator, most p53-targeting drugs in active clinical development/trials are small molecules that stabilize WT p53 by interrupting p53-MDM2 interaction or inhibiting MDM2's ubiquitin ligase activity (**Figure 4**).

Therapeutic Peptides for p53 Activation

Although small molecules still dominate the drug discovery landscape, other modalities have been explored as p53 activators, such as therapeutic peptides (Marqus et al., 2017). Small peptides derived from N-terminal MDM2-binding domain of p53 were shown to induce p53-mediated anti-tumorigenic activities more than 20 years ago (Böttger et al., 1997; Kanovsky et al., 2001). Efforts to apply p53/MDM2-targeting therapeutic peptides for cancer treatment culminated in the development of a p53-derived stapled peptide, ALRN-6924. ALRN-6924 exhibits dual MDM2/MDMX inhibitory activities and has shown promise in preclinical studies and early-stage clinical trials to halt progression of cancers bearing WT p53 (Carvajal et al., 2018; Pairawan et al., 2021; Saleh et al., 2021). A recent study showed that ALRN-6924 induces inflammatory response in melanoma to alter TME and overcome tumor immune evasion, suggesting its potential utility in combination with immunotherapy (Zhou et al., 2021a). Therapeutic peptides also have potential to treat cancers with mutp53. Soragni et al. (2016) showed that a cell-penetrating peptide (CPP) derived from DNA binding domain of p53, ReACp53, inhibits mutp53 aggregation and rescues WT-like p53 functions in high-grade serous ovarian carcinomas. The concept of using targeted protein degradation (TPD) to treat

cancers with mutp53 is also being explored (Dale et al., 2021). Isobe et al. (2020) identified a small molecule, asukamycin, that serves as a "molecular glue" linking mutp53 with E3 ubiquitin ligase UBR7. Interestingly, however, that instead of degrading mutp53, treatment of asukamycin results in non-proteolytic ubiquitination and activation of mutp53 to promote cell death in TNBC cells.

Novel Therapeutic Strategies Targeting p53-MDM2 Hub

Despite the large number of candidate drugs at different stages of preclinical/clinical development, no MDM2-p53 antagonist has been approved for cancer treatment due to challenges regarding efficacy and undesired toxicity (Zanjirband and Rahgozar, 2019; Mullard, 2020). Other than identifying more drug candidates based on the similar concept, further understanding of intricate relationship between p53 and MDM2 could provide valuable insights. As mentioned previously, most MDM2-p53 antagonists were designed to disrupt N-terminal binding between MDM2 and p53 or inhibit MDM2's ubiquitin ligase activity mediated through its C-terminal RING domain. A single residue in central zinc finger domain, cysteine 305, was shown to control p53 function through interaction with RP (Lindström et al., 2007; Macias et al., 2010; Meng et al., 2015). In a mouse model ($Mdm2^{C305F}$) carrying this human cancer-associated single mutation of MDM2, it was shown that RP-MDM2-p53 pathway plays important roles in lipid metabolism and cells' response to metabolic stress (Liu et al., 2014; Liu et al., 2017b). These findings support increasing effort to develop therapies targeting zinc finger domain of MDM2, especially in the context of exploiting metabolic vulnerabilities associated with MDM2-p53 pathway. Multiple mouse models have also been utilized to suggest delicate distinctions between MDM2's ubiquitin ligase activity and ability to control p53 function. Two separate mutants of *Mdm2* (*Y487A*–Y489A in human; *I438K*–I440K in human) have been demonstrated to partially restrain p53 response to DNA damage despite losing its ability to promote p53 degradation (Tollini et al., 2014; Humpton et al., 2021). Interestingly, while $Mdm2^{Y487A}$ causes no developmental defect yet promotes p53-dependent mortality in response to sub-lethal stress in adult mice, $Mdm2^{I438K}$ leads to embryonic lethality but is tolerated when only switched on in adult mice to allow enhanced p53 response to DNA damage. These confusing discrepancies reflect a delicate balance in p53-MDM2 relationship. How to therapeutically target this equilibrium in order to control p53 dynamics could be the key to achieve balance between maximum efficacy and minimum toxicity (Purvis et al., 2012).

Another potentially useful approach is to stratify patients based on predicted response to MDM2-based therapies. It has been shown that sensitivity of cancer cells to MDM2 inhibitors could be predicted by gene signatures containing subsets of p53 target genes (Jeay et al., 2015; Ishizawa et al., 2018). Applicability of this approach remains to be seen, depending on its ability to model oscillatory relationship between p53 and MDM2. In cancer cells with mutp53, MDM2's pro-tumorigenic potential might be outweighed by its ability to suppress gain-of-function oncogenic activity of mutp53. This was recently demonstrated in pancreatic ductal adenocarcinoma, in which pharmacologic inhibition of valosin-containing protein (VCP) promotes MDM2-mediated degradation of mutp53 and cell death (Wang et al., 2021). This concept could be applied to 1) inhibit other factors disrupting MDM2-mutp53 interaction, such as HSP90 and BAG2 (Li et al., 2011b; Yue et al., 2015); or 2) tip the dynamics of MDM2-mutp53 interaction towards p53 degradation to amplify MDM2's anti-tumorigenic functions in cancers possessing mutp53 (Yang et al., 2019). Intrinsic characteristics of mutp53 could also dictate the functional consequence of p53-MDM2 interaction. A recent study demonstrated that some temperature sensitive (ts) mutp53, such as R282W and A138V, are resistant to MDM2-mediated degradation despite their ability to induce MDM2 upon reactivation. This result predicts favorable outcome of p53 reactivation in cancers possessing ts mutp53, and rationalizes including hypothermia-based treatment as part of cancer therapeutic strategy (Lu et al., 2021).

Potential Therapies Targeting Pan-MDM2 Functions

As more p53-independent functions of MDM2 are discovered, more efforts are devoted to identifying therapies targeting pan-MDM2 functions instead of MDM2-p53 interaction. A variety of small molecule inhibitors were identified to induce MDM2 auto-ubiquitination and degradation, or inhibit its interactions with non-p53 binding partners (Wang et al., 2014; Burgess et al., 2016; Singh et al., 2016; Xu et al., 2016; Nguyen et al., 2017). These inhibitors not only provide dual advantages inhibiting both p53-dependent and -independent functions of MDM2, but also demonstrate critical roles of MDM2 regulators and cofactors such as Nuclear Factor of Activated T cell (NFAT1), and X-Linked Inhibitor of Apoptosis (XIAP) (Gu et al., 2016; Gu et al., 2018; Wang et al., 2019). Inhibition of p53-independent functions of MDM2 also contributes to activities of established chemotherapeutic agents, including Adriamycin and Nilotinib (Ma et al., 2000; Zhang et al., 2014). Increasing knowledge in this field will facilitate repurposing and tailoring existing therapies towards cancers that can benefit from MDM2-targeting interventions.

TPD strategy has also been applied to develop MDM2-targeting therapies. A first-in-class MDM2 degrader using proteolysis targeting chimera (PROTAC) concept, MD-224, was shown to be highly potent in inducing MDM2 degradation and achieving durable tumor regression *in vivo* (Li et al., 2019). MD-224 consists of a modified MDM2 inhibitor conjugated with a small-molecule ligand (lenalidomide) of an E3 ligase (cereblon) degradation system. Interestingly, since MDM2 is an E3 ligase itself, MDM2-recruiting PROTAC are being developed to target itself and other pro-tumorigenic proteins to maximize p53-dependent and -independent effects in tumor suppression (Hines et al., 2019; He et al., 2021).

MDMX-Targeting Therapeutic Approaches

MDMX has emerged as a viable target for cancer therapy, both for its own ability to inhibit p53 and its role in the MDM2/MDMX complex, especially in cancers where amplification of MDMX is more prevalent than MDM2 (Gembarska et al., 2012; Burgess et al., 2016). The highly homologous yet non-identical sequence comparison between MDM2 and MDMX (>50% identical amino acid sequence in both N-terminal p53-binding and C-terminal RING domains) provides opportunities to target either MDMX specifically or the MDM2/MDMX complex. A series of molecules have been identified through MDMX-specific screens, including imidazoline derivative SJ-172550 that competes with MDMX to release functional p53 (Reed et al., 2010). SJ-172550 and other molecules subsequently identified through this approach have shown anti-tumorigenic effects and more importantly, abilities to synergize with MDM2-specific inhibitors (Reed et al., 2010; Wang et al., 2011; Wang and Yan, 2011; Karan et al., 2016). MDMX-targeting inhibitors have also been identified through indirect discoveries. Originally found to reduce proto-oncogene Survivin expression, camptothecin analogue FL118 was shown to activate p53 by promoting degradation of MDMX (Ling et al., 2014). Hsp90 inhibitor 17AAG was also found to be a potent MDMX degrader and synergize with MDM2 inhibition to activate p53 (Vaseva et al., 2011).

Specific structural features and conformational alterations upon interacting with p53 or inhibitors can inform rational drug design targeting MDM2 or MDMX. Structures of p53-MDM2 and p53-MDMX complexes revealed that their respective binding pockets are significantly different in depth and shape (Kussie et al., 1996; Popowicz et al., 2007). Distinctive conformational changes of MDM2 and MDMX upon inhibitor bindings were also identified by performing computer-aided analysis of molecular dynamics simulations (Chen et al., 2013; Chen et al., 2015). Taking advantages of these unique characteristics has led to the identification of p53 activator Inauhzin using computational structure-based screening (Zhang et al., 2012). Although Inauhzin was later found to activate p53 through inhibiting SIRT1 instead of MDMX or MDM2, similar approaches could lead to development of inhibitors distinguishing or combining MDM2-and MDMX-targeting activities.

The close structural and functional relationship between MDM2 and MDMX means that some molecules, originally identified as MDM2 inhibitors, were found to exert their activities through interfering with the MDM2/MDMX complex. The examples include MEL23 and its analogs, a number of MMRi (MDM2-MDMX RING domain inhibitors), and a pyrrolidone derivative that inhibits E3 ligase activity of MDM2/MDMX complex to activate p53 (Herman et al., 2011; Zhuang et al., 2012; Wu et al., 2015). Graves et al. (2012) instead discovered a couple of indolyl hydantoin compounds that restore p53-mediated apoptotic activity by promoting formation of dimeric complexes between MDM2 and MDMX to sequester them away from p53.

The aforementioned p53-derived stapled peptide, ALRN-6924, represents another approach to disrupt protein-protein interactions between p53 and both MDM2 and MDMX (Bernal et al., 2010; Brown et al., 2013). Interestingly, recent data from early clinical trials of ALRN-6924 showed superior toxicity profiles compared to other MDM2 inhibitors (Konopleva et al., 2020; Saleh et al., 2021). It is speculated that this observation might be attributed to ALRN-6924's dual MDM2/MDMX inhibitor status, making it a milder MDM2 inhibitor in certain tissues to minimize toxicity. It suggests that ALRN-6924, or other MDM2/MDMX dual-inhibitors, have potential as chemoprotective agents when used alongside other potent yet highly toxic chemotherapeutic drugs (Carvajal et al., 2005).

As our understanding of mechanisms surrounding MDM2 and MDMX grows (comprehensively reviewed by Klein et al.), so will our ability to design and develop cancer therapies based on disease/tissue-specific relationships between p53, MDM2 and MDMX (see reviews by Nguyen et al. and Burgess et al. for detailed overview of therapies targeting MDM2/MDMX-p53) (Burgess et al., 2016; Nguyen et al., 2017; Klein et al., 2021).

Justify the Value of ARF-Targeting Cancer Therapies

Development of ARF-targeting therapies has been handicapped by following misperceptions: 1) Linear relationship between ARF and p53: ARF and p53 are often thought to act in a linear pathway to inhibit tumorigenesis. With progress already made in developing p53-activating therapies and general difficulties in activating tumor suppressors, there is little need to devote much attention on ARF. 2) Emergence of CDK4/6 inhibitors: Recent development of selective CDK4/6 inhibitors resulted in, compared with previous generations of CDK inhibitors, lower toxicities, higher tumor-suppressive activities, and enhanced tumor immunogenicity (O'Leary et al., 2016; Goel et al., 2017). These drugs are considered magic bullets against *CDKN2A*-deficient cancers and have demonstrated promising results in preclinical/clinical settings. 3) Promise of cancer immunotherapy: Harnessing patients' own immune system to treat cancer has long been believed to be the holy grail in cancer therapy. Within the last 10 years, that belief has come to fruition with numbers of modern cancer immunotherapies, including checkpoint blockade and chimeric antigen receptor (CAR) T-cell therapies among others, dominate our attention in the fight against cancer. Cancer immunotherapy, theoretically, battles cancers in the most systematic way, bypassing needs to consider any specific aberrations in tumor-associated factors, such as tumor suppressors (Waldman et al., 2020).

A compelling argument can be made, however, to counter these misperceptions and support a strong pursuit of ARF-based cancer therapies: 1) With the number of p53-independent functions of ARF identified, there is a clear need to focus on developing therapies specifically targeting ARF-mediated pathways. ARF-based therapies have potential to synergize with p53-targeting drugs to inhibit tumorigenesis through shared tumor-suppressive mechanisms like apoptosis, autophagy and ferroptosis. 2) Despite early clinical promise, intrinsic and acquired resistance to CDK4/6 inhibitors have hindered their effectiveness (Xu et al., 2021). Mechanisms underlying resistance to CDK4/6 inhibitors, such as loss of

retinoblastoma (RB1) function, are being investigated to develop complementary or combination strategies. There is little known, however, about the role of ARF in both resistance and potential complement to CDK4/6 inhibitors. It is reasonable to believe that ARF-based therapies can provide synergistic effects with CDK4/6 inhibitors, especially in *CDKN2A*-deficient cancers. 3) Cancer immunotherapy has brought great promise, but also inevitably raised significant questions. Among challenges faced by the future of cancer immunotherapy, is understanding cancer-intrinsic factors regulating TME leading to immune evasion (Wellenstein and de Visser, 2018; Hegde and Chen, 2020). Recent studies found that genomic *CDKN2A* loss-of-function is associated with worse clinical outcome in patients treated with cancer immunotherapy in multiple cancer types (Adib et al., 2021; Gutiontov et al., 2021; Zhu et al., 2021). The reduced benefit of cancer immunotherapy can be attributed to altered tumor-immune microenvironment and compromised immune cell functions. With previous studies demonstrating ARF's ability to activate innate and adaptive immune responses within cancer cells to suppress tumorigenesis *in vivo*, ARF-targeting strategies present opportunities to augment existing cancer immunotherapies (Yetil et al., 2015; Cerqueira et al., 2020).

Development of ARF-Based Therapeutic Strategies—Therapeutic Peptides

Strategies to develop ARF-based therapies have so far been limited to gene therapy and therapeutic peptides. Adenovirus-mediated delivery of ARF had mostly been used experimentally *in vitro*, until recent studies showing its potential application using *in vivo* mouse cancer models (Saadatmandi et al., 2002; Tango et al., 2002; Cerqueira et al., 2020). This approach is expected to encounter similar obstacles faced by other gene therapies, including safety concerns and regulatory challenges, before reaching clinics (AuthorAnonymous, 2021).

In the absence of pharmaceutically proven activators, therapeutic peptides are viewed as viable alternatives to restore ARF functions. Development of therapeutic peptides in cancer therapy has seen more success and broader applications recently (Marqus et al., 2017; Xie et al., 2020). Compared to small molecules, therapeutic peptides generally have advantages of high potency, high specificity, wider range of targets and low toxicity. Recent advance and maturation of technologies for peptide synthesis, modification and delivery have helped overcome many of therapeutic peptides' shortcomings, such as poor metabolic stability, lack of oral bioavailability and high manufacturing cost (Muttenthaler et al., 2021). As peptides of 40 or less amino acids in length are regulated as small molecules for clinical applications, therapeutic peptides are uniquely positioned to fill the gap between small molecules and biologics for unmet medical needs (Rastogi et al., 2019). Peptide-based therapies also possess intrinsic characteristics, such as their propensity to cross blood-brain barrier, to make them superior drug candidates over small molecules for certain diseases (ex. central nervous system cancers) (Zhou et al., 2021b). Interference peptides designed to disrupt protein-protein interactions, like previously mentioned ALRN-6924, are relatively easy to design to achieve high target specificity and selectivity (Sorolla et al., 2020). To directly rescue or supplement for defective or deleted genes, such as tumor suppressors like ARF, peptide mimetics containing functionally significant motifs represent a new and flexible class of cancer therapeutic drugs.

A peptide containing N-terminal portion of ARF (aa 1–20) was found to bind MDM2 and inhibit p53 ubiquitination *in vitro* (Midgley et al., 2000). This observation confirmed functional significance of the N-terminal region of ARF, and synthetic peptides containing this region showed cytotoxic activity against cancer cells (Johansson et al., 2008). Although N-terminus ARF peptides display intrinsic cell-penetrating ability, potent CPPs of ARF have been generated by addition of a poly-arginine protein transduction domain (PTD) known to promote cell permeability, stability and efficacy of therapeutic peptides (Kondo et al., 2008; Allolio et al., 2018). Poly-arginine PTD has also been used to generate ARF-CPPs containing mitochondria-targeting domain (aa 38–65) to show tumor-suppressive activities in multiple cancer types (Saito et al., 2013; Saito et al., 2016). The main challenge for future development of ARF-CPPs is to achieve an acceptable balance between anti-tumor efficacy and undesired toxicity, often seen in arginine-rich CPPs to dampen confidence for their eventual clinical applications (Li et al., 2017; Lafarga et al., 2021).

Development of ARF-Based Therapeutic Strategies—Functional Antagonists Against ARF Deficiency

Another approach to develop ARF-based therapies is to identify points of synthetic lethality associated with ARF deficiency. This concept is behind the clinical success of Poly-(ADP-ribose)-polymerase (PARP) inhibitors in treatment of *BRCA1/2*-mutant cancers and has been used to identify therapeutic targets associated with defective tumor suppressors, including p53 (Gurpinar and Vousden, 2015; Patel et al., 2021). With recent advancements in cancer cohort datasets and experimental toolkits, functional proteogenomic analysis has been used to discover synthetic lethality driven by loss-of-function tumor suppressors (Xiao et al., 2020; Lei and Zhang, 2021). This strategy has been applied in cancers with high level of *CDKN2A* deficiency, but further analyses and functional validations will be needed to delineate synthetic lethality associated specifically with ARF deficiency, as most efforts to identify therapeutic opportunities associated with *CDKN2A* deficiency begin and end at p16-CDK4/6-RB pathway intervention (Oh et al., 2020; Cao et al., 2021; Satpathy et al., 2021). Using a similar approach, Zhu et al. found that breast cancer cells with *CDKN2A* mutations are more sensitive to a TTK/CLK2 inhibitor, CC-671. Whether this discovery can be attributed to ARF deficiency requires further investigation (Zhu et al., 2018).

Alternatively, pharmacogenomic screens based on concept of functional antagonism can be used to identify targetable vulnerabilities associated with dysfunctional tumor suppressors. Functionally defined or novel/diverse drug libraries are used in high-throughput screening to determine if

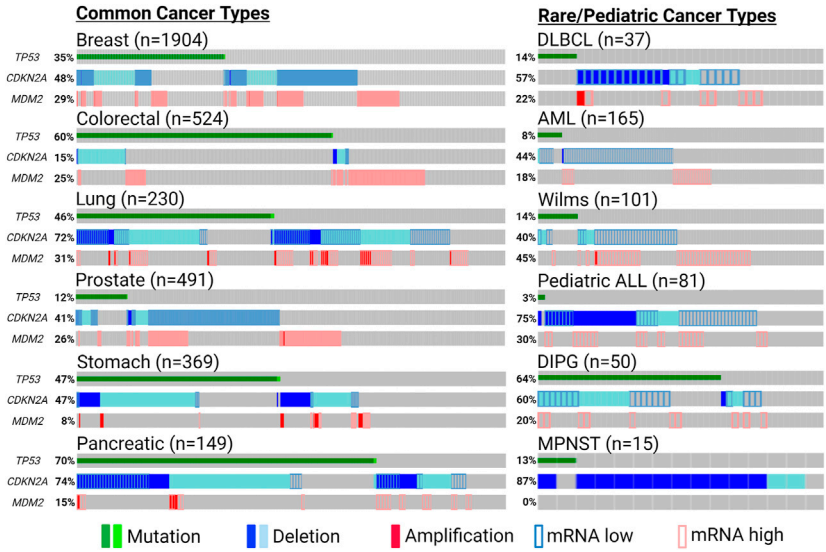

FIGURE 5 | Significant genetic alterations of p53, MDM2 and ARF in cancers. Tumor-promoting genetic events of *TP53* (non-synonymous mutation), *MDM2* (amplification or induced mRNA expression) and *CDKN2A* (deletion or reduced mRNA expression) are summarized using publicly available patient data from cBioPortal (cbioportal.org) and pediatric cBioPortal (pedcbioportal.org). Percentages shown indicate accumulated fraction of patient samples with highlighted genetic alterations. The sources of the data presented are the following: Breast—METABRIC; Colorectal/DLBCL (diffuse large b cell lymphoma)/AML (acute myeloid leukemia)—TCGA PanCancer; Lung/Prostate/Stomach/Pancreatic—TCGA Firehose; DIPG (diffuse intrinsic pontine glioma)—PNOC; Wilms/pediatric ALL (acute lymphoblastic leukemia)—TARGET; MPNST (malignant peripheral nerve sheath tumor)—MSKCC. Expression of mRNA levels (except for MPNST) are shown based on expression z-scores relative to all available diploid samples (<−0.5: mRNA low; >0.5: mRNA high). Created with BioRender.com.

the presence/absence of tumor suppressor genes in cancer cells dictates their response. This strategy could be useful to identify novel therapeutic targets or repurpose existing drugs by matching pharmacological sensitivity and genetic alterations. Bitler et al. used this approach to identify EZH2 methyltransferase as a novel target in *ARID1A*-mutated ovarian cancers, and EZH2 inhibition has since been explored as a viable therapy in other cancers with *ARID1A* mutations (Bitler et al., 2015; Alldredge and Eskander, 2017; Ferguson et al., 2021; Yamada et al., 2021). The same approach was also utilized in recent studies to identify novel therapeutic opportunities against cancers with defective RB1 tumor suppressor. Witkiewicz et al. used TNBC cells treated with CDK4/6 inhibitors and an FDA-approved drug library (1,280 compounds) to identify CHK and PLK1 inhibitors specifically antagonized by functional RB, while Gong et al. applied a limited set of drugs (36 cell-cycle inhibitors) to show that inhibition of Aurora A kinase is synthetic lethal with *RB1* mutation in a panel of diverse cancer cell lines (Witkiewicz et al., 2018; Gong et al., 2019). Interestingly, Oser et al. (2019) showed that *RB1*-deficient cancer cells are dependent on Aurora B kinase for survival by performing a synthetic lethal CRISPR/Cas9 screen in lung and breast cancer cell lines. These studies demonstrated the value of using pharmacogenomic screens to identify novel therapeutic strategies against cancers with defective tumor suppressors. It is unclear if these findings can be linked to ARF deficiency in these cancers, as ARF and p16-CDK4/6-RB function through distinctive signaling pathways. What it highlights, however, is an opportunity to fill the scientific gap by applying similar approaches with ARF-specific screens, which have not been reported in the existing literature to the best of our knowledge.

The quest to identify ARF-associated synthetic lethality could benefit from publicly curated database, such as the Biological General Repository for Interaction Datasets (BioGRID) (Oughtred et al., 2021). BioGRID compiles literature-informed data for protein/genetic/chemical interactions and CRISPR-based screens. Although no *CDKN2A*/*ARF*-specific CRISPR screens have been reported, other functional interactions revealed by the literature curation could bring interesting insight. A combinatorial CRISPR/Cas9 screen identified functional/phenotypic links between *CDKN2A* and *PTEN*, *IGF1R* and *RRM2* (Shen et al., 2017). The functional relationship between *CDKN2A* and *PTEN* has been reported, while the roles of *IGF1R* and *RRM2* might shed new light in the functions of *CDKN2A* or ARF specifically upon further studies (Carrasco et al., 2006). In another example, TRIM28 interacts with ARF to maintain chromosome integrity (Neo et al., 2015). As TRIM28 was recently shown to regulate antitumor immunity, its role in ARF-mediated immune regulation could warrant further investigation (Lin et al., 2021). With ever-growing data from multi-omics analyses being fed into databases like BioGRID, artificial intelligence-aided literature mining tool, such as CompBio (https://gtac-compbio.wustl.edu/), could facilitate our ability to extract useful information more effectively (Sapkota et al., 2021).

CONCLUSION

Countless discoveries are unquestionably to come dissecting functional interactions in and out of p53-MDM2-ARF pathway,

and many questions remain regarding how to harness their relationship to maximize clinical benefits. Does co-inactivation of p53 and ARF warrant more attention as a defective tumor-suppressive entity, for which independent investigations should be conducted instead of inferring biological meanings from their loss-of-function individually? In addition to common cancer types in which p53/MDM2/ARF alterations are prevalent, could we unveil more clinical benefits in rare and pediatric malignancies targeting this axis? Pediatric cancers have much lower mutation burdens compared to adult tumors, but most of their mutations occur in a few significant cancer driver genes, such as *TP53* and *CDKN2A* (Ma et al., 2018) (**Figure 5**). Higher significance of these pathognomonic genetic alterations could translate to better response to targeted therapies in rare and pediatric cancers (Boyd et al., 2016; Laetsch et al., 2021). Does collective status of all three genes provide additional biomarker values in helping us tailor therapeutic strategies? For example, in cancers with functional p53 and ARF in addition to MDM2 amplification, would p53-MDM2 inhibitors sensitize tumors to ferroptosis-inducing treatments? In ARF-deficient cancers with mutant p53 and MDM2 amplification, could p53/ARF-based therapeutic peptides synergize with MDM2-targeting PROTAC? With their expanding roles identified in metabolism and TME, could p53/MDM2/ARF-based interventions synergize with metabolic and immunogenic regulations? For example, mitochondrial apoptotic priming through targeting Bcl-2/Bcl-xl was recently found to significantly enhance WT p53 activity, and might have similar effects on MDM2/ARF-targeting treatments (Sánchez-Rivera et al., 2021).

To develop genetically tailored therapeutic strategies targeting cancer vulnerabilities, open access databases play critical roles in providing up-to-date and customizable resources from cancer patients, such as The Cancer Genome Atlas (TCGA) Program (https://portal.gdc.cancer.gov/) and cBioPortal for Cancer Genomics (https://www.cbioportal.org/); from diverse mouse models of human cancer, like Mouse Models of Human Cancer Database (MMHCdb: http://tumor.informatics.jax.org/mtbwi/index.do); from patient derived xenograft (PDX) models, including PDX Finder (https://www.pdxfinder.org/) and Patient-Derived Models Repository (PDMR) Database (https://pdmr.cancer.gov/); and from cancer cell lines widely available to the research community at the Cancer Dependency Map (DepMap: https://depmap.org/portal/).

Among these resources, DepMap offers an easy-to-access, genome-scale catalog to enable research in genetic and pharmacological dependencies from hundreds of cancer cell lines. Genetic dependency scores were curated from a cohort of genome-wide RNAi and CRISPR loss-of-function screens, while pharmacological dependency data were obtained from publicly sourced drug sensitivity screens. More importantly, DepMap provides built-in analytical tools to highlight genetic co-dependencies and predict novel cancer cell vulnerabilities using multi-omics gene expression profiles (Dempster et al., 2020). For example, strong co-dependencies are identified between *TP53-MDM2*/*MDMX* (negatively correlated) and *MDM2-MDMX* (positively correlated), consistent with known biological functions. Therefore, vulnerabilities associated with the p53-MDM2-ARF pathway, such as unique targets in ARF-deficient cells, could be identified for further validations. Additionally, the consolidated database for genetic information (mRNA/protein expression, copy number, mutation, methylation … etc.) from an impressive number of cancer cell lines allows identification of cell models with the desired genetic composition to conduct relevant research.

It is worth recognizing, however, limitations with these datasets. With tissue-specific tumorigenic pathways, such as p53 signaling, data to inform cancer vulnerabilities need to be considered within the proper context and cancer indications (Schneider et al., 2017). Moreover, current genetic dependency data were mostly obtained from perturbation screens against individual genes. As the dataset grows with more input from combinatorial screens targeting multiple genes simultaneously, inaccurate/incomplete connections between genetic manipulations and their physiological significance could be better avoided (Zhao et al., 2021). The same improvement could be expected as more in-depth genetic information (ex. epitranscriptomic and epigenetic modifications) are included (Kan et al., 2021). It is also important to note that, despite its increasing applications in studying cancer vulnerability, multiple recent studies have shown that CRISPR/Cas9-based technology significantly alters p53-mediated functions and signaling pathways (Haapaniemi et al., 2018; Enache et al., 2020; Jiang et al., 2021; Sinha et al., 2021). These observations indicate that this approach might compromise the critical component of unbiasedness when identifying unique cancer vulnerabilities associated with p53-surrounding networks. Despite these caveats, these resources will continue to play important roles in developing novel cancer therapies informed by genetic signatures, including the p53-MDM2-ARF complex.

The once simple triangle between p53, MDM2 and ARF has steadily grown into a complicated network merely >20 years after it was first assembled. The only thing for certain is that our fascination with this (dys)functional complex will continue for years to come, and knowledge we gain from studying its expanded network will shape the future of cancer therapy.

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Writing—original draft, formal analysis, visualization: C-PK. Supervision, funding acquisition: JW. Conceptualization, writing—review and editing: C-PK and JW.

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