Placenta 36 (2015) 951–955

Contents lists available at ScienceDirect

Placenta

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

Short communication

Genetic ablation of placental sinusoidal trophoblast giant cells causes fetal growth restriction and embryonic lethality

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ARTICLE INFO

Article history:
Accepted 20 May 2015

Keywords:
Placenta
Sinusoidal trophoblast giant cell
Cathepsin Q
Transgenic mouse
Cre recombinase
Diphtheria toxin

ABSTRACT

A specialized subtype of trophoblast giant cells (TGCs) line the torturous sinusoids of the murine placental labyrinth, and can be distinguished from most other TGCs by the expression of *Ctsq*. We generated a transgenic mouse line expressing Cre recombinase from the *Ctsq* promoter. Crosses with Cre-inducible tdTomato reporter mice indicated Cre activity was restricted to the sinusoidal TGCs of the labyrinth, as well as the recently characterized channel TGCs. When crossed with Cre-inducible DTA transgenic mice, ablation of sinusoidal TGCs was achieved in double transgenic embryos, resulting in fetal growth restriction by E16.5, and embryonic lethality by term.

1. Introduction

The maternal vasculature of the mouse placenta is lined not by endothelial cells, but by several subtypes of trophoblast giant cells (TGCs), which differ in their developmental origin, size, ploidy, gene expression profiles and location along the maternal circulation [1–3]. The small sinusoids of the labyrinth are lined by "sinusoidal-TGCs" (S-TGCs), which overlie the two transporting syncytial cell layers and together comprise the interhemal membrane. While considered part of the interhemal membrane, their capacity for nutrient transport is unclear. A scarcity of reported transporter expression, and the development of perforations in the cell membrane that expose the underlying syncytiotrophoblast directly to maternal blood, suggests that S-TGCs may not have a major role in transfer across the fetal–maternal interface [4,5], at least later in gestation when perforations are prevalent. They are however well situated to mediate delivery of secreted factors such as hormones, which they produce in abundance [4,5]. There is no clear analogous cell type in the interhemal membrane of the human placenta, which consists of a single syncytiotrophoblast layer. However, human syncytiotrophoblast does have distinct intracellular regions, organelle-rich "enteroid regions" and thin transporting vasculosyncytial regions [6,7], suggesting a physical compartmentalization of key endocrine and transport functions. It is tempting to speculate that S-TGCs of the mouse placenta represent a cellular equivalent to the enteroid regions of the human syncytiotrophoblast.

A member of the placentally-expressed cathepsin gene cluster on chromosome 13 [8], cathepsin Q (*Ctsq*), is expressed exclusively by the S-TGCs and the TGCs lining the channels that drain the deoxygenated blood from the labyrinth (Ch-TGCs) [3,9,10]. Herein we report the creation of a transgenic mouse line that utilizes the *Ctsq* promoter to drive Cre expression in S-TGC/Ch-TGCs of the labyrinth, providing a molecular tool for the investigation of S-TGC biology. Furthermore, we find that ablation of the S-TGC population results in fetal growth restriction and embryonic lethality by E18.5.

2. Methods

2.1. Animals

Ctsq-Cre – A fragment of the *Ctsq* promoter (10.3 kb upstream from the *Ctsq* start codon) was placed in front of an NLS-Cre-Rabbit beta globin polyA cassette and injected into the pronucleus of C57BL/6 embryos. tdTomato reporter mice (B6.Cg-Gt(ROSA)26Sortm9(CAG-tdTomato)Hze/J) [11] and a Cre-inducible DTA strain (Gt(ROSA)26Sortm1(DTA)Jpmb/J) [12] were obtained from Jackson Labs (Maine, USA). Animals were housed in accordance with the University of Queensland animal facility guidelines, and the University of Queensland Animal Ethics Committee approved all experiments.

2.2. Histology

Placentae from time-mated pregnancies (morning of a vaginal plug = E0.5) were dissected in cold DEPC-treated PBS and fixed overnight in 4% PFA. In situ hybridizations were done as previously described [1,13] and tdTomato expression was visualized following fixation, embedding in O.C.T. (Tissue Tek) and sectioning (10 μm).

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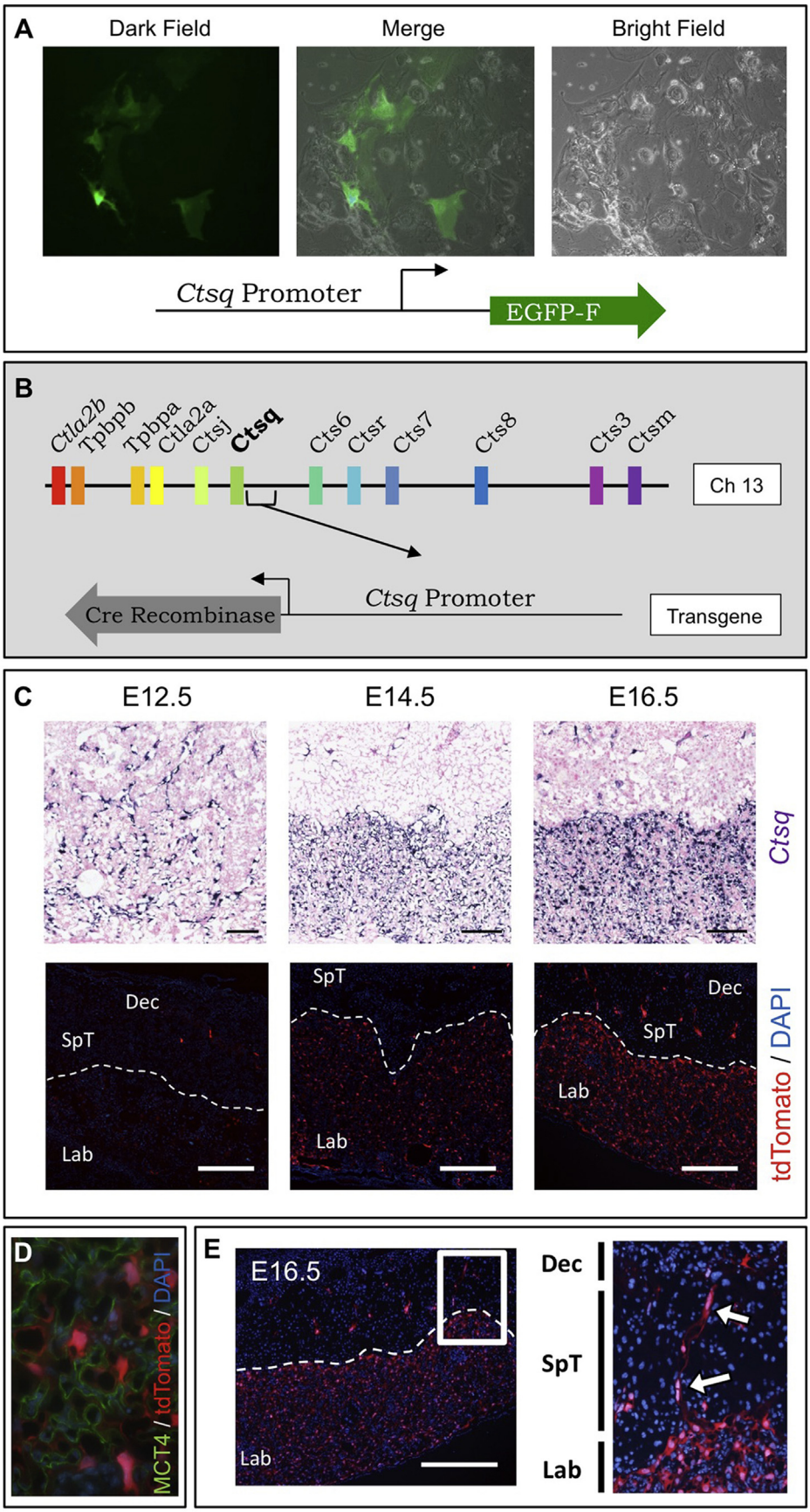
http://dx.doi.org/10.1016/j.placenta.2015.05.013
0143-4004/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