Journal of Theoretical Biology 394 (2016) 43–56

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

A mathematical model for the induction of the mammalian ureteric bud

Brodie A.J. Lawson [a], Mark B. Flegg [b,*]

[a] School of Mathematics and Physics, University of Queensland, St. Lucia, QLD 4072, Australia
[b] Monash Academy for Cross and Interdisciplinary Mathematics Applications (MAXIMA), School of Mathematical Sciences, Monash University, Wellington Road, Clayton, VIC 3800, Australia

HIGHLIGHTS

- Presented is a mathematical model for the chemical kinetics of kidney induction.
- We validate a Turing mechanism for the creation of a single ureteric bud.
- Our model predicts various developmental phenotypes observed in genetic experiments.
- A role of Gremlin is to stabilise single bud induction against fluctuations in BMP.

ARTICLE INFO

Article history:
Received 17 April 2015
Received in revised form
22 December 2015
Accepted 24 December 2015
Available online 20 January 2016

Keywords:
Turing patterning
Kidney morphogenesis
Partial differential equations
Developmental biology
Mathematical biology

ABSTRACT

Congenital abnormalities of the kidney and urinary tract collectively form the most common type of prenatally diagnosed malformations. Whilst many of the crucial genes that direct the kidney developmental program are known, the mechanisms by which kidney organogenesis is achieved is still largely unclear. In this paper, we propose a mathematical model for the localisation of the ureteric bud, the precursor to the ureter and collecting duct system of the kidney. The mathematical model presented fundamentally implicates Schnakenberg-like ligand-receptor Turing patterning as the mechanism by which the ureteric bud is localised on the Wolfian duct as proposed by Menshykaul and Iber (2013). This model explores the specific roles of regulatory proteins GREM1 and BMP as well as the domain properties of GDNF production. Our model demonstrates that this proposed pattern formation mechanism is capable of naturally predicting the phenotypical outcomes of many genetic experiments from the literature. Furthermore, we conclude that whilst BMP inhibits GDNF away from the budding site and GREM1 permits GDNF to signal, GREM1 also stabilises the effect of BMP on GDNF signalling from fluctuations in BMP sensitivity but not signal strength.

1. Introduction

Congenital abnormalities of the kidney and urinary tract, collectively known as CAKUT, represent approximately one-third of all prenatally diagnosed malformations (Moritz et al., 2008). Abnormalities associated with the kidneys are a major cause of chronic kidney disease in children and young adults, often requiring transplantation or dialysis (Sanna-Cherchi et al., 2009). Furthermore, less severe congenital abnormalities of the kidney can have life-long implications including hypertension and/or proteinuria (Sanna-Cherchi et al., 2009). In approximately one in 4000 births, CAKUT can result in bilateral renal agenesis (also known as classic Potter's syndrome: the absence of any kidney or ureter phenotype) and is typically fatal within the first few hours after birth (Potter, 1965).

Despite the severity and frequency associated with disruptions in kidney development, the full picture of metanephros (kidney) organogenesis is still poorly understood. For the current state of scientific understanding of normal embryonic kidney development, interested readers are referred to recent reviews (Blake and Rosenblum, 2014; Costantini, 2012; Costantini and Koplan, 2011; Little and McMahon, 2012).

Embryonic kidney epithelium precursor cells originate in the intermediate mesoderm (IM) which is situated between the paraxial mesoderm and the lateral plate (see Fig. 1). From embryonic day 9.5 (E9.5), an epithelial tube forms from derivatives of a portion of the intermediate mesoderm expressing PAX2, LHX1 and GATA3 (Saxen,

* Corresponding author.
E-mail addresses: brodie.lawson86@gmail.com (B.A.J. Lawson), mark.flegg@monash.edu (M.B. Flegg).

http://dx.doi.org/10.1016/j.jtbi.2015.12.025
0022-5193/

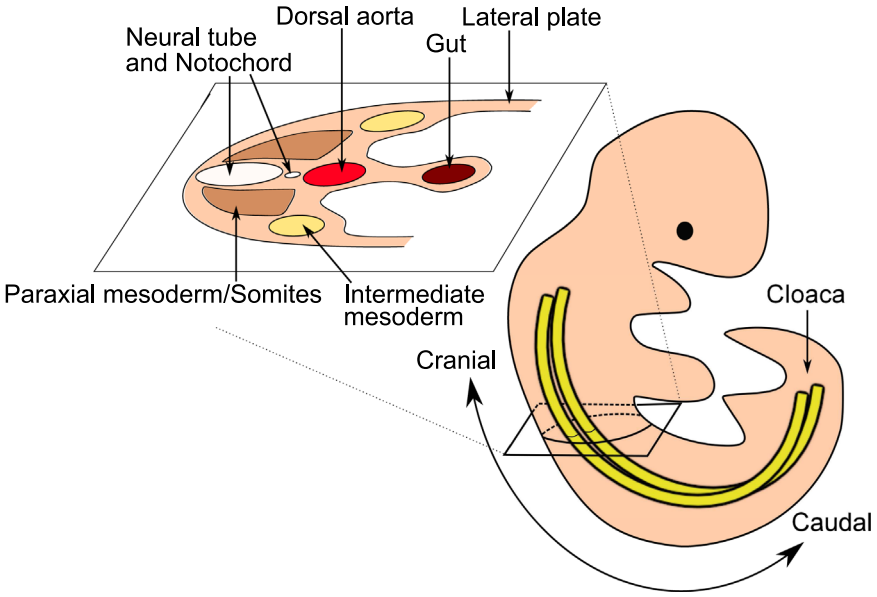

Fig. 1. Schematic diagram of embryo at approximately embryonic day E8 showing the location of the intermediate mesoderm (IM). A cross-section is taken showing the location of the IM in the context of the embryonic anatomy. The adult kidney (metanephros) will form at the caudal end near the cloaca.

1987). This tube, known as the Wolffian duct (WD), extends in a caudal direction towards the cloaca (see Fig. 2a).

Hox gene activity at approximately E10 allows for the formation of the metanephric mesenchyme (MM) as a derivative of the IM (Mugford, 2008). The MM forms at the caudal end of the WD. Characteristic of the MM is the expression of specific transcription factors. Precisely how these transcription factors interact to determine MM characteristics is unclear. Importantly, specific to the MM is the expression of glial cell line-derived neurotrophic factor (GDNF) and other growth factors.

At approximately E10.5 the ureteric bud (UB) forms as a localised bulging and subsequent outgrowth of the WD; a process known as UB induction. Whilst GDNF signalling has been shown to be critical to UB induction, outgrowth is permitted only because of Gremlin(GREM1)-mediated inhibition of bone morphogenetic protein 4 (BMP4) which otherwise blocks GDNF signalling (Michos et al., 2007).

The number and initial positioning of the ureteric bud/s along the WD, especially with respect to the surrounding MM is critical to the subsequent branching and functionality of the mature kidney. Loss of genes controlling single UB outgrowth can lead to duplicated (duplex) ureters, multiplexed kidneys, and commonly, vesicoureteric reflux (VUR) (Song and Yosypiv, 2011) (see Figs. 2b and c). If UB induction fails, no kidney is formed (see Fig. 2d). A duplicated ureter can occur when, for various reasons, multiple UBs are induced in the WD. Duplicated ureter is the most common type of renal abnormality, occurring in approximately 1% of the population (Siomou et al., 2006). Whilst having multiple ureters may not be lethal, one of the ureters is often ectopic and can increase the risk of conditions such as urinary tract infections. Displacement of the single UB in either the cranial or caudal direction from its normal location on the WD can lead to kidneys with dysplasia, VUR, abnormal draining through the ureter and/or diminished functionality or capacity.

During the establishment of the UB, the cellular changes in the bud and the MM are substantial (Costantini and Koplan, 2011). Cells in the bud epithelium which have high expression of RET receptors (a member of the receptor tyrosine kinase family of proteins) migrate towards the ureteric bud tip (UT) (Chi et al., 2009b). Reciprocally, MM cells, progenitors of the nephron epithelium, condense on the tip through an unknown mechanism and form cap mesenchyme (CM) (Kobayashi et al., 2008). Interactions between CM and UB/UT cells drive the kidney development program. The CM provides UT cells with growth factors such as GDNF and other less crucial growth factors whose precise role is still being investigated: fibroblast growth factors (FGFs), vascular endothelial growth factors (VEGFs), hepatocyte growth factor (HGF) and epidermal growth factor (EGF).

Autocatalysis of GDNF/RET signalling between CM and UT cells lead to the branching of the UB after a period of outgrowth (Chi et al., 2009a). Understanding branching morphogenesis has been the focus of a large experimental research effort. Recently, a mathematical model by Menshykaul and Iber proposed that branching of the UB arises from the redistribution of GDNF signalling due to a naturally formed patterning between the rapidly diffusing GDNF free ligand and its slowly diffusing receptor complex at the epithelium surface (Menshykaul and Iber, 2013). This spontaneous generation of patterns in systems of interacting molecules was first explored by the renowned British mathematician Alan Turing. In his seminal paper, he described the possibility of diffusion-driven instabilities of an otherwise stable uniform steady state of a chemical system leading to spatial self-organisation (Turing, 1952). A particular type of simplified reaction–diffusion system displaying similar characteristics to the model of Menshykaul and Iber was presented by Gierer and Meinhardt (1972). Schnakenberg (1979) elaborated on the properties of the chemical system, and therefore reaction–diffusion models of this type are often named after him. Whilst epithelium cells are known to undergo migration and structural changes, these changes are triggered, largely, by GDNF signalling (Costantini and Koplan, 2011). Since GDNF signalling appears to be the driving cause of UT cell behaviour and because there currently are no models to suggest otherwise, it is the opinion of the authors that the initial cause of branching is likely due to morphogen self-organisation as proposed by Menshykaul and Iber (2013).

Once the UB branches, it forms two UTs each with its own associated CM. For a review of branching morphogenesis as well as the proceeding development of the kidney see Little and McMahon (2012). Fig. 2a is a diagrammatic summary of the stages of normal kidney morphogenesis as described in the introduction, whilst Figs. 2b–d show developmental phenotypes that have been observed in response to genetic experimentation.