Is Class I Homeobox Genes Implicated in Celiac Disease?

Procino Alfredo

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Abstract

Celiac disease (CD) is a permanent intolerance to gliadin contained in gluten proteins found in wheat, barley, rye, barley and other cereals. Celiac disease is not a disease to Mendelian genetic transmission, but there is a certain degree of genetic disposition in the patient's relatives. An intolerance to gluten determine severe damage to the intestinal mucosa, as villous atrophy. The intolerance to gluten is contrasted by the body with the production of antibodies that, in turn, damage the intestinal mucosa causing a decrease of intestinal absorption. Recently, 39 genomic regions were identified associated with CD and located on chromosome 2; the genes located in this area are physically in contiguity with the HOXD locus present on chromosome 2q31. The Class I homeobox genes (HOX in human), are 39 transcription factors able to control embryonic development and the cell memory program interacting with non coding RNA. I consider the HOX network “The Rosetta stone” of human biology; therefore, is HOX gene network able to control the change of the cell memory program in the CD?

Keywords: Celiac disease; Inflammation; HOX; Homeodomain; IncRNA

1. Celiac Disease

The CD is a complex genetic disorder involving multiple chromosomal regions. Some of them (and CELIAC2 CELIAC4) were also described in inflammatory bowel diseases (Inflammatory Bowel Disease-5 and -6 genes), suggesting at least part of a common susceptibility to the disease; as a result, more loci, appear to be involved in the pathogenesis of CD (Curely et al., 2006). The major histocompatibility complex genes (HLA / MHC) located on chromosome 6, play a crucial role in the CD: about 95% of patients are carriers of the genes encoding the molecules haplotype HLA-DQ2 (DQA1 * 0501 / DQB1 * 0201). Conversely, the subjects who do not have it, have haplotype HLA-DQ8 (DQA1 * 0301 / DQB1 * 0302) (Louka et al., 2003; Van Heel et al., 2007; Hunt et al., 2008; Sollid et al., 1989). In celiac patients, it has been demonstrated the specific CD4 T-cells HLA-DQ sensitive to peptides of the transglutaminase. However, the prevalence of HLA-DQ2 is high even in non-celiac disease (25% -30%), suggesting
the involvement of additional genes, in the pathogenesis of the CD. In details, some of these genes were located on a region in the long arm of Chr-2 (2q33), called CELIAC3, containing CD28, CTLA4 (Cytotoxic T-lymphocyte-associated antigen 4) genes and ICOS (Inducible Co-stimulator genes), on the arm along of the chr-5 and the short arm of the chr-19 (Dubois et al., 2010).

Innate and acquired immunity, are both crucial for the phenotypic expression of the disease. The cytokines involved in celiac disease, is represented above all by IFN-, moreover the increase of IL-15, IL-18, and IL-21 is linked to the assumption of gluten, which can drive the inflammatory response probably supported by IL-18, IL-21 and IL-27 through the signal STAT1 and STAT5. Conversely, neither IL-12 nor IL-23 play a significant role in the pathogenesis of CD (Jose’ et al., 2008).

2. HOX Genes

HOX genes are 39 transcription factors, mainly involved in the regulation of embryonic development, characterized by a sequence of 183 nucleotides encoding a homeodomain of 61 amino acid that binds to DNA, as a biological gripper (Fig. 1), activating or repressing specific genes (Graham et al., 1989; Krumlauus, 1994). The HOX genes are organized into four chromosomal clusters or loci (HOXA Chr 7p15.3, HOXB Chr 17q21.3, HOXC Chr 12q13.3 and HOXD Chr 2q31), each having 9-11 genes. Based on the sequence similarity and their position into the locus, the corresponding genes, of the four clusters, can be aligned with each other in 13 paralogous groups (Apiou et al., 1997). New crucial functions have recently been ascribed to HOX genes, mostly related to their interaction with miRNAs and ncRNAs to guarantee transcription and translation of specific RNA transcripts (Cobb et al., 2004; Rinn et al., 2007) (Fig. 2). Moreover, the HOX network controls the cell memory program (Procino et al., 2013). The memory program contains much information crucial to the cell life cycle: where the daughter cell will be located; what phenotype identity will acquire; when both these properties will be express; the number of cell division the daughter cell will be able to perform; and when, if ever, will they go through apoptosis (Bantignes et al., 2006) (Fig. 3). The cellular memory was regulated by three gene families: the Polycomb genes, able to block DNA-chromatin interaction leading to HOX gene silencing. The Trithorax genes, able to induce mRNA transcription through an open configuration of DNA-chromatin interaction and leading to HOX gene activation; finally the HOX genes involved in the orchestration of phenotype specific gene program mostly through the fine regulation of mRNA transcription (Procino et al., 2013).

Fig. 1. Alfa-helix homeodomain structure (see the text)
3. HOX Genes, miRNAs and ncRNAs

Six encoding microRNA (miRNAs) have been identified within the HOX network; miRNAs 196 (mir-196b, mir-196a-1 and mir-196a-2) located between paralogous HOX9 and HOX10. miRNAs 196 are involved in several neoplastic transformation such as gastric and colorectal cancer (Procino, 2014). Two genes coding for the mir-RNAs 10a and 10b between the paralogous group HOX4 and HOX5. Moreover, On the locus HOXC has been identified a ncRNA called HOTAIR is the first IncRNA that control the gene expression in trans. In particular, it is able to block the transcription of the HOXD genes from HOXD9 to HOXD13 on Chr-2. Moreover, the overexpression of the HOTAIR has been linked to several diseases; primarily it was found in
colorectal cancer and hepatoma mainly by means the interaction with miRNA196a, located on Chr-2 within the HOXC locus exactly between HOXC9 and HOXC10 (Fig. 2). The miRNA196a is up regulated in CD (Sollid, 2000; Capuano et al., 2011; Kogo et al., 2011). Close the 3’ end of the HOXA locus, between HOX A1 and HOX A2, has been identified another ncRNA called HOTAIRM1; HOTAIRM1 modulates the gene expression of HOXA locus, during myelopoiesis (Procino, 2014). Recently has been identified a IncRNA, HOTTIP, transcribed from the 5’ end of the HOXA locus that coordinates the activation of several 5’HOX A genes in vivo (Wang et al., 2011). HOTTIP is positive markers of the Hepatocarcinoma and play a crucial role in the transcriptional control of HOXA13 (Quagliata et al., 2014). The paralogous group HOX13, specifically HOX A13, is implicated in colon cancer (Procino, 2014).

4. Conclusion

In conclusion, many evidences confirm the role HOX network, miRNAs and ncRNAs in the several pathology of gastrointestinal tract. Moreover, in the pathogenesis of CD specific genes located on Chr-2 close to HOXD locus play a crucial role. Therefore, I hypotize the involvement of HOX system in the control of CD, maybe reprogramming the cell memory in the bowel tissue after ingestion of gluten.

References

http://dx.doi.org/10.1159/000134320

http://dx.doi.org/10.1016/j.ceb.2006.04.003

http://dx.doi.org/10.1371/journal.pone.0029094

http://dx.doi.org/10.1038/ng1004-1033

http://dx.doi.org/10.1038/sj.ejhg.5201687

http://dx.doi.org/10.1038/ng.543

http://dx.doi.org/10.1016/0092-8674(89)90912-4

http://dx.doi.org/10.1038/ng.102

http://dx.doi.org/10.1097/MPG.0b013e3181818f8b9

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Procino A. The paralogous group HOX 13 discriminates between normal colon tissue and colon cancer. (2014) J Molec Gen medicine; 8:3


