Autophagy and apoptosis are regulated by stress on Bcl2 by AMBRA1 in the endoplasmic reticulum and mitochondria

Bojie Yang¹, Quansheng Liu¹* and Yuanhong Bi²,³

Abstract

Background: Autophagy and apoptosis are two important physiological processes that determine cell survival or death in response to different stress signals. The regulatory mechanisms of these two processes share B-cell lymphoma-2 family proteins and AMBRA1, which are present in both the endoplasmic reticulum and mitochondria. B-cell lymphoma-2 family proteins sense different stresses and interact with AMBRA1 to regulate autophagy and apoptosis, which are respectively mediated by Beclin1 and Caspases. Therefore, we investigated how different levels of stress on B-cell lymphoma-2 family proteins that bind to AMBRA1 in the endoplasmic reticulum and mitochondria regulate the switch from autophagy to apoptosis.

Methods: In this paper, we considered the responses of B-cell lymphoma-2 family proteins, which bind to AMBRA1 in both the endoplasmic reticulum and mitochondria, to two different levels of stress in a model originally proposed by Kapuy et al. We investigated how these two stress levels affect the transition from autophagy to apoptosis and their effects on apoptosis activation over time. Additionally, we analyzed how the feedback regulation in this model affects the bifurcation diagrams of two levels of stress and cell fate decisions between autophagy and apoptosis.

Results: Autophagy is activated for minor stress in mitochondria regardless of endoplasmic reticulum stress, while apoptosis is activated for only significant stress in mitochondria. Apoptosis is only sensitive to mitochondria stress. The time duration before apoptosis activation is longer in the presence of high AMBRA1 levels with high endoplasmic reticulum and mitochondria stress. AMBRA1 can compete with B-cell lymphoma-2 family proteins to bind and activate Beclin1 and thus promote the autophagy process for a long time before apoptosis. Furthermore, apoptosis is prone to occur with increasing activation of Caspases, inactivation of Beclin1-A and the Michaelis constant of Caspases.

Conclusion: A novel mathematical model has been developed to understand the complex regulatory mechanisms of autophagy and apoptosis. Our model may be applied to further autophagy-apoptosis dynamic modeling experiments and simulations.

Keywords: Autophagy, Apoptosis, B-cell lymphoma-2, AMBRA1, Endoplasmic reticulum, Mitochondria

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Background

Autophagy and apoptosis play crucial roles in deciding cellular survival and death in response to different stress signals, such as nutrient starvation and endoplasmic reticulum (ER) stress [1–3]. Autophagy, a cellular survival process, provides energy through degrading abnormal cytoplasmic components in the lysosomal pathway and can be activated by the Beclin1 protein in the ER [4–9]. However, excessive levels of autophagy can lead to apoptosis with increased stress levels [7, 10–13]. Apoptosis, a kind of programmed cell death, can be triggered by the proapoptotic protein Bax, which causes mitochondrial membrane permeabilization to release mitochondrial cytochrome c into the cytoplasm, further activating Caspases to induce apoptosis [14–17]. An increasing number of studies confirm that the autophagy and apoptosis networks are linked at various levels through common regulatory elements [18, 19].

B-cell lymphoma-2 (Bcl2) proteins in the mitochondria and ER are important regulators of autophagy and apoptosis [20–23]. Bcl2 in the ER (ER-Bcl2) and mitochondrial Bcl2 (mito-Bcl2) play different roles in activating the different responses of autophagy and apoptosis [24]. ER-Bcl2 negatively regulates the Beclin1-dependent autophagy program, while mito-Bcl2 has been shown to exert an antiapoptotic effect [25–27]. Several mathematical models of the autophagy-apoptosis network, including crosstalk between Bcl2 proteins, have been established [28, 29] to explore cell fate decisions [30–32]. Kapuy et al. presented a minimal model that contains interplay between crucial autophagy and apoptosis proteins; however, they did not compare simulations and experimental measurements. Tavassoly et al. addressed this disadvantage; however, the important AMBRA1 protein was not included in their assessment. The AMBRA1 protein translocates from mitochondria to the ER and regulates both Beclin1-dependent autophagy and apoptosis [33, 34]. AMBRA1 positively regulates the Beclin1-dependent autophagy program through functioning with ER-Bcl2 and mito-Bcl2 [35]. AMBRA1 binds preferentially to mito-Bcl2 under normal conditions; after autophagy initiation upon stress, AMBRA1 is released from mito-Bcl2 to ER-Bcl2, and binding to Beclin1 is increased to promote autophagy in the ER [36]. Therefore, AMBRA1, ER-Bcl2 and mito-Bcl2 should be included in the autophagy and apoptosis network in further analyses of cell fate decisions upon different stress levels.

Various stress signals in the ER and mitochondria can activate autophagy or apoptosis. For example, nutrient-induced stress of the ER activates autophagy to recycle damaged organelles [37, 38]. DNA damage can cause apoptosis through promoting the release of cytochrome c from the mitochondria to the cytosol [39–41]. Bcl2, a coregulator of autophagy and apoptosis in both the ER and mitochondria, can sense different stresses [42–44]. Therefore, it is important to explore how different levels of stress on ER-Bcl2 and mito-Bcl2 regulate the switch from autophagy to apoptosis. In this work, ER-Bcl2 and mito-Bcl2 protein binding to AMBRA1 is considered in a previously reported model [29], and different levels of stress are imposed in this model. Then, we focus on the effects of these two levels of stress on the switch from autophagy to apoptosis. The results are organized as follows. First, a new model is proposed. Second, typical time series of both active Beclin1 (Beclin-A) and Caspases and Caspases activation times are given for different stress levels, bifurcation analyses of these two stress levels are described, and the effect of feedback regulation intensity in this model on bifurcation diagrams is studied. Finally, we discuss the results and provide a conclusion.

Methods

Mathematical model

Here, we consider two different levels of stress (such as transient nutrient starvation, DNA damage or growth factor withdrawal) denoted by $S_1$ and $S_2$, respectively, on two modules: the ER and mitochondria, as shown in the network diagram in Fig. 1. Under normal conditions, AMBRA1 binds preferentially to mito-Bcl2 over ER-Bcl2. However, after autophagy induction under stress conditions, some AMBRA1 proteins disassociate from mito-Bcl2 and translocate into the ER to promote Beclin1-A activity. Notably, AMBRA1 binds to Bcl2 and promotes the degradation of Bcl2, but its Bcl2-binding rates in mitochondria and the ER are different. Additionally, Beclin1-A activity is promoted by AMBRA1. In the ER, Beclin1-A, an inducer of autophagy, can cotransform with an inactive form of Beclin1 (Beclin1-I). Beclin1-A and Beclin1-I deactivate and activate apoptosis-inducing Caspases, respectively, which in turn promotes the production of Beclin1-I. Therefore, there is a positive feedback loop between Caspases and Beclin1-I but a double-negative feedback loop between Caspases and Beclin1-A. In the mitochondria, Bax promotes the release of cytochrome c to activate Caspases. Caspases inhibit ER-Bcl2 and mito-Bcl2. Two stresses $S_1$ and $S_2$ are imposed on ER-Bcl2 and mito-Bcl2; while the former inhibits both Beclin1-A and Beclin1-I, the latter inhibits Beclin1-A and Bax.

Dynamic equations

Based on their biochemical interactions shown in Fig. 1, the following eight components are considered: ER-Bcl2 ([Bcl2_e]), mito-Bcl2 ([Bcl2_m]), AMBRA1 ([AMBRA1]), Caspases ([Casp]), active Beclin1 ([Beca]), inactive Beclin1 ([Bec]), Bcl2–Beclin1 complex ([Becac]) and Bcl2–Bax complex ([Baxc]). The rate of every component is described by an ordinary differential equation (ODE) composed of production and consumption terms. The production term is a protein synthesis or activation term,
while the consumption term is a protein degradation or inaction term. Every term on the right-hand side of the ODE corresponds to each biochemical reaction, which is described by using either the law of mass action or Michaelis-Menten kinetics, and the Michaelis constant $J_{cp}$ is the substrate concentration at which the rate is equal to half of the maximal rate \[45\]. The unit of time is h, while protein concentrations are in arbitrary units. The significance and parameter values are shown in Table 1. In this work, the time series and bifurcation curves were computed numerically by XPP-AUT. The rate of every component is described by Eqs. (1)–(10) as follows:

\[
\frac{d[Bcl_2]}{dt} = k_1 - (k_2 + k_3 \cdot S_1 + k_4 \cdot Casp + k_5 \cdot AMBRA1) - Bcl_2
\]  
(1)

\[
\frac{d[Bcl_2_m]}{dt} = k_1 - (k_2 + k_3 \cdot S_2 + k_4 \cdot Casp + k_6 \cdot AMBRA1) - Bcl_2_m
\]  
(2)

\[
\frac{d[AMBRA1]}{dt} = k_7 - (k_8 \cdot Bcl_2_e + k_9 \cdot Bcl_2_m + k_10)
\]  
(3)

\[
\frac{d[Casp]}{dt} = (k_{12} + k_{13} \cdot Beci + k_{14} \cdot (Baxt - Baxc)) \cdot (Caspt - Casp)/(J_{cp} + Caspt - Casp) - (k_{15} + k_{16} \cdot Beca) \cdot Casp/(J_{cp} + Casp)
\]  
(4)

\[
\frac{d[Beca]}{dt} = k_{11} \cdot AMBRA1 - k_a \cdot (Bcl_2_e - Becac - Becic) - Beca - (k_{18} + k_{19} \cdot Casp) \cdot Beca + (k_6 + k_2 + k_3 \cdot S_1 + k_4 \cdot Casp) \cdot Becac + k_{17} \cdot Beci
\]  
(5)

\[
\frac{d[Beci]}{dt} = -k_a \cdot (Bcl_2_e - Becac - Becic) - Beci + (k_{18} + k_{19} \cdot Casp) \cdot Beca + (k_6 + k_2 + k_3 \cdot S_1 + k_4 \cdot Casp) \cdot Becic - k_{17} \cdot Beci
\]  
(6)

\[
\frac{d[Becac]}{dt} = k_a \cdot (Bcl_2_e - Becac - Becic) - Beca - (k_{18} + k_{19} \cdot Casp) \cdot Becac - (k_6 + k_2 + k_3 \cdot S_1 + k_4 \cdot Casp) \cdot Becac + k_{17} \cdot Beci
\]  
(7)
\[
\frac{d[Baxc]}{dt} = k_c \cdot (Baxt - Baxc) \cdot (Bcl2_m - Baxc) - (k_d + k_2 + k_3 \cdot S_2 + k_4 \cdot Casp) \cdot Baxc
\]  
\[
Bcl2t = Bcl2_e + Bcl2_m
\]  
\[
Becic = Bect - Beca - Beci - Becac
\]  

Table 1 Parameters and their descriptions (protein concentrations are in arbitrary units, and the unit of time is h)

| Parameter | Significance | Value |
|-----------|--------------|-------|
| \(k_1\)   | rate of Bcl2 synthesis | 0.05  |
| \(k_2\)   | basal rate of Bcl2 degradation | 0.01  |
| \(k_3\)   | stress-dependent rate of Bcl2 degradation | 0.6   |
| \(k_4\)   | Caspases-dependent rate of Bcl2 degradation | 0.1   |
| \(k_5\)   | AMBRA1-dependent rate of ER-Bcl2 degradation | 0.3   |
| \(k_6\)   | AMBRA1-dependent rate of mito-Bcl2 degradation | 0.4   |
| \(k_7\)   | basal rate of AMBRA1 activation | 0.001 |
| \(k_8\)   | ER-Bcl2-dependent rate of AMBRA1 degradation | 0.3   |
| \(k_9\)   | mito-Bcl2-dependent rate of AMBRA1 degradation | 0.4   |
| \(k_{10}\) | basal rate of AMBRA1 inactivation | 0.01  |
| \(k_{11}\) | AMBRA1-dependent rate of Beclin1 activation | 0.3   |
| \(k_{12}\) | basal rate of Caspases activation | 0     |
| \(k_{13}\) | inactivated Beclin1-dependent Caspases activation constant | 0.05  |
| \(k_{14}\) | Bax-dependent rate of Caspases activation | 0.4   |
| \(k_{15}\) | basal Caspases inactivation constant | 0.1   |
| \(k_{16}\) | Beclin1-dependent rate of Caspases inactivation | 0.37  |
| \(k_{17}\) | Beclin1 activation rate | 1     |
| \(k_{18}\) | basal Beclin1 inactivation rate | 0.01  |
| \(k_{19}\) | Caspases-dependent rate of Beclin1 inactivation | 5     |
| Jcp       | Caspases Michaelis constant | 0.01  |
| \(k_s\)   | rate of Bcl2-Beclin1 complex association | 0.1   |
| \(k_o\)   | rate of Bcl2-Beclin1 complex dissociation | 1     |
| \(k_c\)   | rate of Bcl2-Bax complex association | 8     |
| \(k_d\)   | rate of Bcl2-Bax complex dissociation | 0.1   |
| \(S_1\), \(S_2\) | stress level \(S_1\) and \(S_2\) | 0.5   |
| Bcl2t     | total level of Bcl2 | 1     |
| Baxt      | total level of Bax | 0.25  |
| Caspt     | total level of Caspases | 1     |
| Becic     | inactive, Bcl2-bounded Beclin1 | 0.2   |
| Bect      | total level of Beclin1 | 1     |

Results

We focused on exploring the effect of different stress levels on ER-Bcl2 and mito-Bcl2 on the transition between autophagy and apoptosis. First, typical time series and Caspases activation times are given for different stresses. Then, bifurcation analyses of the two stresses in this model are carried out under different feedback regulation conditions.

Autophagy-apoptosis transition mediated by two different stresses on the ER and mitochondria

In general, autophagy is activated first by Beclin1-A in the ER, and apoptosis is then activated by Caspases in the mitochondria, depending on both the intensity and duration of stress on the ER and mitochondria. In this section, we focus on how two stresses, \(S_1\) and \(S_2\), on ER-Bcl2 and mito-Bcl2, respectively, regulate the transition from autophagy to apoptosis. Without loss of generality, we explore the sensitive of autophagy or apoptosis to two stresses, \(S_1\) and \(S_2\), with different intensities, as shown in Fig. 2 by the time series of the concentrations of Bcl2_e (black, solid curve), Bcl2_m (short, red, dashed...
curve), AMBRA1 (gray, solid curve), Casp (long, blue, dashed curve) and Beca (green, dash-dot curve). First, at a low $S_2(S_2 = 0.2)$, we consider low and a high value of $S_1(S_1 = 0.1$ and $4.5)$, as shown in Fig. 2a and b, respectively. An abrupt increase in Beca with either a low $S_1$ or a high $S_1$, which facilitates the degradation of ER-Bcl2 and dissociation of the Bcl2-e-Beclin1 complex, can activate autophagy. Autophagy induction promotes the release of AMBRA1 from mito-Bcl2, which further promotes the Beclin1-A-dependent autophagy program. Furthermore, Beclin1-A and mito-Bcl2 deactivate Caspases to protect cells from death. Notably, although the high $S_1$ value in Fig. 2b prompts ER-Bcl2 and mito-Bcl2 levels to first decrease rapidly and even remain very low, Caspases are still inactive due to the promotion of Beclin1-A activity in the ER by AMBRA1, promoting autophagy.

In contrast, at a high $S_2(S_2 = 2)$, as shown in Fig. 2c and d, apoptosis with either a low ($S_1 = 0.1$ in Fig. 2c) or high ($S_1 = 4.5$ in Fig. 2d) value of $S_2$ is activated very quickly by increasing Casp levels. In fact, autophagy is first activated by low levels of mito-Bcl2 and high levels of AMBRA1 and $S_2$, while sustained levels of these molecules activate Caspases-induced apoptosis. Additionally, Casp reaches a high level (as labeled by arrows in Fig. 2) are 10 h and 20 h before apoptosis activation for a low $S_1$ and a high $S_1$, respectively. As shown in Fig. 2c and d, apoptosis can be activated at a higher $S_2$, while the Caspases activation time is dependent on the value of $S_1$, and the activation time is shorter for a low $S_1$ (Fig. 2c) than for a high $S_1$ (Fig. 2d). When there is a large difference between low stress levels in the ER and high stress levels in mitochondria, apoptosis can be easily activated. Otherwise, apoptosis activation is delayed with high stress levels on both the ER and mitochondria. This delay occurs because less inhibition of AMBRA1 due to low ER-Bcl2 and mito-Bcl2 levels maintains high AMBRA1 levels for a long time to activate autophagy before apoptosis. Furthermore, we determine the dependence of time before apoptosis activation on the levels of both stresses, $S_1$ and $S_2$, as shown in Fig. 3.

At a low $S_2 = 0.2$, as shown in Fig. 3a, apoptosis can never be activated with increasing $S_1$. However, apoptosis will be activated when $S_2$ is higher than 0.4 with a low $S_1 = 0.1$, as shown in Fig. 3b. Additionally, the time before apoptosis activation shown in Fig. 3b decreases with increasing $S_2$. All these results are displayed in the overall view of grayscale intensities of time as a function of both $S_1$ and $S_2$ in Fig. 3c. As shown in Fig. 3c, apoptosis can easily be activated in a short time with a high $S_2$ and low $S_1$.

As discussed above, low levels of stress on mitochondria activate only autophagy with any stress level on the ER, while high levels of stress on mitochondria can induce a transition from autophagy to apoptosis. Additionally, autophagy is first induced by a high Beca level accompanied by a low Casp level, and apoptosis is then activated when Casp gradually increases. Therefore, autophagy and apoptosis exhibit two steady states, and further necessitate analysis of the stability of these steady states through a bifurcation diagram of different stress levels is discussed in the next section.
Autophagy and apoptosis are determined by bifurcations for different stresses on the ER and mitochondria

Now, we show bifurcation diagrams of the steady state of Casp as well as Becca for two parameters, $S_1$ and $S_2$, in Fig. 4. As shown in Fig. 4a, codimension-one bifurcation curves of Becca and Casp with respect to the parameter $S_1$ when $S_2 = 0.2$ show only a stable steady state with a low Casp level and a high Becca level; this steady state corresponds to the autophagy process. However, the bifurcation curves of Becca and Casp with respect to the parameter $S_2$ when $S_1 = 0.2$ shown in Fig. 4b are bistable switch curves, in which upper and lower branches of the curves are composed of stable steady states separated by middle branches composed of unstable steady states. With a low value of $S_2$, one of two stable steady states corresponds to a high Becca level but a low Casp level for autophagy, while the other corresponds to a low Becca level but a high Casp level for apoptosis. Furthermore, an increase in $S_2$ leads to a transition from bistability to monostability via fold bifurcation point F, and Casp adopts a high steady state for apoptosis. Additionally, a high Casp steady state cannot return to a low steady state of autophagy with decreasing stresses because the other fold bifurcation point does not appear in the positive half-axis of the x-axis.

Furthermore, the codimension-two bifurcation diagram of $S_1$ and $S_2$ in Fig. 4c is divided into two regions by the fold bifurcation curve $f_1$; monostability on the right region corresponds to apoptosis, and bistability on the left region denotes autophagy or apoptosis. Additionally, the $f_1$ curve is an almost vertical line with increasing $S_2$ and intersects the x-axis at only $S_2 = 0.16$, which indicates that the system is sensitive to only $S_2$. In addition, the codimension-two bifurcation diagram can be affected by feedback regulation, which is discussed in the following section.

The effect of feedback regulation on autophagy and apoptosis

In this section, we explore the effect of all feedback regulation parameters on the codimension-two bifurcation diagrams of $S_1$ and $S_2$. All parameters are divided into three groups; the first two groups are related to the activation and inhibition of both Caspases and Beclin1-A, respectively (Fig. 5a–d), and the third group is associated with Bcl2 (Fig. 5e–f). Only one bifurcation diagram for each parameter is shown in every group due to similar effects. Among the Caspases activation rates $k_{12}$, $k_{13}$, $k_{14}$, codimension-two bifurcation diagrams of $S_1$ and $S_2$ for different $k_{14}$ values are shown in Fig. 5a; the fold bifurcation curves move left, and the monostable region is enlarged for an increased $k_{14}$ activation rate. A higher activation rate increases the Casp level and then activates apoptosis with a low $S_2$ value. In contrast, a high Caspases inactivation rate, $k_{15}$, shifts the fold bifurcation curve right and reduces the monostable region on the bifurcation diagram in Fig. 5b, which is similar to the parameter $k_{16}$. Therefore, apoptosis can be activated with only high $S_2$ values when Caspases inactivation rates are high.

In contrast, based on Fig. 5c and d, the fold bifurcation curve moves right and left with an increase in the
Fig. 4 Bifurcation diagrams of both Beca (black lines) and Casp (gray lines). Codimension-one bifurcation curves with respect to a $S_1$ at $S_2 = 0.2$ and b $S_2$ at $S_1 = 0.2$. Stable steady states and unstable steady states are represented by solid and dotted lines, respectively. F is the equilibrium fold bifurcation point. c Codimension-two bifurcation diagram with respect to $S_1$ and $S_2$; the black line is the equilibrium fold bifurcation curve.

Fig. 5 Codimension-two bifurcation diagrams of $S_1$ and $S_2$ for different levels of feedback regulation. a $k_{14}$; b $k_{15}$; c $k_{17}$; d $k_{19}$; e $k_1$; f $J_{cp}$. B and M denote bistability and monostability, respectively.
activation \((k_{17})\) and degradation \((k_{18}, k_{19})\) rates of Beclin1-A, respectively. A high Beclin1-A activation rate increases the level of Beca to activate autophagy for the large bistable region, while a high Beclin1-A inactivation rate decreases the Beca level to easily activate apoptosis for the large monostable region. All parameters related to Bcl2 in the third group have little effect on the codimension-two bifurcation diagrams, except \(k_1\) and Jcp. A high \(k_1\) value moves the fold bifurcation curve to the right for autophagy, while a high Jcp value moves the fold bifurcation curve to the left for apoptosis.

**Discussion**

Autophagy and apoptosis play essential roles in making cell fate decisions between life and death under stress. Autophagy promotes cell survival through activating Beclin1-A in the ER and can switch to apoptosis when Caspases in the mitochondria are activated. The Bcl2 and AMBRA1 proteins in both the ER and mitochondria act as important regulators of autophagy and apoptosis.

In this study, we added Bcl2 and AMBRA1 in the ER and mitochondria to an original model proposed by Kapuy et al. and investigated how two different stresses on Bcl2 in the ER \((S_1)\) and mitochondria \((S_2)\) affect the transition from autophagy to apoptosis. Based on typical time series and bifurcation analyses, we concluded that autophagy is activated upon a low level of stress on mitochondria regardless of the level of stress on the ER (Fig. 2a, b), while apoptosis is activated for a high level of stress on the mitochondria (Fig. 2c, d). Normally, AMBRA1 partially localizes to the mitochondria and translocates to the ER to activate Beclin1 when autophagy is induced. In Fig. 2c, autophagy is maintained for a short time but then turns to apoptosis quickly because the AMBRA1 protein can compete with both ER-Bcl2 and mitochondria-Bcl2 to bind and activate Beclin1. However, in Fig. 2d, autophagy is maintained for a long time before slowly switching to apoptosis. This occurs because higher AMBRA1 levels due to less inhibition lower mitochondrial Bcl2 and ER-Bcl2 levels play a positive role in maintaining autophagy for a much longer time (Fig. 2d). The delay in switching from autophagy to apoptosis shown in Fig. 2c and d was caused mainly by AMBRA1 under stress conditions. Also, the delay for different stresses can be seen clearly in Fig. 3c. Furthermore, apoptosis is sensitive to only \(S_2\) which is the key factor that divides the areas of the parameter plane \((S_1 \times S_2)\) into bistability and monostability (Fig. 4c). Apoptosis is prone to occur with an increased Caspases activation rate, Beclin1-A deactivation rate and Caspases Michaelis constant (Fig. 5). In summary, under two different stress levels on mitochondrial Bcl2 and ER-Bcl2, the process of autophagy is promoted and maintained by AMBRA1 in the ER, while apoptosis is decided mainly by the stress on mitochondria.

Autophagy and apoptosis are important cellular responses to pharmacological interventions for diseases that are controlled by a dynamic network of interacting proteins. It is important to identify and target key components of this network when designing therapeutic regimens for diseases. In this work, Bcl2 and AMBRA1 in the ER and mitochondria are included in a previously described model, and we explored cellular responses to different levels of stress on the ER and mitochondria and feedback regulation in the network. However, the inclusion of more proteins in a more complete autophagy-apoptosis network is necessary, and cell fate in response to different conditions should be quantitatively analyzed.

**Conclusion**

A mathematical model of autophagy and apoptosis regulated by stress on the binding of Bcl2 with AMBRA1 in the ER and mitochondria has been established. This model links experimental evidence and theoretical biology for a more comprehensive understanding of the complex regulatory mechanisms of autophagy and apoptosis. Therefore, our work may provide an application for further experiments and simulations of dynamic autophagy-apoptosis models.

**Abbreviations**

Baxc: Bcl2\(_{m}\)-Bax complex; Bcl2: B-cell lymphoma-2; Bcl2\(_{m}\): B-cell lymphoma-2 in the mitochondria; Beca: Active Beclin1; Becac: Bcl2\(_{m}\)-Beclin1 complex; Beci: Inactive Beclin1; Beclin1-I: Inactive Beclin1; Beclin1-A: Active Beclin1; Casp: Caspases; ER: Endoplasmic reticulum; ER-Bcl2: B-cell lymphoma-2 in the endoplasmic reticulum; mito-Bcl2: B-cell lymphoma-2 in the mitochondria; ODE: Ordinary differential equation

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**Authors’ contributions**

BJY designed the mathematical model, performed the simulations, analyzed the data, and wrote the manuscript. QSL conceived the study, participated in its design and coordination, and analyzed the data. YHB supervised the research, wrote the manuscript, designed the mathematical model, and analyzed the data. All authors read and approved the final manuscript.

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**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.
References

1. Marycz K, Komicka K, Szpak-Kosaizerwicz J, Weiss C. Excessive endoplasmic reticulum stress correlates with impaired mitochondrial dynamics, mitophagy and apoptosis, in liver and adipose tissue, but not in muscles in EMS horses. Int J Mol Sci. 2018;19:165.

2. Song S, Tan J, Mao Y, Li M, Zhang Q. Crosstalk of autophagy and apoptosis: involvement of the dual role of autophagy under ER stress. J Cell Physiol. 2017;232:2977–84.

3. Yu P, Wang HY, Tian M, Li AX, Chen XS, Wang XL, Zhang Y, Cheng Y. Eukaryotic elongation factor-2 kinase regulates the cross-talk between autophagy and pyroptosis in duxorubicin-treated human melanoma cells in vitro. Acta Pharmacol Sin. 2019;01:–8.

4. Senft D, Ronai ZA. UPR, autophagy, and mitochondria crosstalk underlies the ER stress response. Trends Biochem Sci. 2015;40:141–8.

5. Irlbro R, Munoz-Pinedo C. Cell death induced by endoplasmic reticulum stress. FEBS J. 2016;283:2640–52.

6. Jin H, Lei J. A hybrid model of molecular regulation and population dynamics for yeast autophagy. J Theor Biol. 2016;402:45–53.

7. Tang D, Kang R, Berge T, Vandenabeele P, Kroemer G. The molecular machinery of regulated cell death. Cell Res. 2019;01:–8.

8. Hill SM, Wrobel L, Rubinsztein DC. Post-translational modifications of Beclin 1 provide multiple strategies for autophagy regulation. Cell Death Differ. 2019;26:617–29.

9. Mauri MC, Grollio A, Kroemer G. Crosstalk between apoptosis and autophagy within the Beclin-1 interactome. EMBO J. 2012;29:515–6.

10. Oral O, Akkoc Y, Bayraktar O, Gozuacik D. Physiological and pathological significance of the molecular cross-talk between autophagy and apoptosis. Histol Histopathol. 2016;31:479–98.

11. Li M, Gao P, Zhang J. Crosstalk between autophagy and apoptosis: potential and emerging therapeutic targets for cardiac diseases. Int J Mol Sci. 2016;17:332.

12. Clarke AJ, Simon AK. Autophagy in the renewal, differentiation and homeostasis of immune cells. Nat Rev Immunol. 2019;19:170–83.

13. Doherty J, Baehrelr EH. Life, death and autophagy. Nat Cell Biol. 2018;20:110–7.

14. Kapuy O, Lzák B, Steller J, Enahnegi G. A systems biological perspective of cellular stress-directed programmed cell death. Comput Mol Biol. 2014;04:28–34.

15. Martinou JC, Youle RJ. Mitochondria in apoptosis: Bcl-2 family members and mitochondrial dynamics. Dev Cell. 2011;21:92–101.

16. Booth LA, Tavallali S, Hamed HA, Cruickshanks N, Dent P. The role of cell signalling in the crosstalk between autophagy and apoptosis. Cell Signal. 2014;26:549–55.

17. Santos LC, Vogel R, Chipuk JE, Birnwaile MR, Stolovitzky G, Meyer P. Mitochondrial origins of fractional control in regulated cell death. Nat Commun. 2019;10:1313.

18. Gump JM, Thorburn A. Autophagy and apoptosis: what is the connection? Trends Cell Biol. 2011;21:387–92.

19. Gordy C, He YY. The crosstalk between autophagy and apoptosis: where does this lead? Protein Cell. 2012;3:17–27.

20. Chen X, He Y, Li F. Autophagy in stem cell biology: a perspective on stem cell self-renewal and differentiation. Stem Cell Int. 2018;2018:913197.

21. Liu B, Olvai ZN, Bayr H, Silverman GA, Pak SC, Perlmutter DH, Bahar I. Quantitative assessment of cell fate decision between autophagy and apoptosis. Sci Rep. 2017;7:17605.

22. Cooper KF. Till death do us part: the marriage of autophagy and apoptosis. Oxidative Med Cell Longev. 2018;2018:4701275.

23. Singh R, Letia A, Sarosiek K. Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. Nat Rev Mol Cell Biol. 2019;20:175–93.

24. Aki H, Vervloesem T, Vivilcuto S, Bittremieux M, Pans JY, De Smedt H, Bullynck A. A dual role for the anti-apoptotic Bcl-2 protein in cancer: mitochondria versus endoplasmic reticulum. Biochim Biophys Acta. 2014;1843:2240–52.

25. Efrich S, Mizachy L, Segov O, Lindenboi M, Zmira O, Adi-Harel S, Hirsch JA, Stein R, Pinkas-Kramarski R. Differential interactions between Beclin 1 and Bcl-2 family members. Autophagy. 2014;3:561–8.

26. Sohn EJ, Park HT. Natural agents mediated autophagic signal networks in cancer. Cancer Cell Int. 2017;17:110.

27. Kang R, Zeh HJ, Lotze MT, Tang D. The Beclin 1 network regulates autophagy and apoptosis. Cell Death Differ. 2011;18:571–80.

28. Tavassoly I, Parmar J, Shajahan-Haq AN, Clarke R, Baumann WT, Tyson JJ. Dynamic modeling of the interaction between autophagy and apoptosis in mammalian cells. CPT Pharmacometrics Syst Pharmacol. 2015;4:263–72.

29. Kapuy O, Vinod PK, Mandl J, Banhegyi G. A cellular stress-directed bistable switch controls the crosstalk between autophagy and apoptosis. Mol BioSyst. 2013;9:296–306.

30. Fernandez AF, et al. Disruption of the beclin-1-BCL2 autophagy regulatory complex promotes longevity in mice. Nature. 2018;558:136–40.

31. Heath-Engel HM, Chang NC, Shore GC. The endoplasmic reticulum in apoptosis and autophagy: role of the BCL-2 protein family. Oncogene. 2008;27:6419–33.

32. Vogler M, Weber K, Dinsdale D, Schmitz I, Schulze-Osthoff K, Dyer MJ, Cohen GM. Different forms of cell death induced by putative BCL2 inhibitors. Cell Death Differ. 2009;16:1030–9.

33. Yazdankhah M, Farioli-Veccioili S, Tonchev AB, Stoykova A, Ceccconi F. The Bcl-2 autophagy regulators Ambr1 and Beclin 1 are required for adult neurogenesis in the brain subventricular zone. Cell Death Dis. 2014;5:e1403.

34. Firme GA, Corazza M, Antonioli M, Pacentini M, Ambra1 at the crossroad between autophagy and cell death. Oncogene. 2013;32:3311–8.

35. Firme GA, Stoykova A, Romagnoli A, Giunta L, Di Bartolomeo S, Nardacci R, Corazza M, Fuoco C, Ucar A, Schwartz P, et al. Ambr1 regulates autophagy and development of the nervous system. Nature. 2017;547:1121–5.

36. Di Bartolomeo S, Corazza M, Nazzio F, Oliviero S, Lisi G, Antonioli M, Pagliarini V, Matteoni S, Fuoco C, Giunta L, et al. The dynamic interaction of AMBR1 with the dynin neuron complex regulates mammalian autophagy. J Cell Biol. 2010;191:155–68.

37. Sotthibundhoo A, Promjuntuek W, Liu M, Shen S, Noipa P. Roles of autophagy in controlling stem cell identity: a perspective of self-renewal and differentiation. Cell Tissue Res. 2018;374:205–16.

38. Chinchwadkar S, Padmanabhan S, Mishra P, Singh S, Suresh SN, Vats S, Barve G, Ammanathan V, Manjithaya R. Multifaceted housekeeping functions of autophagy. J Ind Inst Sci. 2017;97:79–94.

39. Kaczanowski S. Apoptosis: its origin, history, maintenance and the medical implications for cancer and aging. Phys Biol. 2016;13:031001.

40. Ashkenazi A, Fairbrother WJ, Leverson JD, Souers AJ. From basic apoptosis functions of autophagy. J Indian Inst Sci. 2017;97:79–94.

41. Siddiqui WA, Ahad A, Ahsan H. The mystery of BCL2 family: BCL-2 proteins controversies in BCL-2 protein-mediated apoptosis. FEBS J. 2016;283:2640–52.

42. Ciechomska IA, Goemans GC, Skepper JN, Tolkovsky AM. Bcl-2 complexed to mitochondrial versus endoplasmic reticulum. Biochim Biophys Acta. 2014;1843:2240–52.

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