BioData Mining | Short Report (Biomedcentral.Com) Combinatorial Analyses Identify A Core Response to the CDX2 Homeoprotein During Development and In Pathologies

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Abstract

Whether a gene involved in distinct tissue or cell functions exerts a core of common molecular activities is a relevant topic in the evolutionary, developmental and therapeutic perspective. Here, we addressed this question by focusing on the *CDX2* homeobox gene that encodes a transcription factor with important functions during embryonic development and in adult pathologies. By analysing RNAseq data and ChIPseq data, we unveiled the existence of a core of genes whose expression is responsive to the Cdx2 homeoprotein and also a core of chromosomal regions targeted by Cdx2 at three important steps of mouse development: trophoctoderm formation, posterior body elongation and intestinal specification. In addition, based on human cancer data, we highlighted the relevance of the core of responsive genes by displaying a significant number of human orthologues exhibiting an altered expression along with *CDX2* in human malignancies.

Introduction

That evolution makes new out of old suggests the existence of shared properties between the functions of a given gene at its different times or sites of action. The homeobox gene encoding the Cdx2 transcription factor allows addressing this assumption since it consecutively drives three major developmental processes in mammals. At the blastula stage, *Cdx2* is pivotal for trophoctoderm formation during the segregation of pluripotent cells into the first two lineages of trophoctodermal cells and inner mass embryonic stem (ES) cells [1,2]; then, *Cdx2* actively participates in axial posterior body growth at gastrulation [3]; finally, it determines gut identity of the mid- / hindgut embryonic endoderm [4]. In adults, *Cdx2* expression is physiologically limited to the gut epithelium, involved in the control intestinal homeostasis [5,6] and endowed with tumor suppressor activity [7–9]. However, it becomes ectopically expressed in precancerous metaplastic lesions and adenocarcinoma of foregut-derived organs, and also in leukemia with an oncogenic role (see [10] for a review and Refs therein). On this basis, the present work interrogates whether some elements of the response to *Cdx2* are shared at these three developmental steps and subsequently whether these elements are altered in human pathologies along with *CDX2*.

Materials And Methods

Data sources

Mouse RNAseq and ChIPseq raw data were retrieved from the GEO database (<https://www.ncbi.nlm.nih.gov/geo/>): GSE115541 [11], GSE62149 [12], GSE90752 [13] and GSE84899 [14]. Human RNAseq data from colon adenocarcinoma (COAD), stomach adenocarcinoma (STAD) and acute myeloid leukemia (AML) were obtained from the The Cancer Genome Atlas (<https://www.cancer.gov/tcga>) (Additional file 2.1). Data for non-dysplastic and low-grade dysplastic esophageal Barrett metaplasia (ESOBM-nd, ESOBM-lgd) and esophageal adenocarcinoma (ESOAD) were from [15] (<http://www.ebi.ac.uk/arrayexpress/>; E-MTAB-4054).

Mouse RNAseq data processing

For mouse RNAseq processing, raw RNAseq reads were quality checked with the FASTX toolkit (http://hannonlab.cshl.edu/fastx_toolkit/index.html) and mapped with STAR [16] against the mouse reference genome GRCm38. Levels of transcripts were computed with HTSeq [17] in union mode, normalized by a regression model with DESeq2 [18] and the consistency of biological replicates was tested by hierarchical clustering [18]. Aberrant levels of transcripts were identified with the Cook distance. Levels of transcripts were normalized by calculation of reads per kilobase per million if no replicate was available. The p -values computed with the Wald-test were adjusted with the Bonferroni multiple testing method. Differentially-expressed genes (DEGs) were selected according to the adjusted $p < 0.05$ and the $|\log_2(\text{Fold-Change})| > 2$, and a core of common DEGs was created by comparison among databases. Human orthologues of the mouse DEGs core were identified based on a confidence score of 1 or a minimal sequence homology of 30%, as previously described [19]. Enriched biological functions (GO terms), signalling pathways (KEGG) and protein domains (InterPro) were tested with DAVID [20] and selected with $p < 0.05$.

Mouse ChIPseq data processing

Mouse ChIPseq reads were mapped with BWA [21] against the reference genome GRCm38. Peaks were processed with MACS2 [22] and the signal was normalized by computing fragment pileup per million reads. They were then selected according to $p < 0.05$ and a core of peaks was created by comparison among databases for peaks overlapping with at least 10-bp. Intergenic ChIPseq peaks were further compared to Super-Enhancers from the database dbSUPER [23].

DNA binding motifs analysis

All known DNA binding motifs of vertebrate transcription factors present in the core of ChIPseq peaks and in the gene promoters of the core of DEGs (defined as the 2-kb segment upstream of the canonical transcription start site(s) of each gene) were retrieved from the database JASPAR [24] and classified with TFclass [25]. Enrichments for transcription factor binding motifs was tested with HOMER [26] in the direct vicinity (± 50 bp) of mapped CDX-type binding motifs identified within the promoters of the DEGs and in the overlapping ChIPseq peaks. For this purpose, background sets of DNA sequences were created, composed of the same number of tested regions, i.e. promoters and overlapping ChIPseq peaks. The DNA sequences were of the same size as the tested regions and randomly extracted from the mouse reference genome GRCm38.

Human pathological samples analysis

For human pathological samples of COAD, STAD and AML, raw levels of transcripts were computed with HTSeq [17] and normalized by computing reads per kilobase per million in order to identify groups of high and low levels of *CDX2* transcripts. These groups were defined as upper and lower quartiles or deciles with a purpose of comparable size. For pair-wise comparisons of groups, raw levels of transcripts were

processed with DESeq2 [18]. Genes with significant variations in transcript levels were selected with adjusted $p < 0.05$ (Bonferroni multiple testing method). For ESOBM-nd, ESOBM-Igd and ESOAD, $|\log_2(\text{Fold-Change})|$ and p -value were retrieved from the literature [15]. Statistical tests for enrichment were performed with the one-tailed exact Fisher test.

Results And Discussion

A Core of Common Genes Responsive to Cdx2 during Mouse Development

To address if common genes are regulated by the Cdx2 transcription factor in its consecutive function during trophectoderm formation, posterior growth and intestinal fate determination in the mouse embryo, RNAseq data were compared between *Cdx2*-overexpressing vs wild type ES cells [12,13], E8 *Cdx*-null vs wild type embryos [14] and intestinal epithelial cells of E16 *Cdx2*^{-/-} vs wild type embryos [11]. Using a $|\log_2(\text{Fold-Change})| > 2$ and a $p\text{-value} < 0.05$, a core of 221 common differentially-expressed genes (CDEGs) was identified between these 3 conditions, corresponding to 162 orthologue genes in human (Fig. 1a, Additional file 1.1). Interestingly, the direction of the expression changes of the CDEGs, either up or down, was not always similar at the 3 developmental steps, suggesting a context-dependent response to Cdx2 (Fig. 1b, Additional file 1.2). Term enrichment analysis performed on these 162 human orthologues revealed a significant association with “extracellular exosome”, “extracellular matrix”, “multicellular organism development”, “sequence-specific DNA binding”, “gene regulation”, “metabolic process” and “Wnt signaling” (Fig. 1c, Additional file 1.3). Twenty-eight genes among the 162 orthologues encode nuclear proteins involved in chromatin conformation, DNA transcription and repair, of which 11 are homeobox genes (underlined): *Arid3a*, *Bmyc*, *Cdx1*, *Cdx2*, *Commd3*, *Ets2*, *Gata4*, *Hmgn3*, *Hoxb1*, *Hoxb5*, *Hoxc5*, *Hoxc6*, *Hoxc8*, *Id2*, *Id3*, *Nkx1.2*, *Pbx1*, *Prickle1*, *Prr13*, *Pitx1*, *Rcor2*, *Smarca1*, *Sox2*, *Sp5*, *Tbx4*, *Tfeb*, *Tlx2*, *Znf503*.

A Core of Common Chromatin Regions Bound to Cdx2 during Mouse Development

Next, we compared the location of the Cdx2 protein on chromatin by ChIPseq at the three developmental steps [11,13,14]. This analysis resulted in a core of 1047 common chromosomal regions sharing overlapping peaks in the three conditions (Fig. 1d). Among these peaks, 265 were associated with protein coding genes, 466 with gene promoters (defined as the 2-kb segment upstream of the transcription start site), 52 with non-protein coding genes and their 2-kb promoter, and 264 with intergenic regions (Additional file 1.4). Eight genes of the core of DEGs (*Arid3a*, *Epha4*, *Hoxc6*, *Man1c1*, *Mgat1*, *Mid1ip1*, *Sgsm1*, *Tfeb*) exhibited conserved Cdx2 ChIP peak(s) in their 2-kb promoter or coding sequence. This relative low number of CDEGs linked to adjacent Cdx2 ChIPseq peak(s) suggests that important regulatory elements targeted by Cdx2 might be located far away in intergenic regions. In line with this, 75/264 (28.41%) of the intergenic Cdx2 ChIPseq peaks fell into Super-Enhancer domains (Additional file 1.5). Alternatively, Cdx2 may have both inductive and permissive transcriptional effects, thus uncoupling direct transcription activation from DNA binding, as reported in the gut epithelium [27–29]. Finally, it has

also been shown that Cdx2 controls the expression of several downstream targets by interacting with other DNA-binding proteins, without the presence of a typical Cdx-type binding site [30,31].

Sequence analysis showed that 835 of the 1047 ChIPseq regions (77.75%) harbored at least one analogous motif to the functionally-described consensus Cdx-binding site (Fig. 1e) [32], giving a total of 1801 Cdx-type sites (p -value = 10^{-152}) (Additional file 1.6). Similarly, 214 promoters of the 221 CDEGs (96.83%) identified above exhibited at least one consensus Cdx-type binding site for a total of 1314 sites (Additional file 1.6). Interestingly, the +/-50-bp segments around the Cdx-type sites present in the ChIPseq regions and in the promoters of the CDEGs were enriched in DNA-binding motifs for respectively 149 transcription factors grouped into 25 families and 74 transcription factors grouped into 11 families (p -value < 0.05) (Fig. 1f, Additional files 1.7 and 1.8). The proximity of enriched binding sites for these transcription factors and for Cdx2 suggests possible direct or indirect interactions.

Fate of the Core of Common CDEGs in Human Pathologies

Having established the core of 221 CDEGs during mouse embryonic development, we examined human diseases exhibiting alterations in the *CDX2* transcript levels for the proportion of the 162 human orthologues deregulated in these pathologies (Fig. 1g, Additional files 2.2). Firstly, given that the *CDX2* expression is physiologically limited to the intestine at the adult stage and that it is decreased in a subset of colon adenocarcinoma, we compared the transcriptomes in the deciles of tumors exhibiting the lowest vs highest *CDX2* levels ($n=44$ each) within the TCGA collection of 436 colon adenocarcinoma (COAD). This revealed a significant number of 46 deregulated genes ($p=0.044$) (Fig. 1h, Additional file 2.3). Conversely, we considered pathological situations exhibiting an abnormal ectopic expression of *CDX2* outside the gut, namely in the upper digestive tract, i.e. the esophagus [15] and stomach (TCGA), and in acute myeloid leukemia (TCGA). Retrieving the list of differentially expressed genes between healthy *CDX2*-free esophageal mucosa and *CDX2*-expressing non-dysplastic Barrett metaplasia (ESOBM-nd, $n=14$), low-grade dysplastic Barrett metaplasia (ESOBM-lgd, $n=8$) and adenocarcinoma (ESOAD, $n=12$) revealed respectively 123 ($p=0.16 \times 10^{-73}$), 118 ($p=0.21 \times 10^{-64}$) and 116 ($p=0.96 \times 10^{-44}$) orthologues of the CDEGs core (Fig. 1g,h, Additional files 2.4-6). In the stomach, the list of differentially expressed genes in the quartiles of adenocarcinoma presenting the highest vs lowest levels of *CDX2* ($n=35$ each) within the series of 272 STOAD samples comprised 44 CDEGs of the core ($p=0.0028$) (Fig. 1g,h, Additional file 2.7). Similarly, 35 core DEGs ($p=0.14 \times 10^{-4}$) were recovered among the genes differentially expressed between the quartiles with the highest vs lowest levels of *CDX2* ($n=38$ each) in the series of 151 AML (Fig 1g,h, Additional file 2.8). Altogether, these data indicate that a significant proportion of genes of the core defined on the basis of mouse developmental models are differentially expressed in human diseases along with *CDX2* changes. This proportion was higher when comparing lesions with normal tissues (here, the various types of esophageal lesions) than when comparing tumor samples among them in each pathology (here, colon cancers, stomach cancers and leukemia) because of the variable nature of the specimen in the latter cases.

Conclusion

The combinatorial analyses of data from mouse embryonic developmental have identified cores of common differentially-expressed genes and chromatin regions responsive to the Cdx2 homeoprotein at three steps where this transcription factor plays pivotal roles: trophoctoderm differentiation, posterior growth of the embryonic body and intestinal determination. Similar functions are anticipated for the *CDX2* gene in human embryonic development, because of its specific expression in the trophoctoderm lineage at the blastula stage [35], the association of gene mutations with sirenornelia [33], and its abnormal expression linked to gut-type differentiation in congenital endoderm-derived lesions [34]. Beyond embryogenesis, the current results highlight that a significant number of genes of the DEGs core identified in mouse embryos are deregulated in human diseases along with *CDX2*, which strengthens the relevance of the core in pathologies involving this important developmental gene. Nevertheless, the direction of the changes of several genes of the CDEGs core is not the same at all three developmental stages and also in pathological situations, which emphasizes the context-dependent activity of the *CDX2* transcription regulator (Fig. 1b). It can be seen in the light of its anti-repressing effect preventing the incursion of inactive chromatin marks into chromatin domains to keep them accessible for other transcription partners [28,29]. Therefore, the outcome of *CDX2* might depend not only on the chromatin domains that are kept open, but also on the specific repertoire of nuclear partners present in the cells and able to access the open chromatin regions. Altogether, this study supports the notion that a transcription regulator, while playing distinct functions at different steps during embryonic development, can exert a common subset of molecular activities, and that some of these activities can be subsequently deregulated in adult pathologies along with this factor. This combinatorial approach opens ways to investigate novel functional interactions between developmental genes and to exploit them in a therapeutic perspective.

Abbreviations

AML: acute myeloid leukemia

CDEGs: common differentially expressed genes

Cdx2: Caudal-related homeobox-2

ChIPseq: chromatin immunoprecipitation sequencing

COAD: colon adenocarcinoma

ESOBM-lgd: low grade dysplastic esophageal Barrett metaplasia

ESOBM-nd: non-dysplastic esophageal Barrett metaplasia

RNAseq: whole transcriptome sequencing

STAD: stomach adenocarcinoma

Declarations

Ethics approval and consent to participate

Not applicable. This work used public data.

Consent for publication

Not applicable. This work used public data.

Availability of data and materials

The datasets used for this work are available in public databases:

GEO database (<https://www.ncbi.nlm.nih.gov/geo/>)

The Cancer Genome Atlas (<https://www.cancer.gov/tcga>)

The EBI ArrayExpress (<http://www.ebi.ac.uk/arrayexpress/>).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

J.N.F., V.G., I.D. and C.D-D. conceived the research, analyzed the data and wrote the manuscript; V.G. performed the bioinformatics analyses.

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Figures

orthologues. ** $p < 0.01$, *** $p < 0.001$ (Additional file 1.3). (d) The 1047 common Cdx2 ChIP regions during trophoctoderm formation (blue), embryonic posterior elongation (yellow) and gut specification (green) (Additional file 1.4). (e) Consensus sequence of the Cdx-type motifs present in the Cdx2 ChIP regions and in the promoters of the CDEGs (Additional file 1.6). (f) Enrichment in consensus binding motifs for the indicated transcription factors families in the vicinity (± 50 bp) of the Cdx-type sites present in the 1047 ChIP regions (yellow) and in the promoters of the 221 CDEGs (blue). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.00001$. HD: homeodomain; Zf: zinc finger; h: hormone (Additional files 1.7-8). (g) Differentially expressed genes in colon cancers (COAD), in esophageal non-dysplastic Barrett metaplasia (ESOBM-nd), low-grade dysplastic Barrett metaplasia (ESOBM-lgd) and adenocarcinoma (ESOAD), in gastric adenocarcinoma (STAD) and in acute myeloid leukemia (AML); each spot corresponds to one gene; up: yellow, down: blue (Additional file 2.2). (h) Number of human orthologues deregulated along with CDX2 in the indicated diseases. * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$ (Additional files 2.3-8).

Supplementary Files

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