Developmental Biology 417 (2016) 198–208

Contents lists available at ScienceDirect

Developmental Biology

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

Genetics of enteric neuropathies

Erwin Brosens [a,*], Alan J. Burns [a,b], Alice S. Brooks [a], Ivana Matera [e], Salud Borrego [c,d], Isabella Ceccherini [e], Paul K. Tam [f], Maria-Mercè García-Barceló [g,h], Nikhil Thapar [b], Marc A. Benninga [i], Robert M.W. Hofstra [a,b], Maria M. Alves [a]

[a] Department of Clinical Genetics, Erasmus University Medical Centre – Sophia Children's Hospital, Rotterdam, The Netherlands
[b] Stem Cells and Regenerative Medicine, Birth Defects Research Centre, UCL Institute of Child Health, London, UK
[c] Department of Genetics, Reproduction and Fetal Medicine, Institute of Biomedicine of Seville (IBIS), Seville, Spain
[d] Centre for Biomedical Network Research on Rare Diseases (CIBERER), Seville, Spain
[e] UOC Medical Genetics, Istituto Giannina Gaslini, Genova, Italy
[f] Division of Paediatric Surgery, Department of Surgery, Li Ka Shing Faculty of Medicine of the University of Hong Kong, Hong Kong, China
[g] State Key Laboratory of Brain and Cognitive Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China
[h] Centre for Reproduction, Development, and Growth, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China
[i] Pediatric Gastroenterology, Emma Children's Hospital/Academic Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 8 June 2016
Received in revised form
13 July 2016
Accepted 13 July 2016
Available online 15 July 2016

Keywords:
Enteric neuropathy
Enteric nervous system
Gastrointestinal tract
Aganglionosis
Hypoganglionosis

ABSTRACT

Abnormal development or disturbed functioning of the enteric nervous system (ENS), the intrinsic innervation of the gastrointestinal tract, is associated with the development of neuropathic gastrointestinal motility disorders. Here, we review the underlying molecular basis of these disorders and hypothesize that many of them have a common defective biological mechanism. Genetic burden and environmental components affecting this common mechanism are ultimately responsible for disease severity and symptom heterogeneity. We believe that they act together as the fulcrum in a seesaw balanced with harmful and protective factors, and are responsible for a continuum of symptoms ranging from neuronal hyperplasia to absence of neurons.

Contents

* Correspondence to: Department of Clinical Genetics, Erasmus University Medical Centre – Sophia Children's Hospital, Room Ee971, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands.
E-mail address: e.brosens@erasmusmc.nl (E. Brosens).

http://dx.doi.org/10.1016/j.ydbio.2016.07.008
0012-1606/

1. Introduction

Normal motility of the gastrointestinal (GI) tract is reliant on complex patterns of smooth muscle contractions and is dependent upon the coordinated action of the enteric nervous system (ENS), smooth muscles cells (SMCs) and interstitial cells of Cajal (ICC). Developmental defects affecting specific cell types or disturbing proper functioning of the ENS, SMCs or ICC, result in variable degrees of abnormal motility, eventually leading to the development of intestinal neuromuscular disorders (Goldstein et al., 2016; Knowles et al., 2013; Panza et al., 2012). Based on the cell type affected, these disorders can be divided into three subtypes: neuropathies (neuronal defects), myopathies (SMC defects), or mesenchymopathies (ICC defects). However, it is important to note that the development and function of these cell types are interconnected (Furness et al., 2014; Gulbransen and Sharkey, 2012; Hao et al., 2016; Sanders et al., 2014), and determining whether a defective cell type is the underlying cause of a disorder, or if the cellular defects are instead a consequence, is not always straightforward. In this review we will focus on enteric neuropathies. We will first describe what is known about the genetics underlying the development of these disorders, and the molecular mechanisms involved in their onset. Moreover, we will discuss enteric neuropathies from a "spectrum" point of view, as many of these disorders are characterized by a continuum of symptoms ranging from severe and evident from birth or even antenatally, to relatively mild or late onset.

2. Enteric neuropathies

Enteric neuropathies can be present along the entire GI tract (see Table 1 for examples). Esophageal achalasia, gastroesophageal reflux disease (GERD), gastroparesis and hypertrophic pyloric stenosis are neurogenic disorders of the upper GI tract. Intestinal Neuronal Dysplasia (IND), the neuronal subtype of chronic intestinal pseudo-obstruction (CIPO), functional constipation, Hirschsprung disease (HSCR) and internal anal sphincter achalasia (IASA) on the other hand, are disorders affecting the lower GI tract. However, it is often common that upper and lower Gl symptoms are present in the same individual. In this section we will focus on each of these disorders and outline what is known about them.

2.1. Esophageal achalasia

Patients with esophageal achalasia are characterized by abnormal esophageal contractility with lack of coordinated peristalsis. In addition, the lower esophageal sphincter (LES) does not relax due to disruption of endogenous innervation (Pandolfino and Gawron, 2015), leading to an elevated resting pressure. Achalasia can result from neuronal damage caused by an autoimmune disorder (Kraichely et al., 2010), or due to specific infections (Becker et al., 2016; Boeckxstaens, 2008; de Oliveira et al., 1995). Histological examinations of patient material revealed severe reductions in myenteric ganglia (Goldblum et al., 1994), nitric oxide synthase producing neurons (nNOS) and numbers of ICC (Gockel et al., 2008).

Evidence for a genetic component in specific subsets of patients exists and comes from rare forms of familial esophageal achalasia (Bosher and Shaw, 1981) and genetic syndromes such as Triple A (Achalasia-addisonianism-alacrimia) syndrome (Tullio-Pelet et al., 2000), infantile-onset achalasia and autism (Shteyer et al., 2015; Taketomi et al., 2005), and Alport syndrome (Leichter et al., 1988). Recently, a genetic susceptibility locus was found in the HLA-DQ region (Gockel et al., 2014), linking immune response to an increased genetic risk. Recessive variants present in the Guanylate Cyclase 1, Soluble, Alpha 3 gene (*GUCY1A3*) (Herve et al., 2014), and in the GDP-Mannose Pyrophosphorylase A gene (*GMPPA*) (Koehler et al., 2013) were also found in patients where achalasia is part of a complex series of symptoms. However, mouse models where the expression of these two genes has been abolished showed no signs of impaired esophageal peristalsis (Buys et al., 2013; Lyon et al., 1996). The only mouse models described to date which showed achalasia-type features are the Nitric Oxide Synthase 1 (*Nos1*) (Sivarao et al., 2001), the Association (RalGDS/AF-6) Domain Family Member 1 (*Rassf1a*) (van der Weyden et al., 2009), the Sprouty RTK Signaling Antagonist 2 (*Spry2*), and the Collagen, Type IV, Alpha *4 (Col4a4)* (Arnold et al., 2011) mice. To date, no genetic variations in *RASSF1A* or *SPRY2* have been described in patients with achalasia, but recessive pathogenic variants in *NOS1* result in infantile-onset achalasia and autism (Shteyer et al., 2015; Taketomi et al., 2005), and variants in *COL4A4* were identified in patients with X-linked dominant Alport syndrome – deafness – nephropathy, which can also develop achalasia (Mochizuki et al., 1994).

2.2. Gastroesophageal reflux disease

In gastroesophageal reflux disease (GERD) there is a retrograde flow of stomach contents to the esophagus predominantly due to transient relaxation of the lower esophageal sphincter (LES), independent of swallowing or peristalsis. GERD is a multifactorial condition, in which the autonomic nervous system, sympathetic (Pfeiffer, 2001) and parasympathetic (Chakraborty et al., 1989; Cunningham et al., 1991; Djeddi et al., 2013), fails to properly control relaxation of the LES. As a consequence, GERD is considered to be an autonomic nervous system defect, not an enteric neuropathy, but patients with GERD can also have motility defects in the upper (Lundell et al., 1996) and lower GI tract, as seen for instance in Cornelia de Lange syndrome (Deardorff et al., 2012; Luzzani et al., 2003). Unsurprisingly GERD has also been associated with neurological conditions such as cerebral palsy, and can present after esophageal repair of esophageal atresia (Kovesi and Rubin, 2004). To date, no gene(s) have been identified as the causative factor of GERD, although association studies have pointed towards the involvement of the 13q14 region (Champaigne et al., 2009; Hu et al., 2004). Moreover, there are human genetic syndromes where patients develop GERD and for which the corresponding animal model has GI motility problems (Kiefer et al., 2003; Kiefer et al., 2008; Spring et al., 2005), confirming the involvement of a genetic component in the development of this disorder.

2.3. Hypertrophic pyloric stenosis

Infantile hypertrophic pyloric stenosis (IHPS), a common pediatric disorder characterized by projectile vomiting, has been suggested to be caused by lack of coordination between the movements of the pyloric sphincter and the contractions of the stomach (Hayes and Goldenberg, 1957). Patients with congenital