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Coupled positive feedbacks provoke slow induction plus fast switching in apoptosis

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Abstract **Apoptosis is a form of a programmed cell death for multicellular organisms to remove unwanted or damaged cells. This critical choice of cellular fate is an all-or-none process, but its dynamics remains unraveled. The switch-like apoptotic decision has to be reliable, and once a pro-apoptotic fate is determined it requires fast and irreversible execution. One of the key regulators in apoptosis is caspase-3. Interestingly, activated caspase-3 quickly executes apoptosis, but it takes considerable time to activate it. Here, we have analyzed this "slow induction plus fast switching" mechanism of caspase-3 through mathematical modeling and computational simulation. First, we have shown that two positive feedbacks, composed of caspase-8 and XIAP, are essential for the "slow induction plus fast switching" behavior of caspase-3. Second, we have found that XIAP in the feedback loops primarily regulates induction time of caspase-3. In many cancer cells activation of caspase-3 is suppressed. Our results suggest that reinforcement of the positive feedback by XIAP, which relieves XIAP-mediated caspase-3 inhibition, might favor a pro-apoptotic cellular fate.**

Keywords: Apoptosis; Caspase-3 activation; Long induction; Fast switching; Coupled positive feedbacks; Simulation analysis

1. Introduction

Apoptosis is a critical cellular process that induces death of seriously damaged or unnecessary cells in various biological processes including development, differentiation, proliferation, and immune responses [1,2]. It is a programmed cell death by which cells execute an intracellular suicide program and kill themselves without damaging neighboring cells. Interestingly, a characteristic behavior of "slow induction plus fast switching" has been observed for many of apoptotic cells [3,4]. However, the underlying mechanism remains mostly unsolved.

When an apoptotic stimulus is applied either through extrinsic or intrinsic stress signals, e.g., external death signals or internal DNA-damages [5–9], an array of caspases including caspases-2, -3, -6, -7, -8, -9, and -10 are activated [10–14]. Among those, activation of caspase-3 is one of the key events. Caspase-3 is known to be indispensable for chromatin condensation and DNA fragmentation in many cell types [15,16]. It has been reported that the caspase-3 activation is a bistable (i.e., all-or-none) and irreversible procedure [17–20]. A mathematical model of the caspase-3 activation in the death receptor-induced apoptosis was proposed [17]. Here, to find any hidden topological structure in a caspase-3 activation pathway for apoptosis, we employed a mathematical model building approach. We first divided the systems model into three sub-models, which corresponded to three positive feedbacks through caspase-8, X chromosome-linked IAP (XIAP), and caspase-3-XIAP complex. We then investigated the regulatory mechanism of caspase-3 focusing on topological structures among those positive feedbacks.

Activation of caspase-3 is known to be regulated by the inhibitor of apoptosis (IAP) proteins. In previous studies [21–26], several human IAP family proteins including c-IAP1, c-IAP2, XIAP, and survivin were shown to regulate caspase-3. In particular, XIAP is reported to inhibit caspase-3, -7, and -9, and cleaved by caspase-3. Although a positive feedback formed by XIAP is suggested to be involved in activation of caspase-3 [26,27], the role of interactions of caspase-3 with caspase-8 and XIAP has not been understood. In this paper, we built a mathematical model regarding the caspase-3 activation and attempted to characterize the potential mechanism of "slow induction plus fast switching".

2. Materials and methods

The core pathway on the caspase-3 activation is shown in Fig. 1. Caspase-3 regulates two proteins, i.e., caspase-8 and XIAP, whose quantities are fed back directly or indirectly to the caspase-3 activation [17,26]. There are two positive feedbacks involved in this caspase-3 activation: positive feedback through activation (PFA) (i.e., via caspase-8) and positive feedback through inhibition (PFI), i.e., via XIAP. As the level of caspase-3 increases, PFA increases the rate of caspase-8 activation while PFI decreases the rate of cleavage or inactivation of caspase-3. As observed in Fig. 2B, C3* activates degradation of XIAP, which in turn alleviates degradation of C3*. Consequently, a positive feedback loop is formed for C3*. In a similar manner, C3* stimulates formation of C3*-XIAP, which relieves degradation of C3*. This latter

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Abbreviations: IAP, inhibitor of apoptosis protein; XIAP, X chromosome-linked IAP; C*n*, pro-caspase-*n*; C*n**, activated caspase-*n*; C3*-XIAP, caspase-3-XIAP complex; PFA, positive feedback through activation; PFI, positive feedback through inhibition

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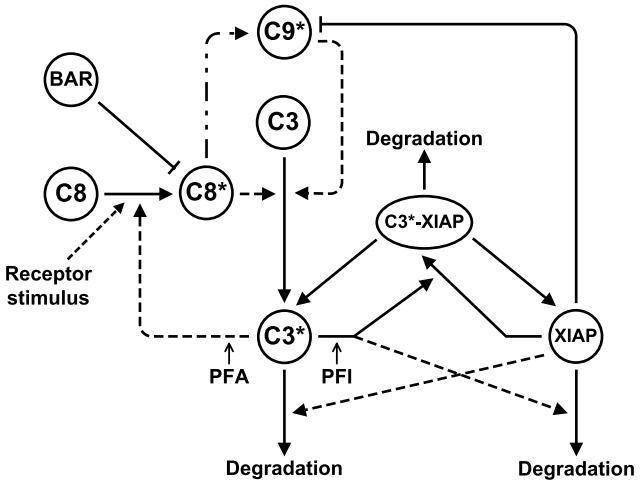

Fig. 1. The regulatory network of caspase-3 activation in apoptosis. The solid arrows indicate the actual reactions and the dashed arrows denote the effective regulation of reaction coefficients. The dashed double-dot arrow indicates activation through multi-step reactions. Caspase-8 is activated by external death signals and it activates pro-caspase-9. Caspase-8 and caspase-9 activate pro-caspase-3. Caspase-8 can be inhibited by bifunctional apoptosis regulator (BAR), and caspase-3 and caspase-9 can be inhibited by XIAP, which is inhibited by caspase-3. In this paper, we have considered caspase-3 activation by caspase-8 as well as caspase-3 inhibition by XIAP. The reactions through caspase-9 are not included. The positive feedbacks through caspase-8 and XIAP form PFA and PFI, respectively. The two different feedbacks are coupled and activate caspase-3.

mechanism also provides a positive feedback loop. Both PFA and PFI have the positive effects on caspase-3 activation.

To present a precise feedback structure in Fig. 1, the coupled positive feedbacks for caspase-3 activation are illustrated in Fig. 2. For details, the positive feedback through caspase-8 is denoted by $PFA_{\_C8^*}$ as shown in Fig. 2A. Two positive feedbacks through XIAP denoted by $PFI_{\_XIAP}$ (Fig. 2B) and caspase-3-XIAP complex ($C3^*$-XIAP) denoted by $PFI_{\_C3^*\text{-}XIAP}$ (Fig. 2C) are shown in Fig. 2.

We have separately described the interacting feedback systems of $PFI_{\_XIAP}$ and $PFI_{\_C3^*\text{-}XIAP}$ to determine the overall effect of these feedbacks on the caspase-3 activation. The interacting feedback systems operate as follows: Caspase-3 inhibits XIAP by cleaving XIAP ((1) in Fig. 2B) through ubiquitination and degradation [21,25,26], and also by inactivating XIAP ((3) in Fig. 2C) through the formation of $C3^*$-XIAP [23,24]. XIAP is fed back to inhibit ((2) in Fig. 2B) caspase-3 by the degradation of caspase-3. Furthermore, $C3^*$-XIAP is fed back to activate ((4) in Fig. 2C) caspase-3 by releasing caspase-3 from $C3^*$-XIAP. If $PFI_{\_C3^*\text{-}XIAP}$ works, the degradation level of caspase-3 by XIAP decreases and the activation level of caspase-3 by releasing caspase-3 from $C3^*$-XIAP increases simultaneously.

We employed the mathematical model developed by Eissing et al. [17] to describe the interacting feedback systems (see Supplementary Information). The mathematical model was implemented using Simulink of Matlab 7.1 (R14) with a particular focus on the embedded feedback systems in apoptosis (see Supplementary Figs. S1–S4).

3. Results

3.1. The coupled positive feedbacks in apoptotic switching

The coupled positive feedbacks are involved in the caspase-3 activation, where four molecules (i.e., caspase-8, caspase-3,

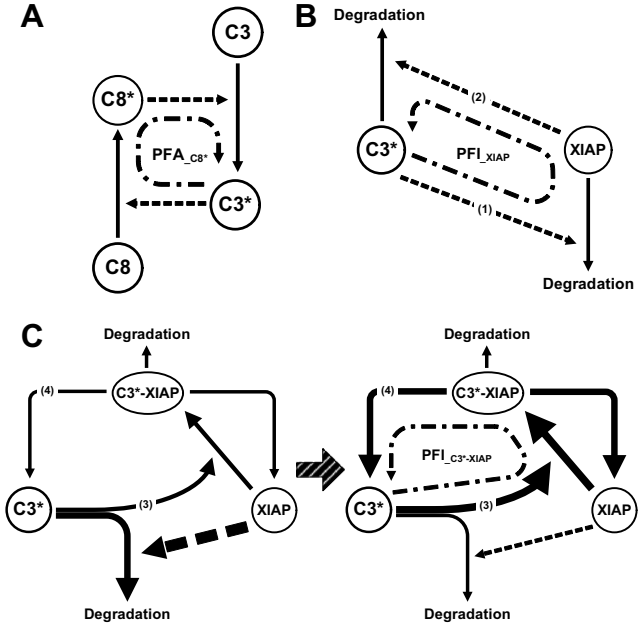

Fig. 2. Illustration of the coupled positive feedbacks for the caspase-3 activation. The solid arrows indicate the actual reactions and the dashed arrows denote the effective regulation of reaction coefficients. The dash-dot arrows indicate the feedback loops. Two different kinds of positive feedbacks, PFA and PFI, work together. PFI consists of two positive feedbacks. (A) The positive feedback through C8* is denoted by $PFA_{\_C8^*}$. (B) The positive feedback through XIAP is denoted by $PFI_{\_XIAP}$. Caspase-3 inhibits XIAP by cleaving XIAP through ubiquitination and degradation (1) and XIAP is fed back to inhibit caspase-3 by the degradation of caspase-3 (2). (C) The positive feedback through $C3^*$-XIAP is denoted $PFI_{\_C3^*\text{-}XIAP}$. Caspase-3 inhibits XIAP by inactivating XIAP through the formation of $C3^*$-XIAP (3) and $C3^*$-XIAP is fed back to activate caspase-3 by releasing caspase-3 from $C3^*$-XIAP (4). If $PFI_{\_C3^*\text{-}XIAP}$ works, the degradation level of caspase-3 by XIAP decreases and the activation level of caspase-3 by releasing caspase-3 from $C3^*$-XIAP increases simultaneously.

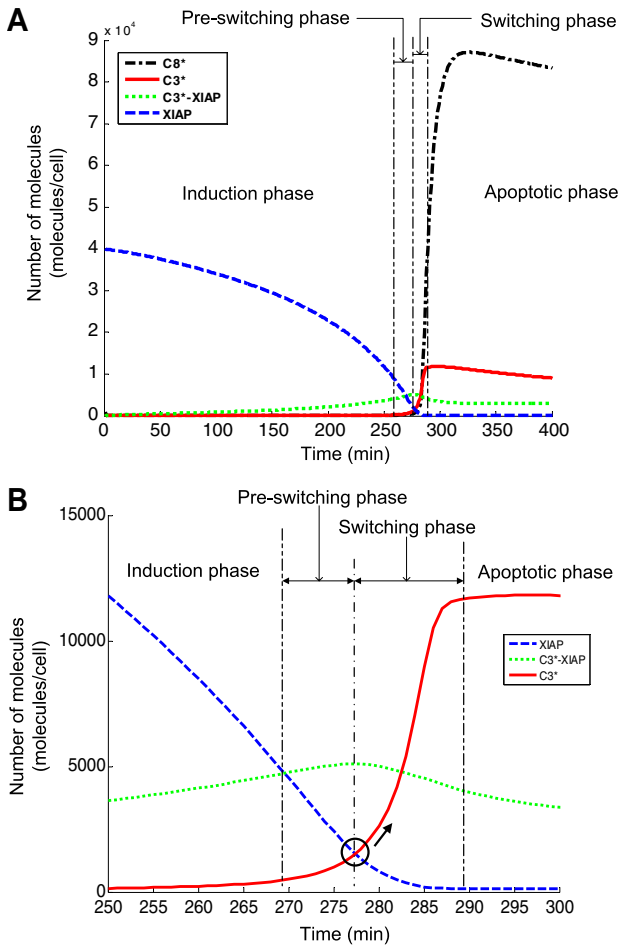

Fig. 3. The fast switching for apoptosis after long induction time. (A) The dynamic behavior of caspase-3 activation can be divided into four phases: induction phase, pre-switching phase, switching phase, and apoptotic phase. The caspase-3 activation is reserved during the induction phase until a fast switching occurs. (B) The dynamics of apoptotic switching. In the induction phase, XIAP decreases and C3*-XIAP increases, but caspase-3 hardly changes. In the pre-switching phase, once the level of XIAP becomes lower than that of C3*-XIAP, caspase-3 starts increasing. In the switching phase, C3*-XIAP starts decreasing while caspase-3 rapidly increases. In the apoptotic phase, caspase-3, XIAP, and C3*-XIAP keep their steady states.

XIAP, and C3*-XIAP) interact with each other. Fig. 3A shows how the levels of molecules related to the caspase-3 activation change along with time. The overall reaction can be divided into four phases according to the level of activated caspase-3: an induction phase, a pre-switching phase, a switching phase, and an apoptotic phase. In the induction phase, the level of activated caspase-3 stays low for a while and then the caspase-3 activation gradually increases in the pre-switching phase. In a little while, the reaction reaches the switching phase where the pro-life state is rapidly changed into an apoptotic state. Next, the apoptotic phase with a high level of caspase-3 sustains.

As shown in Fig. 3A, the caspase-8 activation leads to the caspase-3 activation [28]. The rate of caspase-3 activation depends only on PFA and slowly increases along with time since the XIAP-mediated inhibition of caspase-3 is still dominant [26]. As caspase-3 keeps slightly increasing by PFA, XIAP starts decreasing and PFI becomes stronger. When PFI works stronger than PFA, caspase-3 rapidly increases. Fig. 4 shows how PFA and PFI, consisting of $PFI_{\_XIAP}$, $PFI_{\_C3^*\text{-}XIAP}$ (see Section 2), work together within the system.

3.2. The role of each positive feedback

We have analyzed how the coupled feedbacks work in each phase. The level change of caspase-3 activation is illustrated in details in Fig. 3B. The effects of two positive feedbacks on the caspase-3 activation in each phase are summarized in Table 1.

3.2.1. Induction phase. In the induction phase, PFA is effective while the role of PFI is not significant. The level of caspase-3 rarely increases since most of increased caspase-3 by PFA are inactivated or degraded again by XIAP. Hence, caspase-3 is not significantly activated. As caspase-3 keeps slightly increasing, XIAP begins to decrease and exhibits a positive feedback effect on caspase-3. As a result, the influence of PFI becomes stronger.

3.2.2. Pre-switching phase. From the induction phase to the pre-switching phase, PFI becomes stronger. Therefore, the strength of PFI is enhanced as much as that of PFA. Since PFI weakens the XIAP-mediated inhibition of caspase-3, XIAP does not extensively inhibit caspase-3 as in the previous phase. Hence, the increasing level of caspase-3 is substantially more than the decreasing one. As XIAP keeps decreasing by PFI, it becomes less probable that caspase-3 binds to XIAP. Due to the fewer chance of degradation or inactivation of caspase-3 by XIAP, caspase-3 begins to significantly increase in this pre-switching phase.

3.2.3. Switching phase. In the switching phase, the overall effect of feedbacks is most enhanced by two positive feedbacks simultaneously working together. In this phase, PFI becomes more dominant than PFA and caspase-3 overwhelms XIAP. Note that the caspase-3 activation is switched on when PFI is stronger than PFA. This fast switching behavior of caspase-3 activation is due to the synergistic effect of PFI separating caspase-3 from C3*-XIAP and PFA activating caspase-3 by caspase-8.

3.2.4. Apoptotic phase. After switching, caspase-3, XIAP, and C3*-XIAP maintain their steady states that are called apoptotic steady states.

3.3. Slow induction plus fast switching behavior caused by the coupled positive feedbacks

The primary finding is that the coupled positive feedbacks are essential in provoking the slow induction plus fast switching behavior. Fig. 5 shows the profiles of caspase-3, caspase-8, XIAP, and C3*-XIAP in four different feedback structures: PFA, PFA plus $PFI_{\_XIAP}$, PFA plus $PFI_{\_C3^*\text{-}XIAP}$, and PFA plus PFI (see Section 2). We have investigated the role of the coupled positive feedbacks as follows.

First, we checked the level of caspase-3 (Fig. 5A). If PFA only works, switching occurs in a very short induction time. When PFA plus $PFI_{\_XIAP}$ works, the level of caspase-3 stays low. In case of PFA plus $PFI_{\_C3^*\text{-}XIAP}$, the caspase-3 activation immediately occurs without any noticeable induction time. From these results, we interpret that the caspase-3 activation can have the long induction time and fast switching behavior only if both PFA and PFI work simultaneously.

Second, we examined the level of caspase-8 (Fig. 5B). The profiles of caspase-8 in each feedback structure are similar to those of caspase-3.

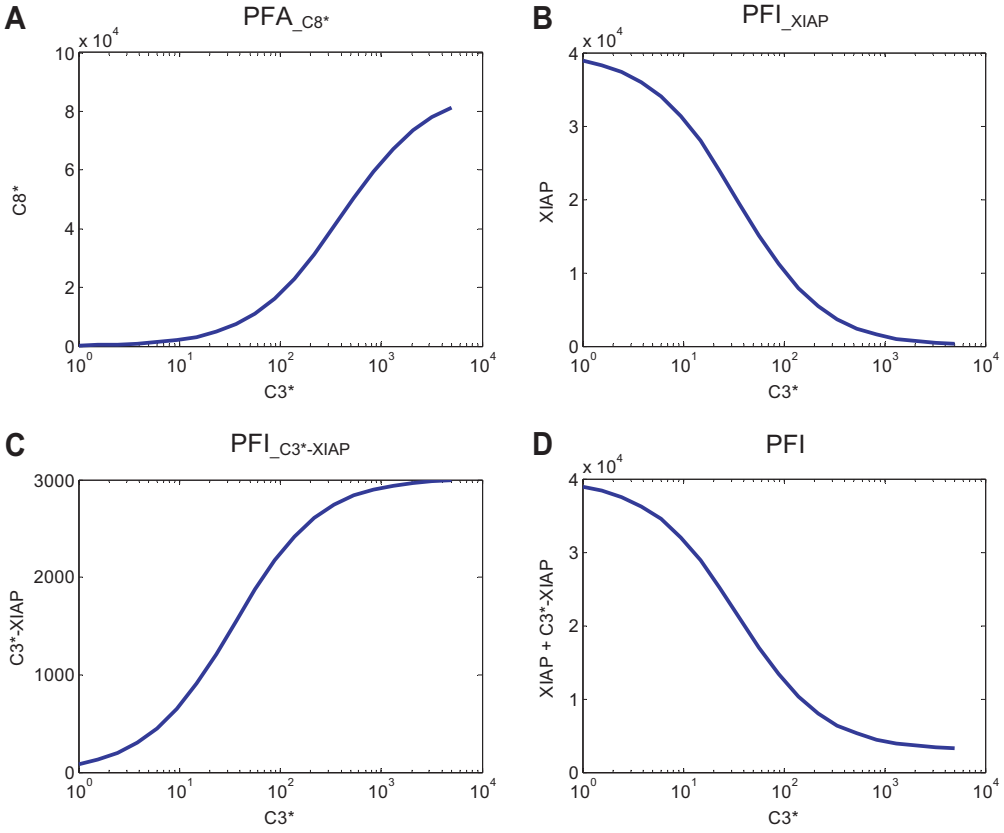

Fig. 4. The strength of each feedback at a steady state. (A) The strength of $PFA_{\_C8^*}$ monotonically increases as caspase-3 increases. (B) The strength of $PFI_{\_XIAP}$ monotonically decreases as caspase-3 increases. (C) $PFI_{\_C3^*\text{-}XIAP}$ monotonically increases as caspase-3 increases. (D) The strength of PFI monotonically decreases as caspase-3 increases. The dynamics of overall PFI are determined by the interaction between $PFI_{\_XIAP}$ and $PFI_{\_C3^*\text{-}XIAP}$. The X-axes are log-scaled.

Table 1
The state of caspase-3 and the relative strength of feedbacks in each phase, where the number of '+' denotes the strength of feedback interaction

	Induction phase	Pre-switching phase	Switching phase
The state of caspase-3	Activation $\ll$ inhibition	Activation $\geqslant$ inhibition	Activation $\gg$ inhibition
The strength of PFA	++	++	++
The strength of PFI	+	++	+++
The number of molecules	Caspase-3 slightly increasing C3*-XIAP increasing XIAP decreasing	Caspase-3 increasing C3*-XIAP increasing XIAP decreasing	Caspase-3 fast increasing C3*-XIAP decreasing XIAP decreasing

Third, we analyzed the level of XIAP (Fig. 5C). If PFA only works, XIAP monotonically decreases through degradation caused by the increasing caspase-3. In case of PFA plus $PFI_{\_XIAP}$, XIAP rarely decreases since caspase-3 does not increase. In case of PFA plus $PFI_{\_C3^*\text{-}XIAP}$, XIAP decreases faster than the case with only PFA since caspase-3 increases more rapidly by PFA and $PFI_{\_C3^*\text{-}XIAP}$. If both PFA and PFI work together, XIAP has a slow decreasing rate and a long activation time, and the long induction time of caspase-3 activation results.

Finally, we evaluated the level of C3*-XIAP (Fig. 5D). If PFA only works, the profile of C3*-XIAP has a large overshoot because of the fast increasing caspase-3. If PFA plus $PFI_{\_XIAP}$ works, C3*-XIAP rarely increases since caspase-3 almost does not increase. If PFA plus $PFI_{\_C3^*\text{-}XIAP}$ works, the profile of C3*-XIAP has a larger overshoot than the case with only PFA because of the fast increasing caspase-3 caused by PFA and $PFI_{\_C3^*\text{-}XIAP}$. If both PFA and PFI work together, C3*-XIAP has a slow increasing rate with a long activation time and a fast decreasing rate.

Taking together, the slow induction plus fast switching behavior results from the coupled positive feedbacks through caspase-8 and XIAP. In particular, PFA uses the activation mechanism to produce caspase-3 while PFI employs the inhibition mechanism to inhibit the degradation and the inactivation of caspase-3. Only if these two positive feedbacks through caspase-8 and XIAP are coupled, the slow induction plus fast switching behavior of caspase-3 activation seems to occur.

3.4. The effect of XIAP in the coupled positive feedbacks

In the foregoing section, we have demonstrated that XIAP regulates the induction time of caspase-3 activation. Fig. 6 shows the responses to different initial concentrations of XIAP, i.e., 20000 molecules/cell (Fig. 6A–C), 40000 molecules/cell (Fig. 6D–F), and 60000 molecules/cell (Fig. 6G–I).

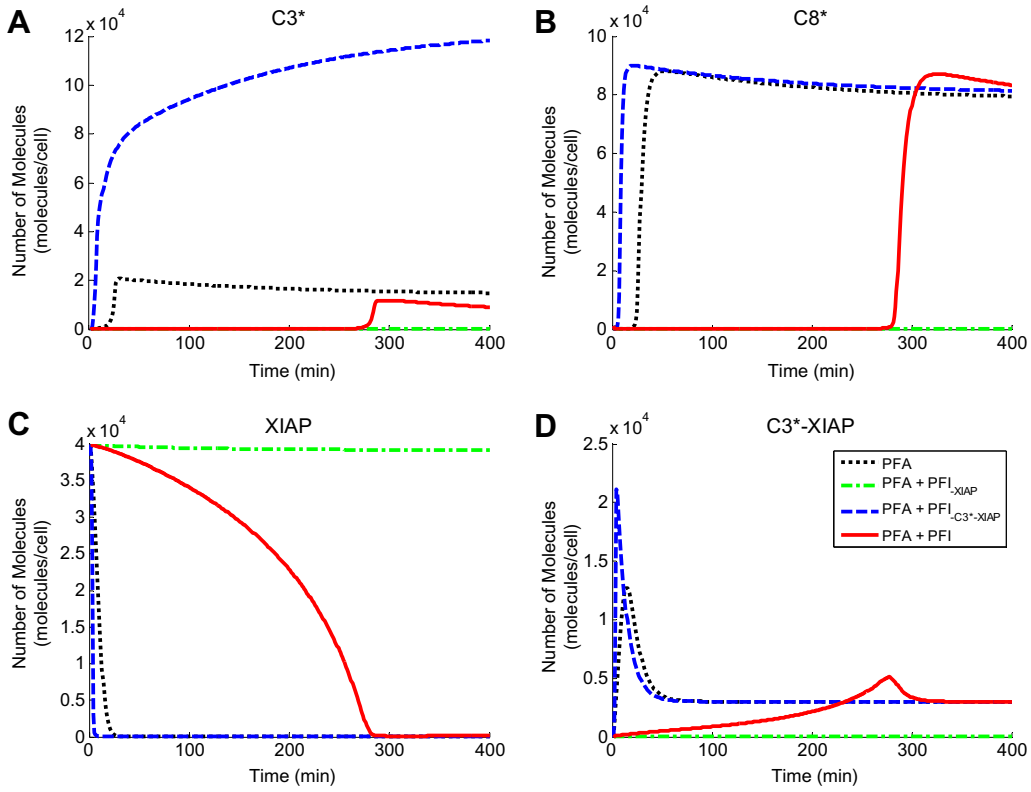

Fig. 5. The dynamics of molecules in four different feedbacks. (A) Caspase-3 is switched on after long induction time when two positive feedbacks, PFA and PFI, work together. (B) The dynamics of caspase-8 is similar to that of caspase-3. (C) XIAP slowly decreases for a long activation time when both PFA and PFI work. (D) C3*-XIAP slowly increases over a long activation period when both PFA and PFI work together.

In the previous study [17], the induction time of caspase-3 activation was observed to become longer as the concentration of caspase-8, i.e., the apoptotic signal input, is lower. This longer induction time results in robustness against noises [29]. In addition, we have found that the initial level of XIAP is highly related to the induction time of caspase-3 activation. The regulation of caspase-3 activation by XIAP properly works only if the two positive feedbacks are coupled. As the level of XIAP is higher at the initial stage, the induction time of caspase-3 activation becomes longer. This finding suggests that the induction time of caspase-3 activation can be shortened by enhancing the role of PFI in the coupled positive feedbacks.

4. Discussion

Apoptosis is a crucial cellular process by which cells decide their fate through a complex regulatory mechanism. From a systems design viewpoint, reliability and robustness are two of the required features. In this respect, the process could have a slow induction step to facilitate a reliable decision making process and a fast switching step to enforce a robust execution process [17]. In addition, slow induction is required to assure robustness against noises [29] and fast switching is desirable to realize an irreversible all-or-none response to apoptotic signals [3].

We have shown that the core apoptosis pathway has two different positive feedbacks, i.e., PFA and PFI, and they are intimately coupled. Caspase-3 activation is regulated by weakening the caspase-3 inhibition. In the beginning, only PFA works along with caspase-8. As PFI starts to affect the level of XIAP, PFI diminishes the effect of inhibiting caspase-3 activation. Finally, fast switching occurs when the strength of PFI becomes stronger than that of PFA (Fig. 3B). We have found that the coupled positive feedbacks through caspase-8 and XIAP in the core apoptosis pathway are essential for the slow induction plus fast switching behavior (Fig. 5). We have also demonstrated that this switching behavior is closely linked to the level of XIAP (Fig. 6). In the previous studies [30], it was observed that XIAP, an endogenous inhibitor of caspase, is over-expressed. Resistance to apoptosis, which prevents activation of a caspase family, commonly occurs in many cancer cells. Based on the current study, we postulate that apoptosis of cancer cells might be stimulated by strengthening the effect of PFI. For instance, polyphenylurea, known as an antagonist of XIAP, inhibits XIAP from its binding with caspase-3. Thus it might enhance the role of PFI. As the effect of PFI becomes stronger, the induction time of caspase-3 activation is shortened and apoptosis might become a favorable pathway in cancer cells.

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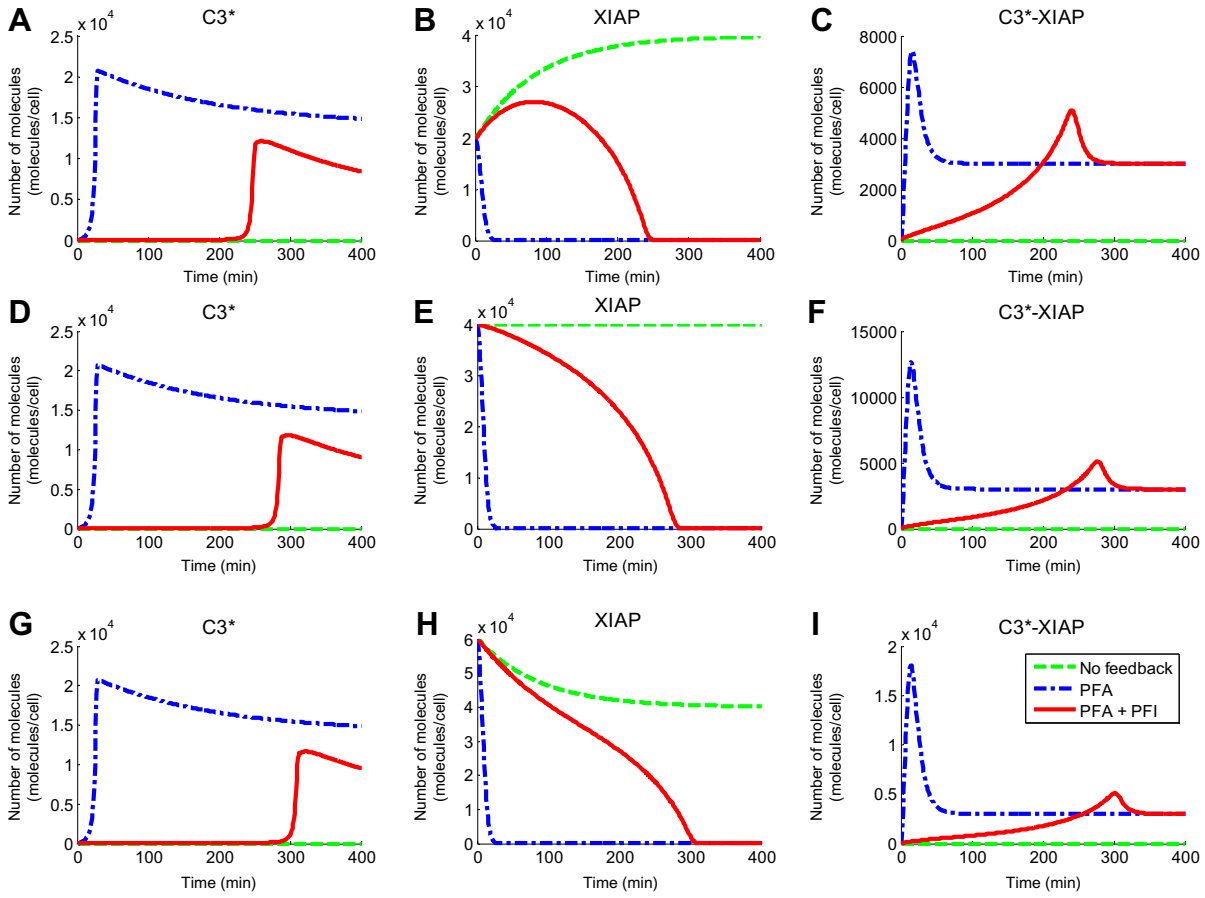

Fig. 6. The different dynamics caused by different initial levels of XIAP. The higher the initial level of XIAP is, the longer the induction time is. The concentration of caspase-8 is regarded as an input for induction of apoptosis. We examined varying initial concentrations of XIAP while keeping others the same to those in the previous simulations (see Supplementary Information). In three graphs (D–F), the initial level of XIAP was set to 40 000 molecules/cell [17]. Three graphs in the first row (A–C) show the responses for a lower initial level of XIAP, i.e., 20 000 molecules/cell. Three graphs in the last row (G–I) correspond to 60 000 molecules/cell as a higher initial concentration of XIAP.

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Appendix A. Supplementary data

Supplementary material is available at the FEBS Letters website. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.febslet.2007.05.016.

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