

*Review*

# The role of JMY in p53 regulation

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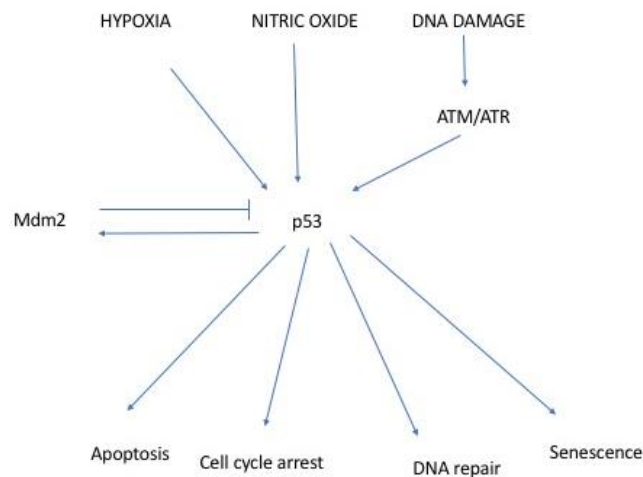
**Abstract:** Following the event of DNA damage the levels of tumour suppressor protein p53 increases inducing either cell cycle arrest or apoptosis. Junctional Mediating and Regulating Y protein (JMY) is a transcription co-factor involved in p53 regulation. Hence in the event of DNA damage, JMY levels are also upregulated in the nucleus where JMY forms a complex with p300/CREB-binding protein (p300/CBP), Apoptosis-stimulating protein of p53 (ASPP) and Stress responsive activator of p53 (Strap). This co-activator complex then binds to and increases the ability of p53 to induce transcription of proteins triggering apoptosis but not cell cycle arrest. This then suggests that the increase of JMY levels due to DNA damage putatively “direct” p53 activity toward triggering apoptosis. JMY expression is also linked to increased cell motility as it: downregulates the expression of adhesion molecules of the Cadherin family and induces actin nucleation; making cells less adhesive and more mobile, favouring metastasis. All these characteristics taken together imply that JMY therefore possesses both tumour suppressive and tumour promoting capabilities.

**Keywords:** p53; JMY; regulation; apoptosis; motility

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## Introduction

A salient observation in cancer biology has been that TP53 is frequently mutated in many human tumours [1,2]. p53 protein was identified in SV40 transformed cells where it was associated with Large T Antigen. It was later discovered to be a prominent transcription factor whose function is essential in preventing inappropriate cell proliferation and maintaining genome integrity following genotoxic stress (Figure 1) [2] [3]. Consequently, in response to cellular stress such as DNA damage, hypoxia oncogene overexpression, viral infection, the p53 protein expression level is augmented. Post translational modifications which include phosphorylation, acetylation, ubiquitination and methylation, stabilize p53 enabling it to activate multiple promoter elements of target genes effecting cellular processes such cell cycle arrest, senescence and apoptosis [2,4].



**Figure 1 Basic functions of p53.** P53 levels are tightly controlled and, in unperturbed cells, Mdm2 is its main regulator by inducing its degradation. Between the two proteins a negative feedback exists: P53 itself induces Mdm2 transcription, hence, as p53 levels increases, more Mdm2 is produced and p53 levels are down regulated again. In presence of DNA damage and other stresses, p53 degradation stops and its levels increases. Increased levels of stable p53 induce transcription of proteins involve in different types of responses, the main one being cell cycle arrest and apoptosis. Modified from: KEGG P53 pathway hsa04112 ([http://www.kegg.jp/kegg-bin/show\\_pathway?map=hsa04115&show\\_description=show](http://www.kegg.jp/kegg-bin/show_pathway?map=hsa04115&show_description=show))

P53 regulation of apoptosis (programed cell death) is at the heart of neoplastic proliferative control. In mammalian cells, apoptosis can be either P53 transcriptional dependent or P53 transcriptional independent. The P53 transcriptional dependent mechanism is set in motion by cellular stress like DNA damage which triggers p53 post translational modification of phosphorylation and acetylation that stabilizes it. This process enables p53 to bind and activate pro-apoptotic genes upon interaction with transcriptional co-activators such as p300/CREB-binding protein (p300/CBP), Junctional and regulatory protein(JMY), Stress responsive activator of p53 (Strap) and Apoptosis-stimulating protein of p53 (ASPP) [2,5].

Some studies have shown that inhibition of mRNA and protein synthesis that could inhibit transcription of p53 target genes did not inhibit p53 dependent apoptosis. A plausible explanation of this phenomena is the existence of an alternative p53 dependent apoptosis that is transcriptionally independent. According to Bossi et al, there are corroborating studies that have shown that upon DNA damage, p53 can localize to the mitochondria where it triggers a rapid apoptotic response that occurs even before p53 target genes are activated in the nucleus. This alternate apoptotic response is attained by the p53 DNA binding domain directly binding pro-apoptotic proteins BCL-XL and BCL2 within the mitochondria facilitating the release of BH3 protein that induces mitochondrial permeabilization and apoptosis [2,6].

The activity of p53 is tightly controlled and regulated at multiple levels and the importance of co-factors that influence these regulations is becoming increasingly evident (**Figure 1**) [5]. MDM2 for instance is a major negative regulator of p53 and its regulatory capacity can be by direct p53 ubiquitination targeting it for degradation or indirectly via p53 cofactors ubiquitination also marking them for degradation [5,7]. MDM2 further negatively regulates p53 through its E3 ubiquitin ligase activity that promotes proteasome-dependent p53 degradation and modulates nuclear export of p53[2].

CBP and p300 are a family of acetyltransferase which act as transcriptional activators for several transcription factors including p53[8]. Following DNA damage, p53 is phosphorylated at Serine15 stabilizing and enabling it to link to p300. Upon ligation with p300, two sites on the C terminal region

of p53 are acetylated. It has been proposed that following acetylation, p53's stability and recruitment of its targets are further enhanced leading to a preponderant transcription of p53 target proteins [8].

The Junctional Mediating and regulator Y protein (JMY) was originally identified as a CBP/p300 co-factor regulating p53 activity [9]. Upon DNA damage, it was observed that JMY interacts with and forms a complex with p300 and Strap while recruiting PRMT5 into a co-activator complex that triggers p53 response [10]. According to Coutts et.al JMY's functional role in p53 response is evident in its associated increase with p53-dependent transcription induced apoptosis. The transcriptional co-factor role of JMY is observed where its increased expression transduces to increased transcription of factors downstream to p53 without altering p53 protein levels [8]. Studies have also shown JMY to be an MDM2 target for ubiquitination and degradation as discussed in the above being one of the mechanisms via which MDM2 regulates p53 activity. This speculation is also consistent with the fact that upon DNA damage, JMY is released from MDM2, allowing it to contribute to p53's response to DNA damage [8].

JMY localizes both in nucleus and cytoplasm [11], but following stress or DNA damage JMY starts to migrate from the cytoplasm to accumulate in the nucleus [10]. Metastasis is facilitated by increased cell motility, allowing tumour cells to invade and colonize surrounding as well as distant tissues. In addition to its role in p53 induced apoptosis, JMY also participates in the enhancement of cell motility [10]. JMY contains a series of WH2 domains that promote actin nucleation or elongation enabling it to promote cell motility [10]. Studies have shown that JMY also nucleates actin in vitro and induces actin filament formation in vivo due its inherent WH2 domain series [10,12]. Via its WH2 domain, JMY is also able to down-regulate E-cadherin, an adherent junction protein required for cell-cell adhesion that is known to be lost during the course of tumor progression [13,14]. This loss of E-cadherin also favors cell motility, metastasis and invasion. Interesting, Coutts et al have demonstrated that when JMY shuttles into the nucleus to transcriptionally enhance P53's response to DNA damage, JMY's contribution to cell motility diminishes [10]. This then implies that JMY is playing a dichotomous role in cancer biology: (1) having a tumour suppressive capacity in the event of DNA damage where it enhances p53 activity; (2) functioning as a putative tumour metastasis promoter with its ability to downregulate E-cadherin and nucleate actin filament. It is then important to reconcile the role and cue of JMY in the two different cellular processes of programmed cell death versus actin dynamic regulation of tumorigenesis.

### Identification of JMY

JMY was originally identified by Shikama et al [9] while using the two-hybrid method to screen for proteins which are participating in the p300/CPB proteins complex and are involved in the regulation of p53 transcription [9]. JMY was found to be a protein of 110kDa whose gene is located on chromosome 5 at the 5q 13.2 band. Zuchero et al demonstrated in HL60 cells that JMY primarily localizes in the nucleus but can move between the nucleus and cytoplasm [12]. DNA damage is one of the triggers for activation of factors that regulate JMY such as: E2F1 which mediates increased expression of JMY; Strap and p300 that form a co-activator complex with JMY switching on p53 induced apoptosis; MDM2 that releases bound JMY to participate in p53 induced apoptosis response.

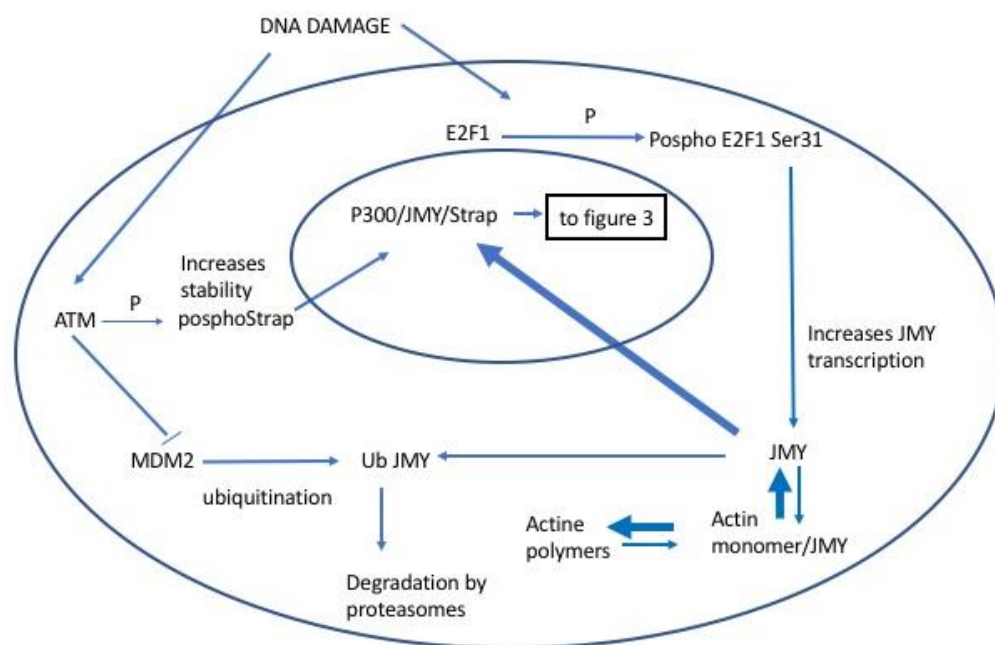
#### *JMY regulation by E2F1*

Transcription of E2F family of proteins can lead to either cell proliferation or apoptosis, hence suggesting a dichotomy in their function [16]. DNA damage activates Retinoblastoma (Rb) triggering it to bind E2F and block transcription [16]. In tandem, E2F1 which is most potent apoptotic inducer of the E2F family (**Figure 2**), is activated causing transcription at the proapoptotic promoters and effecting apoptosis. There are two main forms of E2F1 residual phosphorylation that both induce apoptosis in the event of DNA damage. While E2F1 phosphorylation at the Serine364 residue links to Retinoblastoma (Rb-E2F1), E2F1 phosphorylation at Serine 31 remain free. Both the Rb-E2F1 complex and the free E2F1 are essential for maximal induction of apoptosis [16]. Levels of JMY protein increases in cells treated "in vitro" with DNA damaging compounds like ultraviolet light, etoposide and actinomycin D [5]. This Jmy transcription and JMY protein accumulation are induced

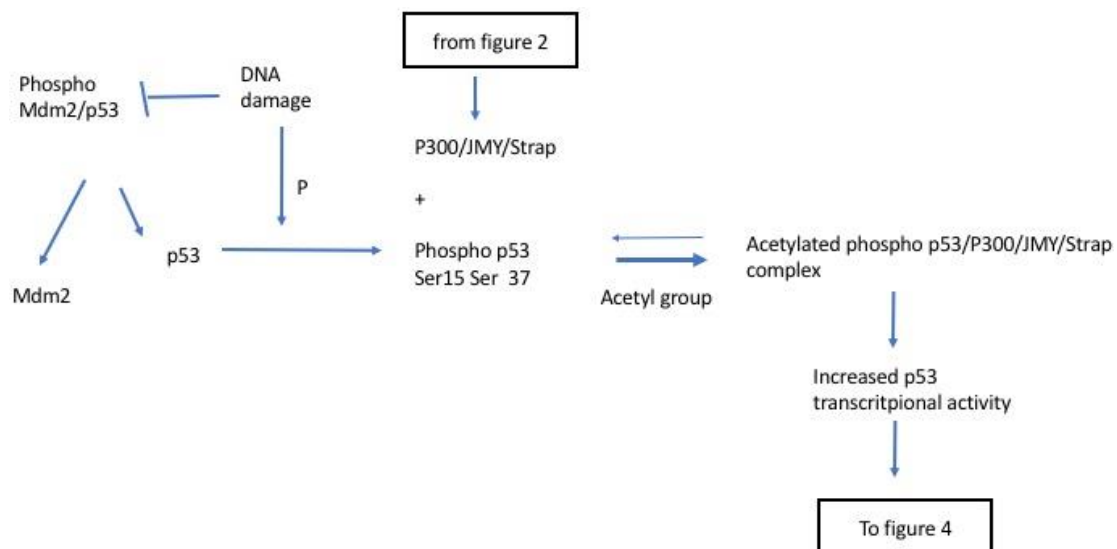
by the transcription of E2F1 that occur due to the DNA damage[17]. Per Carnevale et al, DNA damage signals orients and engages pRB and E2F1 in functions leading to apoptotic induction [16]. Studies have shown that active E2F1 introduced into the human cell line U2OS induces transcription of JMY and three others pro-apoptotic p53 co-factors: Aspp1, Aspp2 and TP53Inp1 [17]. Also, inhibition of protein synthesis did not prevent the increased transcriptions of these factor in presence of E2F1 suggesting that these genes are directly targeted by E2F1. Interestingly, while Aspp1, Aspp2 and TP53Inp1 have putative E2F1 binding sites, no such region has been found on JMY. However this finding does not exclude the possibility of interaction between E2F1 and JMY [17].

### *Jmy regulation by Strap*

Strap is another co-factor involved in the p53 regulation through its interaction with both p300/JMY in a complex. Strap contains six tetratricopeptide (TPR) repeat motifs, having several of these protein binding regions one Strap protein can link to different substrates forming multiple complexes [8,19,20]. Following DNA damage, a protein kinase Atm phosphorylates Strap on Serine 203 (**Figure 2**). Phosphorylated Strap has increased stability and accumulate in the nucleus where it links to the CBP/p300/ Jmy complex. Strap in fact upregulates JMY and strengthens its interaction with p300. Co-immunoprecipitation studies have shown that there is increased level of JMY in p300 immunocomplex in the presence of Strap. This is speculatively due to the influence of Strap and it's TPR on the recruitment of JMY into the p300 co-activator complex [19]. Using a two-hybrid assay and challenging free p300 and JMY with added Strap, it was demonstrated that the presence of Strap increased the number of p300/ Jmy complexes. Ultimately, the stabilization of the p300/ Jmy complex lead to increased p53 activity (**Figure 3**)[8,19,20].



**Figure 2 JMY regulation.** In unperturbed cells, JMY levels are maintained at a constant state by a balance between transcription and degradation. The latter is controlled by Mdm2 which ubiquitinates JMY leading to its degradation by proteasomes. Following DNA damage, the newly phosphorylated E2F1 induces increased transcription of JMY, while ATM dampens MDM2 activity. Furthermore, actin monomers forms polymers and therefore are no longer available to link to JMY and sequester it in the cytoplasm. As it is no longer linked to actin monomers, JMY can then link to Importin and translocate to the nucleus. This causes the levels of JMY in the nucleus to increase and form a complex with P300. Stability of this complex is further increased by linkage with phosphorylated Strap. Based on: [19], [20],[17],[27].



**Figure 3.** Jmy effect on p53. Following DNA damage, p53 is phosphorylated and escapes degradation resulting in upregulating p53 levels. Phosphorylated p53 links to the Jmy /p300/Strap complex and its transcriptional activity increases. Based on: [8].

#### JMY regulation by MDM2

MDM2 ubiquitinates p53 causing its degradation, however when it is phosphorylated in the event of DNA damage, p53 has minimal interaction between it and MDM2 allowing its escaping from degradation (**Figure 3**) [5] [8]. Levels of JMY protein are also subject to regulation by MDM2 in stress-free cells. JMY and MDM2 physically interact through the C-terminal domain of MDM2 which harbours E3 ligase [5]. Appropriate ubiquitylation of JMY requires intact E3 ligase. Coutts et al have shown that when stress free mouse embryonic fibroblast is treated with inhibitors of MDM2 ligase, levels of JMY protein increase. This finding suggests that in absence of stress, JMY protein production and degradation is maintained in a steady state by regulation mediated via MDM2.

Following induction of DNA double strand break by ultraviolet or by actinomycin-D, JMY levels increases, not only because of increased transcription, but also because of diminished degradation by MDM2 [5] [7]. With diminished restriction of JMY by MDM2, Jmy, Strap and p300 induces acetylation of p53, protecting it from degradation by MDM2 [7]

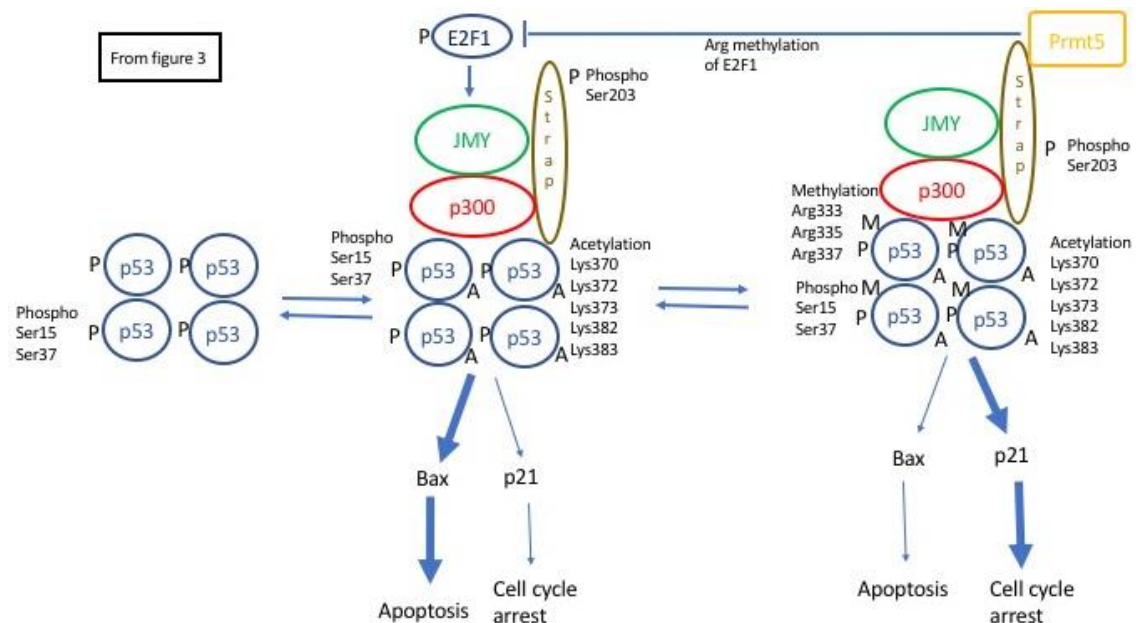
#### JMY increases p53 dependent transcription leading to selective increase of Apoptosis.

Higher levels of p300/JMY increases p53 transcriptional activity leading to increased apoptosis but not cell cycle arrest [9]. As discussed above, this coactivator complex's activity is further enhanced in presence of Strap. Studies has been carried out where two p53 downstream genes- Bax which leads to apoptosis and p21 which induces cell cycle arrest, were investigated in regards to their association with p300/JMY complex. Levels of Bax were increased in presence of p300/ JMY while that of p21 was very modest (**Figure 4**) [9]. This substantiates the hypothesis that when activated, the p300/JMY co-activator complex in association with P53 forge towards apoptotic pathway with upregulation of apoptotic proteins like Bax.

P53 activation can leads to both cell cycle arrest and apoptosis, or just one of the two. However, the cue for p53 to activate just one of either processes/pathways had remained unknown. It is was recently unveiled that the path to apoptosis was via JMY and activation of other proapoptotic factors [17]. In event of DNA damage, phosphorylated p53 links to the p300/Jmy/Strap complex which causes acetylation of five Lysine residues located on the C terminus region of p53. This leads to an increased ability of p53 to transcribe Bax, but not p21, and resulting in a preferential activation of the apoptotic pathway over cell cycle arrest. However, if Prmt5 is recruited to Strap linked to the Jmy /p300 complex, this triggers the methylation of p53 shifting the process away from Bax transcription and



apoptosis to increased transcription of p21 and induction of cell cycle arrest. This also in turn causes the downregulation of JMY that drives the pro-apoptotic pathway (**Figure 4**) [21,22].



**Figure 4. Formation of molecular complexes and their effects on apoptosis and cell cycle.** Following DNA damage, p53 is phosphorylated and released from Mdm2. It links to the p300/Jmy/Strap complex which causes acetylation of five Lysine residues located on the C terminus region of p53. This leads to an increased ability of p53 to transcribe Bax, but not p21, resulting in a preferential activation of the apoptotic pathway over cell cycle arrest. However, when Prmt5 is recruited to Strap linked to the Jmy /p300 complex, this triggers the methylation of p53 shifting the process away from Bax transcription and apoptosis to increased transcription of p21 and induction of cell cycle arrest. Prmt5 further reinforces this switch by E2F1 inhibition via methylation. This in turn also reduces JMY's transcription. Eventually the ability of p53 to induce more apoptosis than cell cycle arrest, or vice versa, is regulated by the balance between Jmy, p300, strap and Prmt5. Based on and modified from: [8],[21,22,34-36]

### *JMY and cell motility*

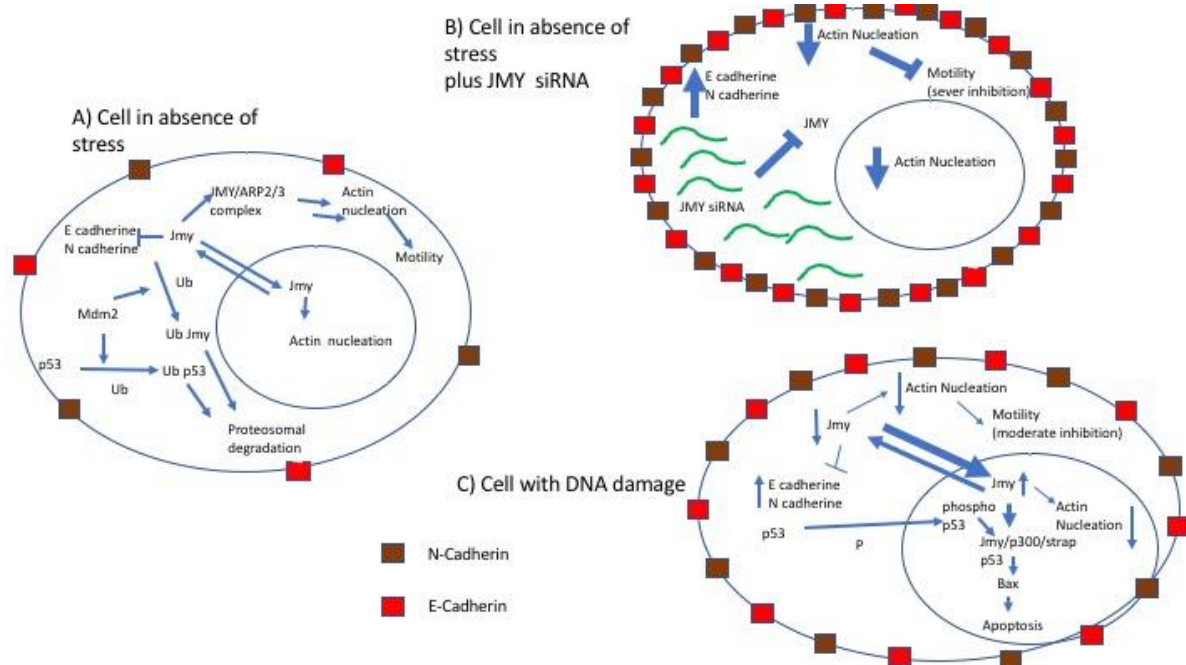
Another prominent role of Jmy is to regulate motility by affecting actin nucleation and cell adhesion [10]. Actin filaments provide the structural basis for cell motility and are critical to numerous physiological processes such as morphogenesis, wound healing, migration, membrane transport and metastasis [23]. Actin filament formation occurs either via branching of already existing actin filament or alternatively via de-novo nucleation of actin monomers [23].

Spontaneous assembly and nucleation of actin trimers and dimers are kinetically unfavorable so to counteract this obstacle cells use actin nucleators and nucleation-promoting factors (NPF) to jump start actin nucleation and filament formation. Actin formation via branching is usually facilitated by the actin nucleator "Actin related protein 2/3 complex" (Arp2/3). Arp2/3 is activated by NPFs via their 'Wiskot-Aldrich Syndrome protein (WASp) homology-2' domain (also known as WH2 domain), which are actin binding motifs that enable assembly of actin monomers [24]. This de-novo nucleation is produced by nucleators such as 'Spire' that themselves contain WH2 domains and do not require activation by NPFs (Nucleation-Promoting Factors) [24] [12].

With the discovery of JMY protein sequence homology to actin regulators and nucleators, came the knowledge of its involvement with actin [12]. JMY's capacity to regulate actin dynamics lies with it possession of WH2 domains that can either independently initiate actin filament formation in

SPIRE-like fashion or activate actin nucleators such as Arp2/3 [24]. Experiments with myeloid lineage HL60 have shown that JMY is mostly nuclear in these cells but when differentiation into neutrophil is induced some JMY protein move to the cell edge where it co-localizes with actin. JMY over expression was found to be associated with increased speed of migrating cells [12]. Additionally, JMY expression and cytoplasmic co-localization with actin is increased under HIF1 stimulation[25]. Of note is that actin filament facilitates cell motility and migration. Hence JMY association implies JMY's significant role in cell motility.

Zuchero et al. [12] and Firat-Karalar et al. [26] demonstrated that purified JMY biochemically activates Arp2/3 (**Figure 5**) induced actin polymerization in a dose dependent fashion. JMY does not induce elongation of preformed filaments but is able to nucleate new filaments, make them to elongate faster and cut filaments to make barbed ends. These authors also demonstrated that JMY possess WH2 domains and was able to catalyze new filament formation in a Spire-like fashion, always in a dose – dependent fashion, even in the absence of Arp2/3 activity [12] [23]. JMY nucleation activity in presence of Arp2/3 complex occurs in the cytoplasm and lead to production of branched filaments. Once inside the nucleus, JMY acts with a mechanism similar to that used by the actin nucleation factor Spire and produces unbranched filaments in an Arp2/3 independent fashion.



**Figure 5. Model of Jmy-mediated co-ordination between cell motility and DNA damage response in cell lines.** A model of how Jmy links p53 response to DNA damage to cell motility in cell lines. **A)** In a motile cell, standing in absence of stress, the amount of JMY in the nucleus and in the cytoplasm, are maintained in equilibrium. The available JMY protein in the cytoplasm inhibits E and N Cadherin adhesion molecules in a dose dependent fashion and induces nucleation both in an Arp2/3 dependent and independent way. **B)** If such a cell is treated with siRNA targeting JMY, the inhibition of Jmy transcription leads to a strong upregulation of the two cadherin and a reduction of actin nucleation and therefore a severe inhibition of motility. **C)** When DNA damage occurs, a more modest drop in motility is observed. The hypothesis behind this is that, on one hand the translocation of JMY from cytoplasm to nucleus diminishes the cytoplasmic JMY level. This however is in part compensated for by the overall increase of JMY levels following the DNA damage.

This implies that JMY is capable of producing both forms of biochemical actin filament formations. Having both forms of biochemical actin polymerization would also imply that JMY's contribution to cell motility is via its nucleation filament and that JMY can promote rapid assembly of a new actin network by harnessing its ability to first nucleate new mother filaments and then

activate Arp2/3 to branch off these filaments. This duality of JMY localization and functions between the cytoplasm and nucleus might be a gained evolutionary advantage of JMY [12] [23].

We previously discussed how JMY accumulates in the nucleus in response to DNA damage. However, another mechanism regulating the subcellular localization has been unveiled, this time in response to actin monomers which are able to link with the WH2 JMY domains blocking its transfer to the nucleus [27]. This is supported by the effect observed on JMY intracellular localization after treatment with Jasplakinolide, a compound which induces polymerization of actin [28]. As all the monomers are recruited to form polymers, no free monomers is available to link to JMY, hence JMY is no longer constrained in the cytoplasm and is able to translocate to the nucleus [28]. This same result is obtained when a mutation of the WH2 domain is introduced that blocks binding to actin monomers [27]. An actin monomer prevents JMY transfer to the nucleus, because it competes with Importin, as the Actin binding region overlaps with the Nuclear Localization Signal targeted by importin [27]. This mechanism has been eventually demonstrated as responsible for the transfer of JMY to the nucleus after DNA damage [27]. As UV-induced DNA damage has been demonstrated to induce actin polymerization in the cytoplasm, just like treatment with Jasplakinolide [29] Zuchero et al demonstrated that nuclear accumulation of JMY is observed after exposure to UV or treatment with other DNA-damaging agents like Etoposide and Neocarzinostatin. JMY nuclear accumulation is conditional to the availability of Importin. The authors conclude that the nuclear accumulation of JMY following DNA damage may therefore be regulated by the assembly into polymers of actin induced by DNA damage [27].

The role played by JMY in actin regulation does not affect only the motility of the cell but, in the case of the neurons, it is also involved in the development of these cells as JMY inhibits the formation of neurites [26]. This inhibiting activity appears to be due to its function as an actin-assembly protein [26].

The second mechanism by which JMY affects motility is the regulation of the levels of E-Cadherin and N-Cadherin [10]. Studies done in our lab have shown that the expression of JMY is inversely correlated to the levels of these two adhesion molecules. Coutts et al have also observed an upregulation of E-cadherin in JMY depleted MCF7 cells and the opposite effect in JMY rich cells [10]. Correlation studies done in our lab between JMY and E Cadherin expression in 235 invasive breast carcinoma also show an inverse correlation between cytoplasmic JMY and membranous E cadherin [11].

### Linking p53 pathway and cell motility

It has become increasingly evident that JMY plays prominent roles in coordinating DNA damage response and cell motility. This affirms the accumulation of evidences demonstrating that p53 has a role as inhibitor of cell motility (**Figure 5**) [30]. P53 has been found to be associated with tubulin, vimentin, F-actin and tubulin indicating a possible role in cytoskeleton regulation. P53's interaction with Cdc42 inhibits both filopodia formation, cellular polarization and "in vitro" cellular spreading. Furthermore, Inhibition or absence of p53 leads to increased activity of the Rho pathway with consequent increase in cell migration [30].

The role played by JMY both in regulating cell motility and cell damage response suggest that JMY could be the link between the two cellular processes. In the model currently being explored, illustrated in **Figure 5**, after DNA damage, the net JMY concentration diminish in the cytoplasm and increases in the nucleus. In the nucleus most of the JMY is sequestered by the Cp300/Strap/p53 complex, ultimately making less JMY available for actin nucleation and cadherin inhibition [31] [10,27,32].

### Conclusion

By being able to drive p53 towards induction of apoptosis on one hand, and promote invasiveness of the cancer cells on the other, Jmy is an example of genes that can act both as suppressor gene and a gene promoting tumour progression [33]. We have discussed here the role of JMY as a tumor suppressor, facilitating p53 induced apoptosis over cell arrest in event of DNA



damage. JMY's putative tumour promoting role could be seen in its ability to increase cell motility which also influences p53 activity. Potentially these unique roles of JMY can be reconciled to be associated with each other: In the event of DNA damage, the net JMY concentration diminish in the cytoplasm and increases in the nucleus where most of the JMY is sequestered by the Cp300/Strap/p53 complex. While less JMY is available in the cytoplasm, hence less potential for increased cell motility, and more JMY in the nucleus is directed toward the tumor suppressive activity. It then seems that the cue to switch from the putative metastatic role to a tumor suppressive role could putatively be DNA damage. While this is speculative, further work is required to decipher the more about these roles. Also, despite this peculiar role played by JMY in cancer biology, there is still very little is known about its role in different types of cancers and in tumours at different stages.

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