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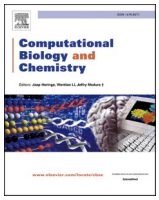

A Boolean model of the oncogene role of FAM111B in lung adenocarcinoma

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ABSTRACT

The ultimate goal of this study is to analyze the gene regulation between FAM111B and p53 in lung adenocarcinoma using Boolean networks. Recent studies have shown that downregulation of FAM111B enhances the G2/M cell cycle checkpoint in the respective cell lines. Upregulation of p53 directly downregulates FAM111B, which is directed to affect cell cycle controllers Cdc25C and Cdk1/CyclinB, thereby controlling G2/M cell cycle arrest. As for apoptosis, down-regulation of FAM111B by p53 directly regulates the BAG3/Bcl-2 axis, which triggers apoptotic cell death. However, the molecular mechanisms involving p53 and FAM111B in G2/M checkpoint regulation are still unknown. Thus, we present a Boolean model of the G2/M checkpoint considering the effect of p53 and FAM111B. Our model indicates that the cell fate between the two cellular phenotypes, arrest, and apoptosis, at the G2/M checkpoint is non-deterministic and is controlled by p53. The model was compared with the experimental data involving gain- or loss-of-function genes and achieved a fair agreement. The model predicts a positive circuit involving p53/FAM111B/BAG3. Our circuit perturbation analysis suggests that this circuit may be essential for controlling cell-fate decisions at the G2/M checkpoint. Our model supports that FAM111B is an engaging target for drug development in lung adenocarcinoma.

1. Introduction

The involvement of p53 at the G1/S and G2/M cell cycle checkpoints in various cell types is well documented (Hyun and Jang, 2014; Innocente et al., 1999). In lung adenocarcinoma cell lines, operable p53 commit to enhanced cell survival under the DNA damage response (Lee et al., 2010). A recent study by Sun et al. (2019). signifies that knockdown of FAM111B drives the G2/M checkpoint via a direct interaction with Cdc25C and Cdk1/Cyclin B in lung adenocarcinoma cell lines (Sun et al., 2019). On the other hand, such a study revealed that FAM111B directly induces BAG3 expression. In this way, Sun et al. (2019). demonstrated that p53 directly inhibits FAM111B, which blocks Cdc25C and the Cdk1/cyclin B complex, triggering cell cycle arrest at the G2/M checkpoint.

Moreover, the authors found that overexpression of p53 inhibits BAG3 expression by targeting FAM111B, which reduces Bcl-2 expression and stimulates BAX expression i.e., activation of apoptotic cell death (Sun et al., 2019). Similarly to this, Wang et al. (2020). recently showed that overexpression of BAG3 suppresses p53 function and accelerates the development of breast cancer. Contrarily, BAG3 knockdown triggers DNA damage and activates the p53 signaling pathway, which limits the replication of cancer cells by causing cell cycle arrest and apoptosis. Nonetheless, the involvement of p53 and FAM111B mechanisms in the joint control of cell fate determination in lung cancer remains unknown. In the current investigation, we propose the regulatory functions of p53 and FAM111B in the G2/M cell cycle checkpoint using the Boolean approach (Gupta et al., 2020a; Gupta and Hashimoto, 2022; Silveira et al., 2020), as shown in Fig. 1.

2. Materials and methods

2.1. Boolean methods

The Boolean technique is grounded in the examination of a regulatory graph, whereby every node represents a signaling component and each straight edge (or arc) represents an activation or inhibition between two nodes. Nodes are Boolean variables that only allow "0" and "1" values, corresponding to "active" and "inactive" states. Each node in the network is given a logical rule based on the interpretation of the biochemical information, which governs its activation level in relation

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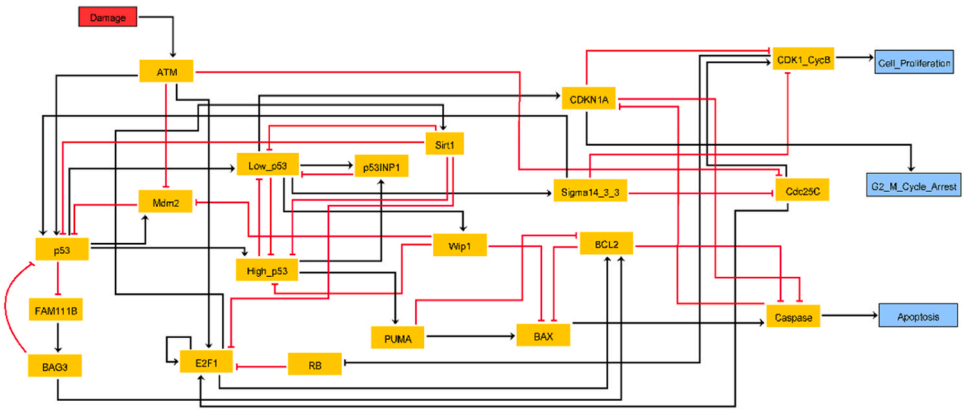

Fig. 1. Proposed network for G2/M checkpoint induced by DNA damage. Yellow nodes represent proteins, whereas red and blue ones denote the input (DNA damage) and outputs (Proliferation, G2/M Arrest and Apoptosis), respectively. Positive and negative interactions are denoted by black and red arcs, respectively.

to the location of its regulators. Established on the understanding of biochemical information, a logical rule is designated per node in the network, which confines its activation level in terms of the state of its controllers. The logical rules are constructed employing the logical operators AND, OR, and NOT (see Supplementary Table S1 along with the official names of molecules and the biochemical literature). The key outcome of simulations utilizing a Boolean network is attractors. A state transition graph (STG) allows us to know the dynamical functioning of a Boolean model. Every node in this graph reflects the present state of the network variables, and the arcs describe conversions between these states. The STG accommodates all potential trajectories from such an initial state to a final state. Stable states (or fixed points) are terminal nodes with no outgoing edges, whereas a cyclic state is considered a series of transitions locked within a fixed group of states in the STG. Asynchronous updates were considered to account for state updates, which may reflect the non-deterministic behavior exhibited in molecular networks. Additionally, negative and positive circuits (also known as feedback loops) govern the dynamics of a gene regulatory network. Negative circuits can stimulate oscillations, while positive circuits are in charge of multi-stable dynamics. Furthermore, this method allows for in silico gain-of-function (GoF) or loss-of-function (LoF) perturbations, in which we constrain node values to be "active" or "inactive", respectively. To investigate the influence of specific nodes on network dynamics and the resulting phenotype. More details about Boolean methods can be found in our previous published studies (Gupta and Hashimoto, 2022; Gupta et al., 2022a, 2022b; Silveira et al., 2022; Gupta et al., 2020b, 2022c, 2023).

GINsim 3.0.0b was then used to simulate and visualize model impacts (Naldi et al., 2018). All attractors are demonstrated by the GINsim algorithm for wild-type instances and numerous mutational situations (Naldi et al., 2018). In the event of a non-deterministic approach, GINsim can assist in predicting the chances of reaching certain attractors (Naldi et al., 2018). The GINsim file for the model is included in the S1 file.

2.2. Molecular mechanism of the G2/M checkpoint regulation in lung adenocarcinoma cells

DNA damage (DNA double-strand break) triggers ATM activation (Huang and Zhou, 2020). The phosphorylation downstream ATM pathway directly activates p53 (Huang and Zhou, 2020). In the lung adenocarcinoma cells line, p53 leads to the induction of the G2/M checkpoint. Indeed (Simabuco et al., 2018), in lung adenocarcinoma cells, knockout of p53 could not arrest cells at G2/M checkpoint (Sun et al., 2019). The protein symbols in the model are 20 nodes and there are 53 direct arcs between these nodes.

The model has one input, Damage (Fig. 1). The logical rules commanding the nodes can be seen in the S1 Table. Rectangular yellow nodes express proteins. Rectangular light blue nodes symbolize model outcomes (Proliferation, Cycle Arrest, and Apoptosis), black arcs point activations and red hammerhead arcs mean inhibitions. The p53 in our model was based on the study of Zhang et al. (2011). Therefore, different functions of p53 can be found in more detail by Zhang et al. (2011).

Upon DNA damage, ATM initiates the p53 expression. Activated p53 induces the expression of E3 ubiquitin-protein ligase homolog protein (MDM2), consequently, it directs to the down-regulation of p53 (Bar-Or et al., 2000). Depending on the different phosphorylation modes of p53 in the model, it is characterized by additional nodes: p53 is associated with the interaction of Mdm2 that is required to initiate p53-low and p53-high. p53-low pinpoints p53, phosphorylated at Ser-15 and Ser-20, whereas p53-high shows p53 to be more phosphorylated at Ser-46 which regulates apoptotic cell death (Zhang et al., 2011). The modification between p53-low and p53-high is governed by Wip1 and p53-INP1 (Zhang et al., 2011). Cyclin-dependent kinase inhibitor 1 A (CDKN1A), protein phosphatase 1D (Wip1), 14–3–3 sigma (S14_3_3), and tumor protein p53 inducible nuclear protein 1 (p53-INP1) are formed by p53_Low (Vousden and Lu, 2002). CDKN1A and S14_3_3, both directly target the CDK1/Cyclin B complex. Cdk1/Cyclin B complex is directly inhibited by p21 and S14_3_3 (Taylor and Stark, 2001). In this way, the CDKN1A or S14_3_3 proteins segregate Cdk1 into the cytoplasm

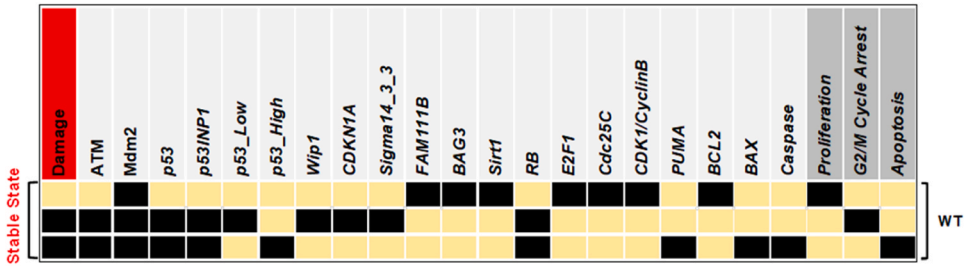

Fig. 2. Stable attractors for the WT condition. The red column shows the status of damage (ON/OFF), while the dark gray columns reflect the outputs: proliferation, arrest, and apoptosis at the G2/M checkpoint. The remaining columns indicate the state of each molecule in the model. Each row represents a stable attractor (fixed points). OFF values are represented by yellow cells. In contrast, black cells signify the value ON. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
In-silico perturbations corresponded with experimental knowledge from Sun et al. (2019). knockdown (KO) or Ectopic expression (E1) represents loss-of-function (LoF) or gain-of-function (GoF), respectively.

Stimulus/Perturbations	Response/phenotype
FAM111B in the absence of Damage	Upregulated
FAM111B KO	Activation of p53
FAM111B and p53 in response to Damage	Negative correlation
FAM111B KO	G2/M arrest, Apoptosis

and directly inhibit the actions of Cdc25c, leading to G2/M arrest (Taylor and Stark, 2001).

3. Results

3.1. Wild-type case attroctors

The model illustrates 3 stable attractors (also known as steady-state or fixed points) for the wild-type case (WT) that are allied with distinguishing phenotypes (Fig. 2). The 1st stable attractor (when damage = inactive or OFF) is the proliferative-stable attractor, caused only by activation of the cell cycle enhancer FAM111B, BAG3, Cdk1-CycB, and Cdc25C. Second and third stable attractors (when damage = active or ON) coordinate to two-stable states (also known as bistable) reflecting two p53-inducible cell fates: arrest and apoptosis, which are described through the activations of Low p53 and High p53 respectively (Zhang

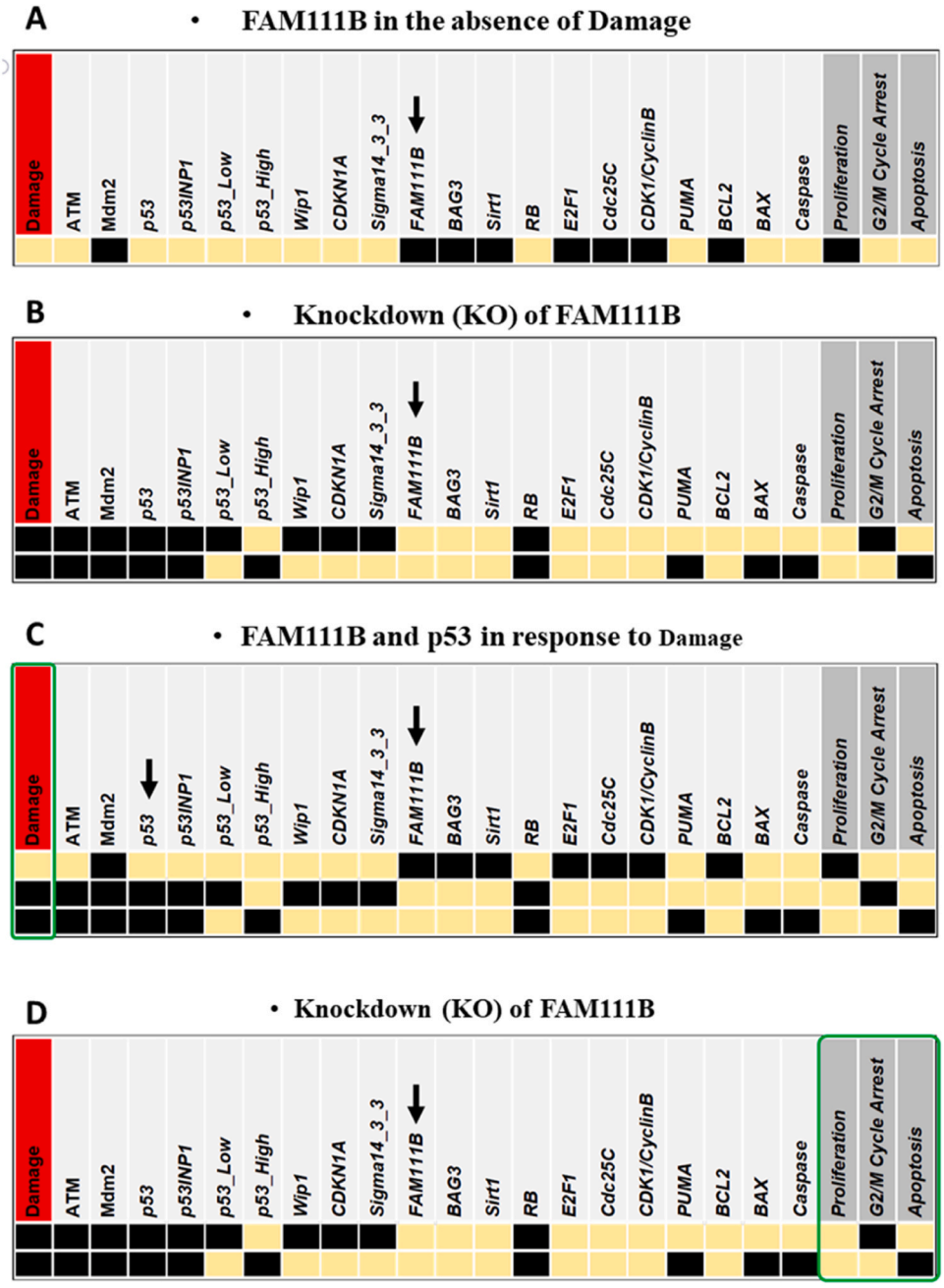

Fig. 3. Model verification. According to Table 1, each Figure stands independently. The red column represents the status of damage (ON/OFF), whereas the dark gray columns represent the outputs: proliferation, arrest, and apoptosis at the G2/M checkpoint. The remaining columns represent the state of each molecule in the model. Each row represents a stable attractor (fixed points). Yellow cells reflect OFF values. In contrast, black cells represent the value ON. For more detail, see Section 3.2. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Functional circuits identified by the GINsim software. Experimental validation of such circuits is listed. Model predictions for which no experimental support was located are denoted by question marks.

Circuits	Reference
Positive	
CDKN1A/CASPASE3	(Zhang et al., 1999)
P53A/P53K	(Zhang et al., 2011)
P53/FAM111B/BAG3	?
E2F1	(Vandel and Kouzarides, 1999)
Negative	
P53/Mdm2	(Bar-Or et al., 2000)
P53A/p53INP1	(Zhang et al., 2011)

Table 3
Experimental confirmation of the positive-circuit interactions.

Positive Circuits	Circuit Elements	Target	Direct/Indirect Interaction	References
P53/ FAM111B/ BAG3	P53	FAM111B	Direct inhibition	(Sun et al., 2019)
	FAM111B	BAG3	Direct Activation	(Sun et al., 2019)
	BAG3	P53	Direct inhibition	(Wang et al., 2020)

Table 4
Identification of phenotypic response of the predicted circuit under perturbation. Ectopic expression (E1) or knockdown (KO) illustrates gain-of-function (GoF), or loss-of-function (LoF), respectively.

Positive Circuit	Perturbations	Phenotypes
P53/FAM111B/BAG3	KO/KO/KO	Proliferation
	E1/KO/KO	Cell cycle arrest and Apoptosis
	KO/E1/KO	Proliferation
	KO/KO/E1	Proliferation
	E1/E1/KO	Cell Cycle arrest and Apoptosis
	E1/KO/E1	Cell Cycle arrest and Apoptosis
	KO/E1/E1	Proliferation
	E1/E1/E1	Cell Cycle Arrest and Apoptosis

et al., 2011). In more detail, p53 coordinates to the interaction of Mdm2, which is necessary to begin Low p53 and High p53 and is characterized by additional nodes depending on the different phosphorylation modes of p53 in the model. Low p53 determines p53, which is phosphorylated at Ser-15 and Ser-20 and regulates cell cycle arrest by activating p21. Whereas High p53 denotes p53, which is phosphorylated at Ser-46 and regulates apoptosis. For more detail see (Gupta et al., 2020a; Zhang et al., 2011; Gupta et al., 2020c).

3.2. Model verification

The model was validated by simulating node perturbations with gain-or-loss of functions (GoF/LoF) perturbations of the appropriate components, as conducted by Sun et al. (2019). We constructed Table 1 and Fig. 3 as follows. The agreement between the model and the experiments is summarized in Table 1. In the absence of DNA damage, for example, FAM111B is increased in cancer cells. In response to DNA damage, the knockdown (KO) of FAM111B triggers the activation of p53. In this way, Sun et al. (2019). found that there is a negative correlation between FAM111B and p53 in the DNA damage response. In the end, Sun et al. (2019). determined that knocking down FAM111B induces p53 expression, and once activated, p53 inhibits cancer cell proliferation by triggering cell cycle arrest and apoptosis at the G2/M checkpoint. As can be seen in Fig. 3, our model is in the finest agreement with Sun et al. (2019).

3.3. Feedback loops and its perturbations

GINsim identified eight operational circuits (sometimes referred to as feedback loops). We chose just six of those with a maximum of three components because many of them had been tested experimentally (see Table 2). A new positive circuit involving p53/FAM111B/BAG3 is one of the six circuits. We selected this circuit to investigate since our goal is to confirm the oncogene roles of FAM111B and BAG3 in lung cancer. Although the interactions that constitute this circuit are widely established in papers on lung adenocarcinoma cells (Table 3), their potential at the G2/M checkpoint remains experimentally unexplored. Therefore, we decided to investigate whether this circuit is relevant for determining cell fate. Thus, we used circuit element perturbation to see if this circuit may restrict proliferation; the findings are shown in Table 4. As we can

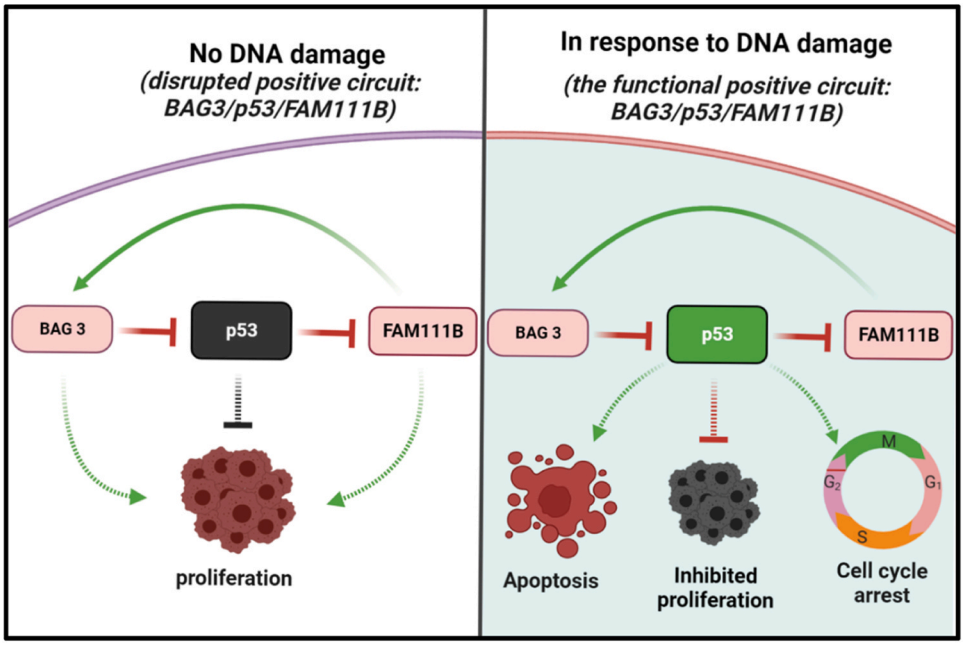

Fig. 4. Disrupted versus functional positive circuit in NSCLC. The left side: positive circuits broken due to the lack of DNA damage in NSCLC cells, i.e., inactivation of p53 expression, enabling uncontrolled growth. On the right, the positive circuit between (BAG3/p53/FAM111B) is activated in response to DNA damage. Active p53 inhibits FAM111B, and FAM111B induces BAG3, which in turn inhibits p53. FAM111B targeted by p53 suppressed tumor formation by inducing cell cycle arrest and apoptosis at the G2/M checkpoint in NSCLC cells. Thus, this positive circuit is critical for inhibiting proliferation in the DNA damage response. Green arrows indicate activation, whereas red hammerhead arrows indicate inhibition. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

see, perturbation of up-regulation (E1) of p53, independently and/or in combination with FAM111B/BAG3, causes cell cycle arrest, and apoptosis. On the other hand, the remaining perturbations only cause the proliferative phenotype. Thus, our findings imply that this novel positive circuit may contribute to limiting cancer growth by modulating cell cycle arrest and apoptosis at the G2/M checkpoint in lung adenocarcinoma. See Table 4 for more details.

3.4. Experimental design proposed by Boolean model

The notion of experimental design is driven by Sun et al. (2019). Who uncover the oncogene role of FAM111B in lung adenocarcinoma. Therefore, we indicate a new therapeutic paradigm described by the network in which a BAG3 acting as a p53 inhibitor can limit cancer growth by activating p21 and RB1, which can control cell cycle arrest and apoptosis at the G2/M checkpoint.

One possible effect of these experiment would be the reduction of tumor development and proliferation in lung adenocarcinoma. We emphasize on these potential perturbations' scenarios suggested by the model to test this advancement.

- Knockdown (KO) of BAG3 → upregulation (E1) of p53 → p21 ↑ and RB1 ↑
- Knockdown (KO) of FAM111B → upregulation (E1) of p53 → p21 ↑ and RB1 ↑
- Knockdown (KO) of FAM111B + knockdown (KO) of FAM111B → p21 ↑ and RB1 ↑

4. Discussion

In the current study, we employed a Boolean model in lung cancer cells to evaluate FAM111B's oncogene function. Our model shows how p53 arrests the cell cycle and promotes apoptosis in response to DNA damage at the G2/M checkpoint. Sun et al. (2019). suggested that DNA damage stimulates the p53 pathway, whereas p53 directly suppresses FAM111B. In the absence of DNA damage, the wild-type instance (Fig. 2) implies only a proliferative stable attractor, which is corroborated by Sun et al. (2019). In response to DNA damage, it activates p53 and its downstream signaling pathways, which.

restrict proliferation via cell cycle arrest or apoptosis (Zhang et al., 2011). Interestingly, all of the phenotypes shown above are consistent with Sun et al. (2019).

Furthermore, biological circuits are important in gene regulatory networks (GRNs) (Thieffry, 2007). These circuits may grasp and represent the dynamics of biological systems (Deritei et al., 2019). In this setting, we found a new positive circuit between p53/FAM111B/BAG3 (see Fig. 4). We also presented evidence for this circuit based on their interaction with lung cancer (see Table 3 for additional information). In addition, we evaluated this circuit (see Table 4) and obtained perturbations of every circuit element. Interestingly, our findings show that this novel circuit is required for controlling cancer progression in lung adenocarcinoma at the G2/M checkpoint. All of these notable findings, however, rely on the discrete core of the model's components. Therefore, one of the limitations of our model is the prediction of time-dependent aspects as the change of exact expression levels over time. Furthermore, the exact molecular mechanism by which p53 accomplishes its functions in lung cancer requires further investigation. In addition, other proteins may play a critical role in the control of cell cycle development in lung cancer. Nevertheless, p53 is required for cell cycle arrest and apoptosis in lung adenocarcinoma by targeting CDK1/cyclin B and BCL-2 at the G2/M checkpoint (Chan et al., 2000).

5. Conclusions

In the end, the model conforms with the experimental outcomes and points out that the FAM111B/BAG3 pathway is an engaging target for drug evolution in the proliferation of lung adenocarcinoma.

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CRediT authorship contribution statement

Shantanu Gupta: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Daner A. Silveira:** Conceptualization, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ronaldo F. Hashimoto:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Data Availability Statement

Data is contained within the article or Supplementary Material.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.compbiolchem.2023.107926.

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