Available online at www.sciencedirect.com
SCIENCE DIRECT
Developmental Biology 283 (2005) 459 – 471
DEVELOPMENTAL BIOLOGY
www.elsevier.com/locate/ydbio

Evaluation of the contributions of ADAMs 9, 12, 15, 17, and 19 to heart development and ectodomain shedding of neuregulins β1 and β2

Keisuke Horiuchi[a,b], Hong-Ming Zhou[b], Kristine Kelly[b], Katia Manova[c], Carl P. Blobel[a,b,*]

[a]*Arthritis and Tissue Degeneration Program, Hospital for Special Surgery, Weill Medical College of Cornell University, New York, NY 10021, USA*
[b]*Cell Biology Program, Weill Medical College of Cornell University, New York, NY 10021, USA*
[c]*Molecular Cytology Core Facility, Sloan-Kettering Institute, New York, NY 10021, USA*

Received for publication 6 April 2005, revised 4 May 2005, accepted 6 May 2005
Available online 4 June 2005

Abstract

Defects in heart development are the most common congenital abnormalities in humans, providing a strong incentive to learn more about the underlying causes. Previous studies have implicated the metalloprotease-disintegrins ADAMs (a disintegrin and metalloprotease) 17 and 19 as well as heparin binding EGF-like growth factor (HB-EGF) and neuregulins in heart development in mice. Here, we show that mice lacking both ADAMs 17 and 19 have exacerbated defects in heart development compared to mice lacking either ADAM, providing the first evidence for redundant or compensatory functions of ADAMs in development. Moreover, we identified additional compensatory or redundant roles of ADAMs 9 and 19 in morphogenesis of the mitral valve and cardiac outflow tract. Cell biological studies designed to address the functions of these ADAMs in shedding of HB-EGF uncovered a contribution of ADAM19 to this process, but this was only evident in the absence of the major HB-EGF sheddase, ADAM17. In addition, ADAM17 emerged as the major sheddase for neuregulins β1 and β2 in mouse embryonic fibroblasts. These results raise the possibility that ADAMs 9, 17, and 19 contribute to heart development in humans and have implications for understanding the mechanisms underlying congenital heart disease.
© 2005 Elsevier Inc. All rights reserved.

Keywords: ADAM; Metalloprotease-disintegrin; Neuregulin; HB-EGF; Ectodomain shedding; Heart development; Endocardial cushion

Introduction

Congenital heart disease is the most common form of birth defects in humans, afflicting about 6–17/1000 live births, yet much remains to be learned about the underlying causes (Basson and Seidman, 1998; Goldmuntz and Emanuel, 1997; Hoffman and Kaplan, 2002; Lamers and Moorman, 2002; Srivastava and Olson, 2000; Vaughan and Basson, 2000). Identifying which molecules are critical for normal heart development and understanding their mechanism of action could therefore lead to improvements in the diagnosis and treatment of congenital heart defects. Recent studies have uncovered a critical role for two members of family of membrane-anchored metalloproteases in cardiovascular morphogenesis, ADAMs (a disintegrin and metalloprotease) 17 and 19 (Jackson et al., 2003; Kurohara et al., 2004; Shi et al., 2003; Zhou et al., 2004). ADAMs are also known to have important functions in a variety of other biological processes, including fertilization, neurogenesis, angiogenesis, and cancer (for recent reviews, see Blobel, 2005; Seals and Courtneidge, 2003; White, 2003).

The heart abnormalities observed in mice lacking functional ADAM17 are thickened and misshapen semilunar valves (aortic and pulmonic valves) and atrioventricular valves (Jackson et al., 2003). A lack of ADAM17 also leads to additional developmental abnormalities in mice, including defects in epithelial structures such as skin and intestines (Peschon et al., 1998), as well as in morphogenesis of the lung (Zhao et al., 2001) and mammary gland (Zena Werb, personal communication). The skin, lung, mammary gland, and heart

* Corresponding author. Arthritis and Tissue Degeneration Program and Cell Biology Program, Caspary Research Building, Room 426, Hospital for Special Surgery, Weill Medical College of Cornell University, 535 East 70th Street, New York, NY 10021, USA. Fax: +1 212 774 2301.
E-mail address: blobelc@hss.edu (C.P. Blobel).

0012-1606/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.ydbio.2005.05.004

valve defects are thought to be caused by a loss of EGFR signaling in these tissues (Jackson et al., 2003; Peschon et al., 1998) (Zena Werb, personal communication). The underlying mechanism appears to be a vital role of proteolytic processing in activating several EGFR-ligands during development (Jackson et al., 2003; Peschon et al., 1998; for review, see Blobel, 2005), all of which are synthesized as membrane-anchored precursors (reviewed in Harris et al., 2003). Specifically, ADAM17 is thought to be critical for processing and activation of at least three EGFR-ligands: heparin binding EGF-like growth factor (HB-EGF) (Hinkle et al., 2004; Jackson et al., 2003; Merlos-Suarez et al., 2001; Sahin et al., 2004), which is important for proper morphogenesis of the semilunar and atrioventricular valves (Iwamoto et al., 2003; Jackson et al., 2003; Yamazaki et al., 2003); transforming growth factor α (TGFα) (Peschon et al., 1998; Sahin et al., 2004), which is needed for skin, hair follicle, and eye development (Luetteke et al., 1993; Mann et al., 1993; Peschon et al., 1998); and amphiregulin (AR) (Sahin et al., 2004), which is essential for branching morphogenesis and ductal outgrowth during mammary gland development (Luetteke et al., 1999 and Z. Werb, personal communication).

Adam19−/− mice also display thickened and misshapen semilunar valves, resembling those in newborn *Adam17−/−* mice (Kurohara et al., 2004; Zhou et al., 2004), which provides a likely explanation for the death of *Adam19−/−* mice shortly after birth. However, the mechanism underlying the defect in semilunar valve development in *Adam19−/−* mice appears to be different from that described for *Adam17−/−* animals, since shedding of HB-EGF is not affected in *Adam19−/−* embryonic fibroblasts (mEFs) (Zhou et al., 2004), while it is abolished in *Adam17−/−* mEFs (Hinkle et al., 2004; Sahin et al., 2004; Sunnarborg et al., 2002). In addition to defects in semilunar valves, *Adam19−/−* mice also have a ventricular septal defect (VSD) and a thickened and misshapen tricuspid valve, but a normal mitral valve (Kurohara et al., 2004; Zhou et al., 2004).

Interestingly, even though two separate studies reported very similar heart defects in independently generated *Adam19−/−* mouse lines, only one found evidence for a potential role of *Adam19−/−* in processing an isoform of neuregulin (NRG), NRG β1, an ErbB ligand which is also synthesized as membrane-bound precursor (see Falls, 2003 for review on NRGs). Specifically, Kurohara et al. reported a lack of phorbol-ester-stimulated processing of this NRG isoform when *Adam19−/−* mouse embryonic fibroblasts (mEFs) were grown under sparse conditions, but not under dense conditions (Kurohara et al., 2004). Based on these findings, Kurohara et al. proposed that decreased shedding of NRG β1 in proliferating endocardial cushion cells during heart development might cause the heart defect in *Adam19−/−* mice. However, this very attractive model could not be corroborated in similar studies using cells from the second *Adam19−/−* mouse line, in which no defects in NRG processing (NRGs β1 and β2) were found, regardless of the cell density (Zhou et al., 2004). Despite these discrepancies, both studies were in agreement that the major sheddase for NRG β1 in confluent mEFs is not ADAM19, and therefore remained to be identified. Since the heart defects in both *Adam19−/−* mouse lines were very similar, it therefore appeared likely that the mechanism underlying the role of ADAM19 in heart development involves other substrates or mechanisms than shedding of NRG (Zhou et al., 2004).

The studies on *Adam17−/−* and *Adam19−/−* mice raise a number of questions about the role of these ADAMs in heart development. The similarity in the heart defects in *Adam17−/−* and *Adam19−/−* mice and the observation that both proteins are expressed in the developing heart and heart valves (Jackson et al., 2003; Zhou et al., 2004) raise the question of whether ADAMs 17 and 19 might have compensatory or redundant functions in heart development. The second question concerns the identity of the NRG sheddase(s), and specifically whether other ADAMs besides ADAM19 might be involved in NRG shedding. A previous study has shown that ADAM17 is required for cleaving NRG α2c (Montero et al., 2000), raising the possibility that it might also be involved in shedding of other isoforms of NRG, at least in densely plated cells. A third question is whether ADAM19 could have a function in cleaving HB-EGF in the absence of the major HB-EGF sheddase, ADAM17.

The essential roles of ADAMs 17 and 19 in heart development also raise questions about the contribution of other ADAMs that are expressed in the heart to cardiovascular morphogenesis. Specifically, the expression patterns of ADAMs 9 and 19 partially overlap in the endocardial cushion (Weskamp et al., 2002; Zhou et al., 2004), and those of ADAMs 15 and 19 overlap in endocardial cells overlying the endocardial cushion (Horiuchi et al., 2003; Zhou et al., 2004). Previous studies have shown that ADAMs 9 and 15 are not required for normal development and adult homeostasis, and even triple knockout mice lacking these two ADAMs together with ADAM12 are viable and fertile with no apparent defects in heart development (Horiuchi et al., 2003; Kurisaki et al., 2003; Sahin et al., 2004; Weskamp et al., 2002). Furthermore, quadruple knockout mice lacking ADAMs 9, 12, 15, and 17 do not have a more severe phenotype than mice lacking only ADAM17, arguing against potential compensatory or redundant functions between these four ADAMs (Sahin et al., 2004). However, ADAMs 9, 12, and 15 are more closely related to ADAM19 than to ADAM17 (Blobel, 2005), thus providing a rationale for evaluating potential heart defects in *Adam9/12/15/19−/−* quadruple knockout mice, as well as in different combinations of double knockout mice lacking ADAMs 19 and 9 or ADAMs 19 and 15.

The results of this study provide the first evidence for potential compensatory or redundant roles among different ADAMs. In addition, we found that ADAM19 can contribute to HB-EGF shedding, but this is only evident in the absence

Download English Version:

https://daneshyari.com/en/article/10934056

Download Persian Version:

https://daneshyari.com/article/10934056

Daneshyari.com