Journal of Theoretical Biology 349 (2014) 150–162

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

A mathematical model of the sterol regulatory element binding protein 2 cholesterol biosynthesis pathway

Bonhi S. Bhattacharya [a], Peter K. Sweby [a], Anne-Marie Minihane [b], Kim G. Jackson [c,e], Marcus J. Tindall [a,d,e,*]

[a] Department of Mathematics and Statistics, University of Reading, Whiteknights, Reading RG6 6AX, UK
[b] Department of Nutrition, Norwich Medical School, University of East Anglia, Norwich NR4 7TJ, UK
[c] Department of Food and Nutritional Sciences, University of Reading, Whiteknights, Reading RG6 6AP, UK
[d] School of Biological Sciences, University of Reading, Whiteknights, Reading RG6 6AJ, UK
[e] Institute of Cardiovascular and Metabolic Research, University of Reading, Whiteknights, Reading RG6 6AA, UK

HIGHLIGHTS

- We formulate and analyse a nonlinear ODE model of the SREBP2 pathway.
- The mathematical model exhibits stable limit cycles under certain parameter conditions.
- Negative feedbacks in the SREBP2 pathway may help regulate cholesterol homeostasis.
- Our model provides a more accurate formulation of genetic regulation using nonlinear ODEs.

ARTICLE INFO

Article history:
Received 18 June 2013
Received in revised form
26 December 2013
Accepted 8 January 2014
Available online 18 January 2014

Keywords:
Genetic regulation
Transcription factor
Nonlinear ordinary differential equation
SREBP-2

ABSTRACT

Cholesterol is one of the key constituents for maintaining the cellular membrane and thus the integrity of the cell itself. In contrast high levels of cholesterol in the blood are known to be a major risk factor in the development of cardiovascular disease. We formulate a deterministic nonlinear ordinary differential equation model of the sterol regulatory element binding protein 2 (SREBP-2) cholesterol genetic regulatory pathway in a hepatocyte. The mathematical model includes a description of genetic transcription by SREBP-2 which is subsequently translated to mRNA leading to the formation of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), a main regulator of cholesterol synthesis. Cholesterol synthesis subsequently leads to the regulation of SREBP-2 via a negative feedback formulation. Parameterised with data from the literature, the model is used to understand how SREBP-2 transcription and regulation affects cellular cholesterol concentration. Model stability analysis shows that the only positive steady-state of the system exhibits purely oscillatory, damped oscillatory or monotic behaviour under certain parameter conditions. In light of our findings we postulate how cholesterol homeostasis is maintained within the cell and the advantages of our model formulation are discussed with respect to other models of genetic regulation within the literature.

1. Introduction and motivation

As an essential constituent of the plasma membrane of mammalian cells, cholesterol is used for the maintenance of both membrane structural integrity and selective permeability (Simons and Iknonen, 2000). However, superfluous cholesterol levels result in cellular toxicity (Yeagle, 1991; Tabas, 1997; Tangirala et al., 1994). Insufficient cholesterol causes cytotoxicity via compromised membrane structure. Furthermore cellular cholesterol metabolism is a key modulator of plasma cholesterol, with the management of plasma hypercholesterolaemia at the cornerstone of population cardiovascular disease management (Grundy et al., 2004). It is therefore crucial that intracellular cholesterol levels are strictly regulated. Cellular cholesterol homeostasis, the property to maintain cholesterol concentration to within narrow ranges, results from a balance of three mechanisms: efflux, influx and biosynthesis.

Understanding the mechanisms which regulate cellular cholesterol content is vital to understanding pathology associated with sub- and supra-optimal cell and blood cholesterol concentrations. These levels are dependent on both the balance between dietary cholesterol intake and *de novo* synthesis of cholesterol within cells.

* Corresponding author. Permanent address: Department of Mathematics and Statistics, University of Reading, Whiteknights, Reading RG6 6AX, UK.
Tel.: +44 118 378 8992; fax: +44 118 378 6537.
E-mail address: m.tindall@reading.ac.uk (M.J. Tindall).

0022-5193/$ - see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jtbi.2014.01.013

The low density lipoprotein receptor (LDLR) protein forms part of the lipoprotein metabolic pathway responsible for the clearance of cholesterol from the circulation (Brown and Goldstein, 1979; Goldstein et al., 1985). Biosynthesis of cholesterol is a multistep reaction in which the rate-limiting step is the reduction of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) in the reaction catalysed by the enzyme HMG-CoA reductase (HMGCR).

Over accumulation or excessive depletion of free cholesterol within the cell is prevented by a negative feedback loop that responds to elevations or depressions in intracellular cholesterol. This feedback loop exerts the majority of its control by regulating the synthesis of the two key proteins: HMGCR and LDLR. In brief, when the intracellular cholesterol level is low, both LDLR and HMGCR synthesis are activated, thereby increasing the influx of cholesterol via the LDLR pathway, and the biosynthesis of cholesterol in the cell. If conversely there are high cholesterol levels in the cell, synthesis of LDLR and HMGCR declines.

There has been much research conducted into the response of cell cholesterol to dietary intake, with the dietary fatty acid composition rather than cholesterol intake reported to have a greater impact on circulating cholesterol concentrations. In particular, partial replacement of saturated fat with either monounsaturated (found in olive oil) or *n*-6 polyunsaturated (found in vegetable oils such as sunflower oil) fatty acids have been associated with significant reductions in both total and LDL-cholesterol concentrations (Mensink et al., 2003; Micha and Mozaffarian, 2010). Dietary fat composition is considered to influence circulating cholesterol concentrations via effects on hepatic cholesterol synthesis and the expression of genes involved in circulating LDL-cholesterol metabolism (Xu et al., 1999).

Previous mathematical modelling has included compartmental models of the lipoprotein metabolic pathway (Knoblauch et al., 2000; Packard et al., 2000; Adiels et al., 2005) and dynamic models of lipoprotein metabolism in conjunction with the LDLR pathway (August et al., 2007; Wattis et al., 2008). Of particular note in these dynamic models is the lack of explicit representation of the cholesterol biosynthesis reaction and as a consequence, the interplay between cholesterol biosynthesis, the LDLR uptake of lipoprotein cholesterol and cholesterol mediated negative feedback is not fully appreciated.

The cholesterol biosynthetic pathway is already the basis of the most common form of pharmaceutical treatment for high plasma cholesterol levels. HMGCR inhibitors, more commonly known as statins, act as competitive inhibitors of the HMGCR enzyme. By inhibiting the biosynthesis of cholesterol, statins deplete intracellular cholesterol concentration and promote the synthesis of both HMGCR and the LDLR, thereby increasing the uptake of lipoproteins (and plasma cholesterol) via the LDLR. It is recognised that individual response to statin treatment varies widely. Genetic variation in *HMGCR* has been associated with a diminished lipid lowering response (Chasman et al., 2004; Krauss et al., 2008), suggesting that the cholesterol biosynthetic pathway plays an important role in the control of plasma cholesterol levels.

However, relatively little modelling has been conducted to investigate the qualitative behaviour of the processes which govern *de novo* cholesterol synthesis at a genetic level, which may provide a better understanding of such phenomena. The mathematical model presented in this paper will examine the underlying genetic mechanisms governing cholesterol biosynthesis as a first step towards elucidating the dynamics of this pathway.

The paper is organised as follows. In Section 2 the biological processes which describe the genetic regulation of cholesterol biosynthesis are reviewed. Following this, the mathematical model is derived in Section 3 and details of model parameter values obtained from the literature are summarised in Section 4. Model analysis is undertaken in Sections 5–7 and the results are summarised and discussed in Section 8.

2. Regulated expression of cholesterol biosynthetic genes

A major point of control of the cholesterol biosynthetic pathway occurs at the level of gene expression in response to cellular cholesterol levels, as shown in Fig. 1. The insolubility of cholesterol dictates that it cannot directly influence a genetic response.

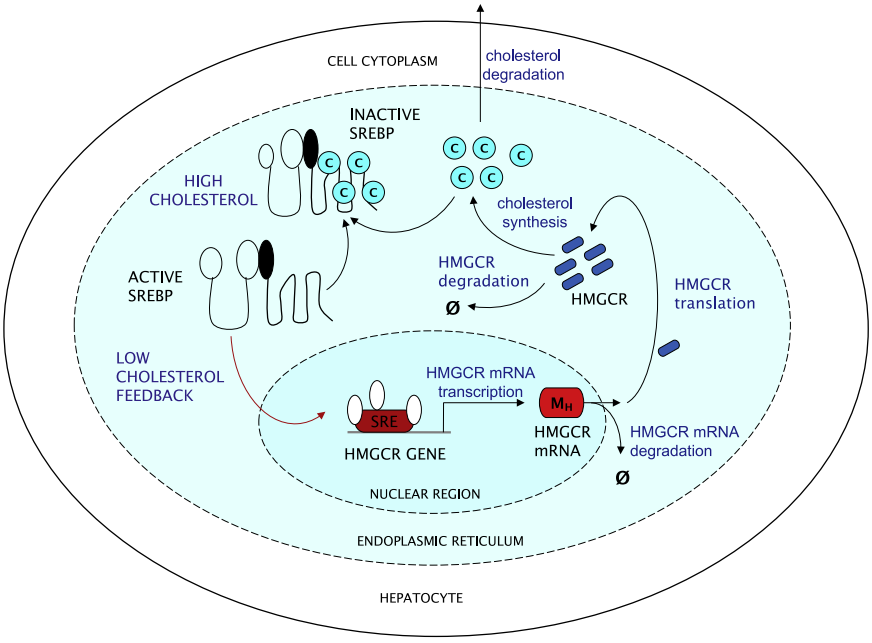

Fig. 1. Genetic regulation of cholesterol biosynthesis by SREBP-2. Hepatocytes synthesise HMGCR mRNA which in turn is translated into the enzyme HMGCR. HMGCR catalyses the synthesis of cholesterol which in turn influences its own transcription rate by interacting with the transcription factor SREBP; the transcription rate increases when cholesterol is low in the cell and declines when cholesterol is high. (SRE – sterol regulatory element; M_H – HMGCR mRNA; C – cholesterol).