Mathematical Biosciences 270 (2015) 126–134

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Partial equilibrium approximations in apoptosis. II. The death-inducing signaling complex subsystem

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ARTICLE INFO

Article history:
Received 24 January 2015
Revised 1 October 2015
Accepted 16 October 2015
Available online 30 October 2015

Keywords:
Apoptosis
Biochemical reactions
Partial equilibrium approximation
The principle of detailed balance

ABSTRACT

This paper is a continuation of our previous work (Huang and Yong, 2013) for simplifying the Fas signaling-induced apoptotic pathway identified by Hua et al. (2005) for human tumor T cells. The previous paper studied the downstream intracelluar-signaling subsystem, while the present one is concerned with the upstream death-inducing signaling complex (DISC) subsystem. Under the assumption that the bind of Fas-associated death domains and FLICE-inhibitory proteins to the DISC is much faster than that of the initiator procaspases, we greatly simplify the upstream subsystem from 35 reactions with 26 species to 6 reactions with 9 species by adopting the classical and recently justified partial equilibrium approximation method. Numerical simulations show that the simplified model is in an excellent agreement with the original model. Most importantly, the simplified model clearly reveals the key reactants and dominated pathways in the Fas signaling process, and thus provides new insights into the apoptosis.

1. Introduction

Apoptosis is a genetically programmed cell death process which ensures normal embryonic development, tissue homeostasis and normal immune-system operation in multicellular organisms. It plays a central role in many physiological processes and its malfunction may result in serious diseases such as cancer, autoimmunity, and neurodegeneration [15,17,29,40,50]. Due to the biological significance of apoptosis, considerable progresses have been made in recent years in uncovering the pathways governing apoptosis.

Apoptosis may be either triggered by extrinsic receptor-mediated or by intrinsic mitochondria-mediated signaling pathways that induce death-associated proteolytic and/or nucleolytic activities. The intrinsic pathway can be initiated by many kinds of factors, like the UV or genotoxic stress which lead to the damage of the cell. The extrinsic pathway is activated by the binding of extracellular ligands to specific transmembrane receptors, such as TNF-R1 (DR1, p55), Fas (DR2, CD95), DR3 (APO-3, TRAMP), DR4 (APO-2, TRAIL-R1) and DR5 (TRICK2, TRAOL-R2) [5,15,26,44]. These two pathways share many components and regulatory mechanisms.

In this study, we focus on the Fas signaling-induced pathway which is among the best characterized [33]. The related signaling processes are described in Fig. 1. It is initiated upon detection of the extracellular death signal Fas ligand (FasL) – a homotrimeric ligand that binds to its cognate transmembrane death receptor Fas, in a 1:3 ratio. This is followed by the bind of an intracellular adaptor protein FADD (Fas-associated death domain) to form the death-inducing signaling complex (DISC) [5,34,35,47]. The latter can recruit, cleave and activate initiator caspases, such as caspase-8 (Casp8) molecules. Meanwhile, this action can be blocked by FLICE-inhibitory proteins (FLIP) through their competition with Casp8 to combine with the DISC. The activated initiator caspases will activate effector caspases such as caspase-3 (Casp3), and the effector caspase Casp3* ultimately executes cell death by a direct cleavage of essential structural components of the cell [16,23,32,51].

The whole Fas signaling-induced cell death process was divided into two modules by Okazaki et al. [33]: the DISC subsystem (DSS) and the intracellular-signaling subsystem (ISS). The DSS is triggered by the bind of FasL to Fas and ends with the activation of Casp8. The ISS is the downstream subsystem where $Casp8_2^*$ can enzymatically activate Casp3 through two major pathways: type-I pathway and type-II pathway [3,20]. In type-I pathway, $Casp8_2^*$ cleaves and activates the executor Casp3 directly. In type-II pathway, $Casp8_2^*$ cleaves Bid (a member of Bcl-2 family) to generate truncated tBid. The tBid then binds to two molecules of Bax (another member of Bcl-2 family) to form a complex tBid:Bax2. This complex then induces Mitochondria outer membrane permeabilization (MOMP), which will cause Cyto.c and Smac released from the mitochondria. The released Cyto.c will combine with an adaptor protein Apaf-1, ATP and caspase-9 (Casp9) to form apoptosome and thereby activate Casp9. The activated Casp9 (Casp9*) cleaves and activates Casp3 at last. In

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http://dx.doi.org/10.1016/j.mbs.2015.10.009
0025-5564/

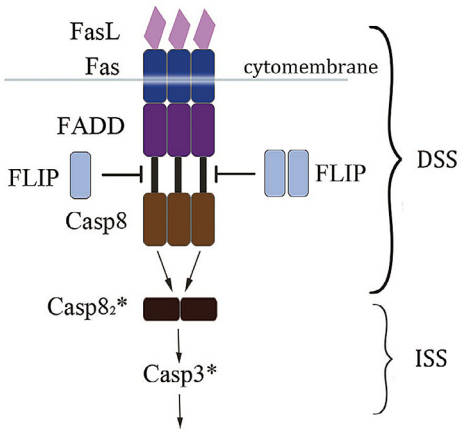

Fig. 1. An illustration of the Fas-induced apoptotic pathway.

addition, the type-II pathway may be blocked by XIAP (X-linked inhibitor of apoptosis protein) and Bcl_2 (another member of Bcl-2 family) through their bindings to the released Smac, Casp9, Casp3*, Bax and tBid.

Like the intracellular-signaling subsystem which has been studied in [33] due to Okazaki et al. and our previous works [19,20], the DSS process involves tens of reacting species, participating in many biochemical reactions with time scales of widely differing orders of magnitude. When the law of mass action [22] is employed, it is mathematically described by a system of tens of ordinary differential equations (ODEs). Such a large scale and stiff system of ODEs can hardly help us to understand the mechanism of the apoptosis. So, it is valuable to simplify the DSS process. In [1,2], Albeck et al. empirically simplified the DSS process by considering the activation of Casp8 by death receptor (R) as the simplest enzymatic reaction mechanism (R + Casp8→ R:Casp→ R+Casp8*). In their model, FLIP acts as an inhibitor to apoptosis. The activation of Casp8 is stopped when the inhibitor FLIP is bound to the active site of the enzyme R (R+FLIP→ R:FLIP). In [14], Harrington et al. imposed some additional conditions on the DSS network, such as the quantity of FADD is in excess. Then they applied the quasi-steady-state assumption method to simplify the DSS network and got the generation rate function $f_{DISC}([FasL]_0, [FasR]_0; K_{DISC})$ of DISC. However, the above models do not involve the multiple binding sits of DISC and their simplifications lack a rigorously mathematical justification. The main purpose of our paper is to derive a systematic and mathematically reliable simplification of the DSS process.

In this paper, we assume the addition of FADD and FLIP to the DISC to be much faster than that of Casp8, which is motivated by the experimental finding [27] that FLIP has a higher affinity to the DISC than Casp8. Under this assumption, we successfully simplify the DSS model from 35 reactions with 26 species to 6 reactions with 9 species by adopting the classical and recently justified partial equilibrium approximation (PEA) method [12,52,55,56]. Based on the simplified system of 9 ODEs, we propose a simplified reaction network, which clearly reveals the key reactants and dominated pathways in the Fas signaling process. We also conduct numerical simulations, such as accuracy and sensitivity analysis, to show the reliability of both the simplified model and the assumption. Furthermore, we fix the simplified reaction network by substituting the reaction rate constants with a Hill function [10,28].

We would like to mention that there are several recent models providing interesting new insights into the upstreaming part of the extrinsic apoptosis. For example, in [11,25,31], different isoform types of FLIP: isoforms FLIP long($FLIP_L$), FLIP short ($FLIP_s$) and isoforms FLIP Raji ($FLIP_R$) were considered. In these models, $FLIP_s$ and $FLIP_R$ block the apoptotic pathway while $FLIP_L$ has two completely opposite functions: pro-apoptotic and anti-apoptotic. In [21], Kallenberger et al. investigated how the autoprocessing mechanism of Casp8 precisely controls the dynamics of apoptosis. In [16,49], the role of the ligand-receptor subsystem, consisting of multiple receptors and/or ligands, in deciding cell fate was studied. All these models are more complicated than Hua et al.'s one and remain to be simplified. In the coming future, we will apply our method to study these models.

2. Model and results

2.1. Reaction network for the DISC subsystem

Consider the Fas signaling-induced apoptosis reaction network identified by Hua et al. [18] for human tumor T cells. In this model, Fas is assumed to be preassociated homotrimer and associate with FasL to form the complex FasC (H1). Then FasC sequentially combines up to three FADD (H2) and up to three Casp8 (H3) to form the DISC. FLIP may also bind to FADD in place of Casp8 (H4) to suppress the activation of Casp8. Besides, due to the limited binding sites, the total number of Casp8 plus FLIP cannot be more than that of FADD for a given DISC in this model.[1] The DISC with more than two Casp8 will decompose and generate the intermediate product $Casp8_2$:p41, which then cleaves itself to produce the activated Casp8 ($Casp8_2^*$) (H5).

The above processes consist of the following biochemical reactions, *i.e.*

(H1) $\mathrm{FasL} + \mathrm{Fas} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{FasC},$

(H2) $\mathrm{FasC{:}FADD}_p{:}\mathrm{Casp8}_q{:}\mathrm{FLIP}_r + \mathrm{FADD} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{FasC{:}FADD}_{p+1}{:}\mathrm{Casp8}_q{:}\mathrm{FLIP}_r,$

(H3) $\mathrm{FasC{:}FADD}_p{:}\mathrm{Casp8}_q{:}\mathrm{FLIP}_r + \mathrm{Casp8} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{FasC{:}FADD}_p{:}\mathrm{Casp8}_{q+1}{:}\mathrm{FLIP}_r,$

(H4) $\mathrm{FasC{:}FADD}_p{:}\mathrm{Casp8}_q{:}\mathrm{FLIP}_r + \mathrm{FLIP} \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} \mathrm{FasC{:}FADD}_p{:}\mathrm{Casp8}_q{:}\mathrm{FLIP}_{r+1},$

(H5) $\mathrm{FasC{:}FADD}_p{:}\mathrm{Casp8}_q{:}\mathrm{FLIP}_r \overset{k_5}{\rightarrow} Casp8_2^* + \mathrm{FasC{:}FADD}_p{:}\mathrm{Casp8}_{q-2}{:}\mathrm{FLIP}_r,$

where $k_1, \ldots, k_5$ and $k_{-1}, \ldots, k_{-4}$ are the forward and backward reaction rate constants, respectively. In each reaction group, the reaction rate constants are assumed to be the same for simplicity. In this way, the number of the degrees of freedom in the model was kept small by using only nine kinetic parameters. We would like to remark that this assumption is purely for simplicity due to the lack of experimental data and is consistent with the treatment by Hua et al.. But it is definitely unnecessary for the application of the PEA method in the following context. We note that there are in total 35 biochemical reactions and 26 species above. $\mathrm{FasC{:}FADD}_p{:}\mathrm{Casp8}_q{:}\mathrm{FLIP}_r$ ($p, q, r = 0, 1, 2, 3$ and $p \geq q + r$) stand for various kinds of apoptotic complexes (see Fig. 2). For convenience, we use the symbol F_{pqr} to denote the complex $\mathrm{FasC{:}FADD}_p{:}\mathrm{Casp8}_q{:}\mathrm{FLIP}_r$ throughout this paper.

According to the law of mass action [22], the dynamics of the DISC subsystem is governed by 26 ordinary differential equations (ODEs), which can be written into a compact form as

$$\frac{dU}{dt} = Q(U). \tag{1}$$

[1] The studies of Schleich et al. [43] and Dickens et al. [9] showed that this may not be the case. Schleich et al. revealed in [43] that the amount of Casp8 and FLIP at the DISC exceeds that of FADD by several-fold. Dickens et al.'s data [9] indicated that there is up to 9-fold more Casp8 than FADD in the DISC. However, the specific combining mechanism among FADD, Casp8 and FLIP is not completely clear yet and how the updated results affect the apoptotic process is not clear either. So we do not consider these new results in this work.