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REVIEW

Mucin 2 (MUC2) promoter characterization: an overview

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Abstract

Transgenic livestock have been studied with a well-known interest in improving quantitative and qualitative traits. In order to direct heterologous gene expression, it is indispensable to identify and characterize a promoter suitable for directing the expression of the gene of interest (GOI) in a tissue-specific way. The gastrointestinal tract is a desirable target for gene expression in several mammalian models. Throughout the surface of the intestinal epithelium, there is an intricate polymer network, formed by gel-forming mucins (especially MUC2 and MUC5AC, of which MUC2 is the major one), which plays a protective role due to the formation of a physical, chemical and immunological barrier between the organism and the environment. The characterization of the gel-forming mucins is difficult because of their large size and repetitive DNA sequences and domains. The main mucin in the small and large intestine, mucin 2 (MUC2), is expressed specifically in goblet cells. MUC2 plays an important role in intestinal homeostasis and its disruption is associated with several diseases and carcinomas. This mucin is also an important marker for elucidating mechanisms that regulate differentiation of the secretory cell lineage. This review presents the state of the art of MUC2 promoter structure and functional characterization.

Keywords Gel-forming mucin · Gene regulation · Gastrointestinal tract · Transgenic animals · Biotechnology

Introduction

Genetically modified organisms (GMOs) have been studied and produced for the last four decades. Since the first GMO was produced, this genome manipulation technology has made well-publicized progress (Fraiture et al. 2015). Transgenic animals and livestock have been studied with a particular interest in improving quantitative and qualitative traits and increasing their productive performance (Bertolini et al. 2016; Melo et al. 2007).

Promoters are regions of the genetic material that are essential for gene expression, since they are responsible for the control of the initiation and intensity of RNA polymerase transcription activity (Mikhaylichenko et al. 2018). The correct characterization of a promoter is essential to planning and building a transgene expression cassette, which will drive the precise expression of a gene of interest (GOI) in a specific cell type and time (Woodfint et al. 2017). The efficiency of promoter sequences in driving gene expression in a particular tissue was broadly verified in transgenic studies, using the promoter and regulatory upstream sequences of albumin gene to target expression in liver (Lee et al. 2003), adipocyte fatty acid-binding protein sequences to target expression in adipocytes (Lee et al. 2003) and insulin gene to target pancreatic beta cells (Wang et al. 2015). The regulatory regions of many genes have already been used to direct transgene expression in the gastrointestinal tract (Woodfint et al. 2017). For example, the promoter of intestinal fatty acid-binding protein can lead to the expression of transgenes such as growth hormone and cystic fibrosis transmembrane conductance regulator genes (Stoltz et al. 2013; Sweetser et al. 1988).

Currently, gastrointestinal tract mucus is attracting interest because its structure and function are divided into two layers in the colon: an inner layer, close to the mucosal surface and free from bacteria and the outer layer, colonized by bacteria and other types of commensals (Johansson et al. 2011; Johansson et al. 2008; Maynard et al. 2012). The viscoelastic gel formed by mucins is essential in the protection of the intestinal cells, since its disruption causes several pathologies (Ridley et al. 2014).

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Trapping and eliminating microorganisms is a function of the mucus barrier composed of gel-forming mucins (Lang et al. 2007). This family of high molecular mass *O*-glycoproteins (2–50 MDa) is composed of five polymeric mucins: MUC2/Muc2, MUC5AC/Muc5ac, MUC5B/Muc5b, MUC6/Muc6 and MUC19/Muc19 (Ridley et al. 2014). MUC2 is the major gel-forming mucin on the intestinal epithelium (Ambort et al. 2012). MUC5AC is the most abundant on the stomach surface (Johansson et al. 2011) but is also present in the respiratory tract (Thornton et al. 2008). MUC5B is found in the respiratory tract as well and it is highly expressed in salivary glands, gallbladder and vagina (Lang et al. 2016). MUC6 can be found in stomach glands, endometrium, gallbladder and in the pancreatic exocrine duct (Corfield 2015). However, MUC19 seems to be restricted to the gland area (Zhu et al. 2011) and it is not well-characterized so far, in terms of function and structure (Lang et al. 2016).

MUC2 is one of the most plentiful gastrointestinal gel-forming mucins (Rodriguez-Pineiro et al. 2013) and it displays a constitutive expression throughout the gastrointestinal tract (Ambort et al. 2012; Hoorens et al. 2011; Woodfint et al. 2017). MUC2 has been demonstrated to be a very interesting protein to study due to its high complexity and size (van der Post et al. 2014). The objective of this review is to present the state of the art of the gel-forming mucin 2 gene (*MUC2*) promoter structure and its functional characterization. Since the gel-forming mucins have very similar structure and many repetitive DNA domains and sequences, it is hard to tell them apart and characterize them without cross-contamination (van der Post et al. 2014). Therefore, a cohesive compilation of the available data is essential to support further studies concerning the secreted-mucin family promoter and regulatory regions. Furthermore, the scarcity of published studies regarding the *MUC2* promoter in mammals is a challenge faced by any review work in this area of knowledge.

As for the nomenclature, uppercase letters are used to refer to human proteins; uppercase and italic letters to human genes; and, for other species, only the first letter is capitalized and, if referring to genes, it is also italicized (Lang et al. 2016).

Mucin family

Mucins have a significant protector role, since they overlay all mucosal surfaces forming a physical, chemical and immunological blockade between the organism and the external environment (Hoorens et al. 2011). The composition of gel-forming mucins varies along the gastrointestinal tract but it is the first defense against bacteria (Johansson and Sjovall 2013). Experiments using mice with cystic fibrosis, where the small intestine mucus is attached to the epithelium, incapable of peristaltic movement, demonstrated an increased load of bacteria, which elucidates the importance of the mucins' protective role (Fridge et al. 2007). The gel-forming mucins present in the gastrointestinal tract also prevent colitis, colon cancer and the growth of *Helicobacter pylori* (Roy et al. 2014).

Mucins are heavily *O*-glycosylated proteins that form an intricate polymer network responsible for lubrication and protection of the outer surface of the internal epithelial tissue (Bu et al. 2011; Gum Jr et al. 1994). They are divided into two families: the secreted gel-forming and the cell-surface, or membrane-associated, mucins (Johansson and Sjovall 2013). The gel-forming mucins are usually arranged by closely linked genes (gene families), forming genetic clusters, which are expressed distinctively in a cell-specific manner (Ridley et al. 2014). Many mucin genes have already been identified and characterized but several of them still need to be discovered or better described (Perez-Sanchez et al. 2013). Their identification is difficult due to their large size, complexity and DNA repetitive sequence characteristic of all members of the gel-forming and cell-surface mucins (Desseyn et al. 2008; Lang et al. 2016; Moniaux et al. 2001). Mucin genes seem to be conserved between humans and rodents (Desseyn et al. 2008) but little is known about murine cell-surface mucins' function and expression. Therefore, a more detailed characterization of mice mucins is important to establish mucin function and the transgenic knockout mouse model is pivotal to this goal (Desseyn et al. 2008).

Gel-forming mucins

Gel-forming mucins consist of large proteins with about 5000 amino acids in their monomer chain and contain at least one proline, threonine and serine-rich (PTS) domain (Strous and Dekker 1992). In contrast with the usual protein domains, the PTS domain displays little sequence conservation between close species (Desseyn et al. 2000). A vital feature of this mucin family is the occurrence of several *O*-glycans attached to the PTS domain, specifically to the threonine and serine residues (Backstrom et al. 2013). The gel-forming mucins are distinguished by the presence of other remarkable domains like von Willebrand factor (vWF) and cysteine (CYS) domains (Bonser and Erle 2017; Demouveaux et al. 2018). The CYS domain is a region of 110 amino acids containing 10 invariant cysteine residues close to the PTS domain, which is thought to be important in the protein network (Verdugo 2012). The CYS domain is found always in several copies and only in gel-forming mucin or mucus-associated molecules (Demouveaux et al. 2018). Their amino-terminal region is made of three vWF type D domains (vWD1, vWD2 and vWD3), rich in highly conserved cysteine residues, with a partial D domain between vWD2 and vWD3 domains (Perez-Vilar and Hill 1999; Thornton et al. 2008). At their carboxyl terminal region, they are characterized by the presence of a ~ 80 amino acid cysteine knot domain and additional

vWF domains (Sadasivan et al. 2011; Thornton et al. 2008). The vWF domains correspond to sites of mucin polymerization and dimerization, responsible for the formation of disulfide-bonded polymers that are essential in establishing the gel-forming properties (Thornton et al. 2008). MUC2, MUC5AC and MUC5B have and additional vWF type D domain (vWD4) at the carboxyl terminal region (Demouveaux et al. 2018).

In mammals, the gel-forming mucin family is composed of five genes: *MUC2/Muc2*, *MUC5AC/Muc5ac*, *MUC5B/Muc5b*, *MUC6/Muc6* and *MUC19/Muc19* (Lang et al. 2016). *MUC2*, *MUC5AC*, *MUC5B* and *MUC6* are clustered in the locus 11p15.5 in human chromosome 11 (Griffiths et al. 1990; Pigny et al. 1996) but *MUC19* is located in the human chromosome 12 locus 12p12 (Chen et al. 2004). This region of chromosome 11 is known to be a hotspot of abnormal DNA-methylation in cancer (de Bustros et al. 1988) and the abnormal expression of *MUC2* is present in about 25% of gastric carcinomas (Pinto-de-Sousa et al. 2002; Reis et al. 2000), linking this gene to gastric neoplasia incidence.

The mechanisms of gene expression regulation of the mucin gene cluster at chromosome 11 (11p15.5) are crucial for normal function of epithelia in many organs (Gosalia et al. 2013). Modification in the higher order of chromatin structure regulates this gene cluster by enhancing or restricting the access to regulatory regions by transcription factors (Gosalia et al. 2013). An important transcription regulator for the mucin gene cluster is the CCCTC-binding factor (CTCF), since it prevents the inappropriate activation of MUC promoters (Gosalia et al. 2013). Intergenic and intronic regions of the mucin gene cluster are enriched by CTCF-binding sites compared to their promoter regions (Boyle et al. 2011; Kim et al. 2007) and although 40–60% of these regions are ubiquitous, the residual 60–40% are linked to cell type specificity (Cuddapah et al. 2009; Gosalia et al. 2013; Phillips and Corces 2009). Studies using bacterial LPS (lipopolysaccharides) treatment, which upregulates *MUC2* and *MUC5AC* expression, demonstrated a concomitant decrease in CTCF binding across the cluster, showing that this factor is a negative regulator of mucin expression (Gosalia et al. 2013).

Protective role of gel-forming mucins

The PTS domain is a site of *O*-glycosylation (Backstrom et al. 2013; Bonser and Erle 2017). *O*-glycan is the most important type of glycan in gel-forming mucins and it corresponds to a chain with 6–18 monosaccharides (Corfield 2015; Rana et al. 1987; Robbe et al. 2003). Of the gel-forming mucins, 50–90% of the mass is due to the repetitive PTS sequences linked to the thick glycan structure (Thornton et al. 2008). These *O*-glycosylations are responsible for the generation of the mucin-polymer aggregates and, consequently, the gel structure of these complex glycoproteins (Johansson et al. 2011). Also, another important feature for gel formation in mucins is their large hydrodynamic volume in solution, which confers a physical protective barrier against many pathogenic microorganisms (Thornton et al. 2008).

An example of the protective role conferred by the gel-forming mucins is their role against *Helicobacter pylori* infection. *H. pylori* leads to inflammation of the gastric mucosa, which can cause intestinal metaplasia and, in some cases, gastric carcinoma (Teixeira et al. 2002). However, the development of intestinal metaplasia creates a hostile microenvironment for bacterial colonization due to the antimicrobial activity of mucin carbohydrate chains produced by the mucous cells (Bravo and Correa 1999; Ferreira et al. 2006; Genta et al. 1996; Teixeira et al. 2002). The *O*-glycosylated mucins halt *H. pylori* growth by inhibiting the biosynthesis of cholestery-α-D-glucopyranoside, the major bacterial cell wall component (Craanen et al. 1992; Ferreira et al. 2006; Kawakubo et al. 2004). The consistent high expression of *MUC2* in many cases of intestinal metaplasia is correlated to the *H. pylori* clearance from the gastric mucosa in intestinal metaplasia lesions, due to the property of MUC2 of creating a hostile microenvironment for this bacteria (Ferreira et al. 2006).

Another example is the aberrant expression of MUC2 associated to many gastrointestinal diseases, including nematode infections (Lidell et al. 2006). Nematode infection can cause significant morbidity and mortality in humans, as seen by the Trichuriasis disease (Artis and Grencis 2008). The mucus barrier has a significant role in the response against nematodes, influenced by the T_H2-type cytokines, in particular IL-13, which plays a crucial role in nematode infection (Artis and Grencis 2008; Cliffe and Grencis 2004; Hasnain et al. 2010). MUC5AC, which is a mucin predominantly expressed in airways, stomach and ocular epithelia (Bara et al. 2003; Buisine et al. 1998; Inatomi et al. 1996), is highly expressed during inflammation of the intestinal mucosa (Forgue-Lafitte et al. 2007). Muc5ac is induced by IL-13 and influences the biochemical properties of the mucus, facilitating nematode expulsion and, thus, functioning as a pharmacological regulator in the murine model (Hasnain et al. 2010). The absence of *Muc2* expression results in a delay in worm expulsion (Hasnain et al. 2010) and despite Muc2 and Muc5ac acting together against nematode infection, Muc5ac plays the main role in immune response (Hasnain et al. 2011).

The alterations in mucins' pattern of expression have been described in carcinomas as well as in their precursor lesions (Girling et al. 1989; Hakomori 1989; Ho et al. 1993; Merlo et al. 1989; Springer et al. 1995). Among the precursors of gastric carcinomas are the intestinal metaplasia lesions (Correa 1988). Intestinal metaplasia is observed when the gastric mucosa is replaced by an epithelium that resembles the intestinal mucosa but with underexpression of *MUC1*, *MUC5AC* and

MUC6, which are the normal mucins expressed in gastric epithelium and expression of *MUC2*, which is not expressed in normal gastric mucosa (Reis et al. 1999). There are two main types of intestinal metaplasia: the complete (type I) and the incomplete type (types II and III). Type I is characterized by the secretion of sialomucins and corresponds to the small intestine phenotype through the presence of absorptive cells, Paneth cells and goblet cells (Filipe et al. 1994). The idea that type I characterizes a whole differentiation of the gastric mucosa toward the small intestinal phenotype is supported by the strong decrease in mucin synthesis in normally gastric mucosa (Matsukura et al. 1980). In types II and III metaplasia, the presence is observed of sialo and/or sulfomucins secreted by columnar and goblet cells and co-expression of the gastric mucins (*MUC1*, *MUC5AC* and *MUC6*) with *MUC2*, which shows a mixture of gastric and intestinal expression phenotype (Filipe et al. 1994). In most metaplasia cases, the expression of *MUC1*, *MUC5AC* and *MUC6* is observed and de novo expression of *MUC2* is present in both columnar and goblet cells (Reis et al. 1999).

Mucin 2

The expression of the diverse mucin genes is fairly organ- and tissue-specific and the MUC2 protein is expressed mainly in goblet cells in the intestinal epithelium (Audie et al. 1993; Birchenough et al. 2016; Chang et al. 1994; Gum et al. 1997; Ho et al. 1993). MUC2 is the main constituent of mucus in the small and large intestine (Audie et al. 1993). Mucin 2 has been shown to be an important protective barrier against external pathogens (Ma et al. 2017) and it has diverse functions in intestinal homeostasis (Birchenough et al. 2015; Velcich et al. 2002). *MUC2* knockout leads to an increase in colitis (Van der Sluis et al. 2006), bacterial colonization (Johansson et al. 2008), intestinal inflammation and occurrence of intestinal cancer with spontaneous progression to metastasis (Velcich et al. 2002). Furthermore, studies have demonstrated that *MUC2* is expressed during early embryonic development as early as 9 weeks of gestation (Buisine et al. 1998), which makes it an important marker to elucidate the mechanisms that regulate differentiation of the secretory cell lineage (Aslam et al. 2001). Despite the accumulating data about the physiological role of MUC2 protein and gene, promoter sequences have not been fully identified for all human mucin genes until now and the mechanisms regulating their transcription are mostly unknown (Hoorens et al. 2011).

Characterization of the human *MUC2* promoter

The *MUC2* transcriptional regulatory sequence is positioned inside a 7000-base GC-rich region downstream of its open-reading frame (ORF), or coding sequence (CDS) and includes various repetitive and conserved domains (Griffiths et al. 1990; Gum et al. 1997). The regulation of the *MUC2* gene presumably rests on the balance between positive and negative regulatory transcription factors (Velcich et al. 1997). The TATA box, in mammals, is usually located 30 bases upstream of the transcription start point (Zawel and Reinberg 1995). Furthermore, a singular cell-type transcriptional regulatory sequence, the CACCC box, is present in the *MUC2* gene 5′-flanking sequence. The CACCC box seems to be imperative for *MUC2* transcription and is positioned in the proximal portion (between bases −88/−80) of the transcription start site (Gum et al. 1997), as presented in Fig. 1. The significance of this component in gene transcription can be seen in many studies where its deletion provoked an abrupt downregulation of the reporter genes under the putative *MUC2* promoter sequence (DeVack et al. 1993; Dittmer et al. 1994; Hagen et al. 1992). Moreover, an important feature in *MUC2* promoter function may be the Sp1-like target sequence in the proximal 5′-flanking region (Matsuoka et al. 1999). Another important region of *MUC2* promoter sequence is located between bases −228 and −171, which is thought to confer cell-type specificity (Gum Jr et al. 1999).

Many other transcriptional factors (or binding sites) can affect *MUC2* expression, such as short-chain fatty acids

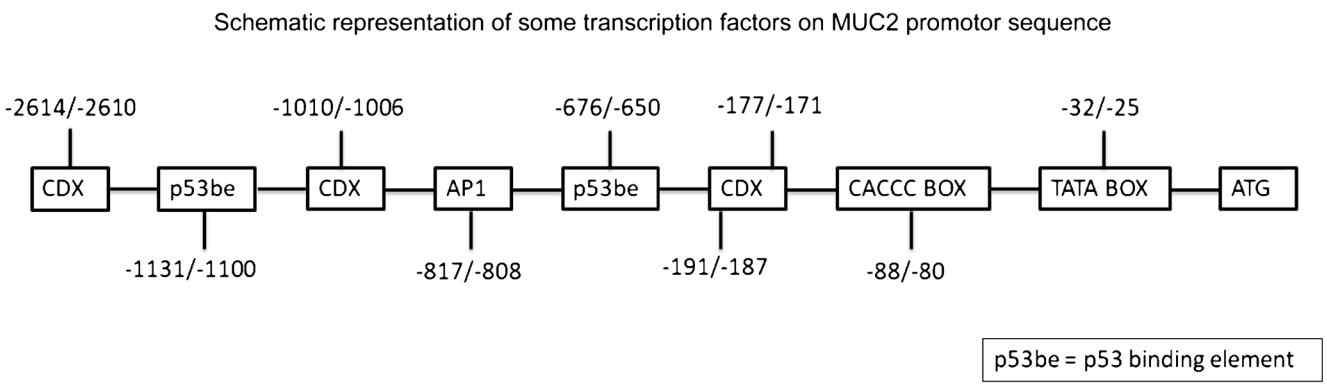

Fig. 1 Schematic representation of some transcription factors of MUC2 promoter sequence

(SCFAs) (Burger-van Paassen et al. 2009), homeobox domains (Cdx) (Mesquita et al. 2003), CCCTC-binding factor (CTCF) (Gosalia et al. 2013), GATA family (Ren et al. 2004), HATH1 (Park et al. 2006) and Sp1 family (Aslam et al. 2001). *MUC2* transcription is also under the influence of DNA methylation and histone modifications (Vincent et al. 2007). Additionally, the tumor suppressor gene p53 has also been reported to be a transcription factor for *MUC2* (Ookawa et al. 2002). The short-chain fatty acids (SCFAs) are the major anions in the large intestine and, among them, acetate, propionate and butyrate are remarkable (Burger-van Paassen et al. 2009). Butyrate alters *MUC2* expression in a dose-dependent manner (Hatayama et al. 2007). At low concentrations, it stimulates *MUC2* expression but at moderate and high concentrations, it decreases *MUC2* expression (Burger-van Paassen et al. 2009). Butyrate mediates its effect via the AP-1 transcriptional factor-binding site that is present in the *MUC2* promoter (Burger-van Paassen et al. 2009). AP-1 is a multiprotein complex formed by c-Jun and c-Fos proto-oncogenes and butyrate is capable of inducing their expression (Burger-van Paassen et al. 2009). Cdx-1 and Cdx-2 are intestine-specific homeodomains that are closely associated with *MUC2* expression (Almeida et al. 2003). The *MUC2* promoter has two Cdx-binding sites, which strongly suggests that Cdx could be a relevant transcriptional regulator for *MUC2* (Mesquita et al. 2003). The Cdx-2 homeodomain is directly involved in the regulation of *MUC2* transcription and the Cdx-1 effect is more important during cell differentiation and the development of the intestine (Mesquita et al. 2003). The GATA family consists of six transcriptional factors with highly conserved zinc finger DNA-binding domains, present in the 5′-flanking region of the *MUC2* gene and is involved in the upregulation of its expression (Ren et al. 2004). HATH1 is a basic helix-loop-helix transcription factor required for goblet cell biogenesis, suggesting that it may be a regulator of *MUC2* expression (Park et al. 2006). Three E-box motifs have been found on the *MUC2* promoter sequence and these sequences are canonical binding sites for HATH1, since mutations on these sites reduce the stimulatory effect of HATH1 on *MUC2* expression (Akazawa et al. 1995; Park et al. 2006).

Characterization of the murine *Muc2* promoter

In mice, the *Muc2*, *Muc5AC*, *Muc5B* and *Muc6* genes are clustered in chromosome 7 band F5 (Desseyn and Laine 2003) and *Muc19* is present in chromosome 15 band E5 (Chen et al. 2004). The mouse *Muc2* gene has 75% homology at the N-terminus compared to the human and it may have similar transcriptional regulation due to the stout sequence resemblance between their ORF downstream sequences (Aslam et al. 2001). Mouse *Muc2* transcription may be under the influence of transcriptional factors involved in intestine development and intestine-cell differentiation because it is expressed during early embryonic development of the intestine (Buisine et al. 1998). Important transcriptional factors involved in this process are GATA factors, which use zinc-finger domains to bind their DNA-target sequences (van der Sluis et al. 2004). Through computer analysis of the *Muc2* promoter sequence, several putative GATA-binding sites can be found in mice (Aslam et al. 2001). GATA-4 induces *Muc2* transcription, which reveals that it is a strong transactivator of gene expression (van der Sluis et al. 2004). Also, Foxa 1- and Foxa 2-binding sequences are responsible for inducing *Muc2* transcription and can be considered strong activators of its promoter activity (van der Sluis et al. 2008). Furthermore, another typical transcription factor-binding site characterized in the human *MUC2* promoter and also identified in a mouse *Muc2* upstream region, is the Sp1 transcription factor target sequence, which is thought to confer cell specificity (Nogami et al. 1997).

Characterization of the quail *Muc2* promoter

Recently, a candidate sequence for chicken *Muc2* promoter was described (Woodfint et al. 2017) and it includes a region of 2.9 kb that was successfully used to generate a transgenic quail with intestine-specific GFP expression. In this study, the conservation of *cis*-regulatory regions, such as GATA-binding protein 4 (GATA4), transcriptional factor 4 (TCF4), caudal type homeobox 2 (CDX2) and hepatocyte nuclear factor 4 α (HNF4A) was established. The putative *Muc2* promoter sequence used to develop the transgenic quail had one GATA4, one TCF4B, nine CDX2 and two HNF4A potential binding sites (Woodfint et al. 2017). The insufficiency of CDX2 results in abnormalities in the large intestine and colon dysgenesis (Gao et al. 2009), so CDX2 is thought to be an important intestinal transcriptional factor for chicken and mammals.

Conclusion

The characterization of specific intestinal promoters will permit the elucidation of not only important elements and factors playing significant roles in the regulation of intestine-specific genes but can also shed light on the mechanisms responsible for the unique differentiation patterns observed in the intestinal mucosa epithelium (Gum et al. 1997). These systematic studies on the mucin 2 regulatory sequences also provide an improved understanding of the direct and precise role of the cis-regulatory sequences on the modulation of the expression of the intestinal-digestion encoding factors and the endocrine and secretory aspects of intestinal physiology (Woodfint et al. 2017). Furthermore, cell-type-specific expression is an important feature when it

comes to genetically modified organisms, since it is important to direct the transgene expression to the right place and time. A possible and interesting application of the mucin 2 promoter sequence is for transgenic livestock, in order to generate animals expressing desirable proteins in the gastrointestinal tract. Another applicable use for MUC promoters is as a noninvasive strategy against intestinal infection and inflammatory bowel diseases (especially ulcerative colitis and Crohn's disease) and it was shown in a study that used CYS domains reinforce the mucus protective barrier (Gouyer et al. 2015).

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