Downregulation of genes in psoriatic patients and the emergence of certain cancers

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Abstract

The up- and down-regulation of gene expression, enzyme activities, and cell signaling systems are just some of the major biological processes taking place in cells. They depend on intrinsically emerging protein circuits that react to a particular signal. Most of these events are reversible, and numerous feedback loops control them. Whenever there is a disruption in any of these mechanisms or loops, it leads to the development of diseases and comorbidities. In this presentation, we have uniquely taken sixty-two genes from prior examinations and enriched them through gProfiler. Besides, ChEA3 was used to find out the transcription regulators for them. A couple of downregulated genes, CRIP1 and ID4 were enriched in the GO BP of gProfiler. Their downregulation revealed the possibilities of restricted cancer in the gastric, colorectum, prostate gland, and breast as comorbidity. SMAD9 and GLIS3 are the two topmost regulators of ID4 transcription among the ten profound regulators clustered.

Keywords – Enrichment, CRIP1, ID4, downregulation, cancers.

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Introduction

Comorbidity, which can be studied using either the “one’s time” or the “present” strategy, is the occurrence of multiple disorders in an individual throughout a certain time frame. Addiction issues and mental illnesses frequently co-occur, and this is the case rather than the norm. When compared to adults, teenage comorbidity incidences are larger (Essau, 2020). Comorbidity is related to less favorable clinical prognoses, greater difficulty in clinical monitoring, and higher medical expenses (Valderas et al., 2009). The management of people with many concomitant illnesses, who are today more common than unusual, is something that healthcare has to concentrate on (Starfield, 2006). The lack of agreement on how to conceptualize and evaluate the notion makes it challenging to determine the effects of comorbidity (Fortin et al., 2007).

Psoriasis patients are more prone to develop comorbidity, for instance, various types of locus-oriented cancers in non-melanoma skin, lung, and lymph as well as general cancers. Quite certainly, a blend of psoriasis's persisting substandard inflammation, the condition's hazardous agents for cancer, and its therapy are to cause the elevated incidence. It's also critical to assess and look into if the several, novel medications to immunomodulate psoriasis that have been developed in modern years have an elevated risk of malignancies. Finally, if psoriasis patients have the habit of consuming excess alcohol, smoke higher, and are more obese than the average demographic group, encouraging them a balanced lifestyle is essential for the reduction of multiple types of cancer. Investigating the

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role of the various mechanisms of comorbidity in psoriasis sufferers should be the subject of future studies (Loft et al., 2020).

g:Profiler, an open-source web interface that allows users to represent and work with the gene sets (Raudvere et al., 2019). The database of gene sets can be acquired now as a GMT format, and the interface is continuously kept up to date. Fisher's exact test and a modified Fisher's test are used by g:Profiler to assess and arrange genes in sets. It allows access via the coding languages, Python and R (Reimand et al., 2019). The software features an easy-to-use online format and contains excellent visual displays. It is presently accessible for more than four hundred species (Raudvere et al., 2019). Taken together, in this evaluation, the over- and down-expressed genes from quaternate research teams collected from psoriasis patients were contemplated to learn about the likelihood of comorbidities (Zhou et al., 2003; Yao et al., 2008; Gudjonsson et al., 2010; Suárez-Fariñas et al., 2010). The DEGs were pasted and enriched by being submitted to this g:Profiler site to gain a deeper comprehension of the comorbidities involved in the sufferers.

Materials and methods

In the g:Profiler platform, we have submitted the residual 62 DEGs from early experiments in the query box (Zhou et al., 2003; Yao et al., 2008; Gudjonsson et al., 2010; Suárez-Fariñas et al., 2010; Raudvere et al., 2019). The level of significance, α was 5% to screen the GO and pathways involved (D and Anand, 2022). The annotated DEGs from GO BP were then pasted in the ChEA3 query box to identify the TFs regulating them with a score less than 100 in the MeanRank table (Keenan et al., 2019).

Results

To identify the function of the DEGs, they were incorporated into the gProfiler. Unexpectedly, there was an absence of GOMF and pathways. CRIP1 and ID4 are the two DRGs that were annotated in GO BP (Table 1). They are connected with the prostate gland stromal morphogenesis (PGSM) (GO:0060741).

Table 1: Distribution of DEGs in the cellular compartments and PGSM process

GO term name	GO term ID	Adj p-val	DEGs	
			URGs	DRGs
PGSM	GO:0060741	0.0402	Nil	CRIP1, ID4
Extracellular region (ECR)	GO:0005576	0.0010	CHI3L2, CLCA2, FCGR3B, FGFBP1, GBP1, GDPD3, GGH, GK, GM2A, HPSE, KLK10, KLK13, LIPG, PDZK1IP1, PLBD1, PRRG4, S100A12, SERPINB1, SERPINB13, SLC6A14, STEAP4, TCN1, TMPRSS11D	CA6, CCL27, NRN1, PIP, SCGB1D2
Extracellular space (ECS)	GO:0005615	0.0046	CHI3L2, FCGR3B, FGFBP1,GDPD3, GGH, GK, GM2A, HPSE, KLK13, LIPG, PDZK1IP1, PLBD1, S100A12, SERPINB1, SERPINB13,SLC6A14, STEAP4, TCN1,TMPRSS11D	CA6, CCL27, PIP, SCGB1D2

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Vesicle	GO:0031982	0.0068	FCGR3B, GBP1, GCH1, GDPD3,GGH, GK, GM2A, HPSE, HYAL4,KLK10, KLK13, LAMP3, LIPG, PDZK1IP1,S100A12, SERPINB1, SERPINB13, SLC6A14, STEAP4, TCN1, TMEM165, TMPRSS11D	CA6, PIP, ZDHHC11
Secretory granule (SG)	GO:0030141	0.0267	FCGR3B, GGH, GM2A, HPSE, KLK10, KLK13, LAMP3, S100A12, SERPINB1, TCN1	Nil
Endomembrane system (EMS)	GO:0012505	0.0448	CLCA2, EHF, EPHX3, FCGR3B, GBP1, GCH1, GDPD3, GGH, GM2A,HPSE, IFI27, KLK10, KLK13, LAMP3, LIPG, RSAD2, S100A12, SERPINB1, STEAP4, TCN1, TMEM165, TRIM22	CRAT, FA2H, ITM2A, ZDHHC11

About the GO CC terms, ECR (GO:0005576), ECS (GO:0005615), vesicle (GO:0031982), SG (GO:0030141), and EMS (GO:0012505), there were annotated 23, 19, 22, 10, and 22 URGs along with 5, 4, 3, 0, and 4 DRGs. In total, 32 URGs and 9 DRGs were enriched under this category. In the case of GO BP, only two DRGs have got annotated. Out of 62 DEGs, 43 genes were mapped in gProfiler. Since the DEGs were located in different regions of the cell, the DEGs involved in GO BP were extracted and uploaded to find the TFs governing them.

When the score was below 100, there filtered 10 TFs in the ChEA3 tool (Table 2). Seven TFs were annotated with ID4 regulation whilst the TFs, PRDM16 and HEY2 have been annotated with both the DRGs. ANHX didn't annotate any input DEGs. However, the TF with the lower score is considered important (Keenan et al., 2019). The fact that SMAD9 has a lower score than the other TFs on the list makes it a crucial regulator.

Table 2: TFs of ID4 and CRIP1 genes

Rank	ChEA3TF	Score	Libraries	Coinciding DRGs
1	SMAD9	38.33	AC,8;EQ,73;GC,34	ID4
2	GLIS3	70.67	AC,5;EQ,180;GC,27	ID4
3	FOXE1	72.67	AC,38;EQ,151;GC,29	ID4
4	PRDM16	74	LC,154;AC,33;EQ,108;GC,1	ID4,CRIP1
5	DACH1	80.67	LC,92;AC,28;EQ,122	ID4
6	IRX2	81.33	AC,22;EQ,86;GC,136	ID4
7	HEY2	83.33	AC,17;EQ,214;GC,19	ID4,CRIP1
8	SP8	84	AC,42;EQ,92;GC,118	ID4
9	ANHX	99	AC,123;GC,75	-
10	LHX1	99.5	AC,150;EQ,49	ID4

*AC - ARCHS4 Coexpression, EQ – Enrichr Queries; GC – GTEx Coexpression, LC – Literature ChIP-seq.

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SMADs comprising SMAD1 to 9 proteins are vital to signal TGF within cells. A linker region joins the intact N- and C-end of SMADs having MH1 and MH2 motifs respectively. At the C-end of R-SMADs, the MH2 motif possesses either ser-met-ser or ser-val-ser residues, which are phosphorylated by type I receptors. SMAD9 alongside SMAD1/5 are phosphorylated by osteogenic BMPs. Even though all three SMADs were connected with SMAD4 and adhered to the specific DNA, SMAD9 had poorer transcriptional efficiency than SMAD1/5. SMAD9's linker region was enough to lower this function (Tsukamoto et al., 2014).

Discussion

A pair of DRGs namely CRIP1 and ID4, from the GO BP annotational study, is confined here for a brief discussion since there were any known pathways annotated for the uploaded DEGs.

Relying on the gene expression profiles, the pericytes in the testis divide into two discrete subgroups each of which may be peculiarly classified as either fibroblastic (f-pericytes) or muscular (m-pericytes) in nature. While f-pericyte markers like CD44, CD36, and ITGA1 are found in the cells surrounding blood vessels as well as in the interstitial space, certain m-pericyte markers including CRIP1, ADIRF, and MCAM are predominantly confined to cells around blood vessels according to the human protein atlas. Compared to f-pericytes, the transcriptome data of m-pericytes was strongly associated with those of myoid and juvenile Leydig cells. On this account, distinct cells inside the testis may give rise to f- and m-pericytes (Shami et al., 2020). This information is indirectly associated with our CRIP1 annotation in GO BP.

In the intracellular environment, CRIP1 was initially identified as a Zn^{2+} uptake and vehicular protein (Fernandes et al., 1997). Belonging to the LIM/double-Zn^{2+} finger family of protein, it has a solitary form of the LIM motif, a cysteine-abundant region (Levenson et al., 1993). It is mostly seen in the intestine and possesses an exclusive, dual Zn^{2+} finger domain (Ludyga et al., 2013; Liu et al., 2021). The findings of the transcriptomes enclosed in the meta-analysis of oxidative stress highlighted the downregulation of CRIP1 and CRIP3 genes from the human cultured cells, suggesting a relationship between oxidative stress and Zn^{2+} equilibrium (Suzuki et al., 2021). Furthermore, CRIP was found in immune cells namely macrophages in the peritoneum and mononuclear cells of peripheral blood, which may indicate that it is engaged in host immunological signals (Cousins and Lanningham-Foster, 2000). Rather than possessing the usual TATA and CAAT sequences, its promoter's proximal end carries GC-rich sites that possibly trigger transcription (Levenson et al., 1993). Besides, it has binding regions for GATA-2, Sp1, IL-6, TNF-α, and many glucocorticoid response elements (Cousins and Lanningham-Foster, 2000). Under in vitro contexts, lower expression of CRIP1 accelerated cellular growth and invasion in the BC cell lines, BT474 and T47D via activating the MAPK, Akt, and Cdc2 signaling pathways (Ludyga et al., 2013). Also, in gastric cancer cells, CRIP1 decreased expression results in a deficit to restore homologous recombination, which improves the susceptibility of the cells to epirubicin, cisplatin, and olaparib (Sun et al., 2021).

In humans, there exist quadruple Id molecular proteins such as Id1, Id2, Id3, and Id4 (Norton et al., 1998). Markedly, the exon-intron borders inside the coding portions of these genes have an almost identical genomic architecture, which is stable with an adaptation from a shared ancestor (Deed et al., 1994). ID3 and ID4 gene expressions are unitedly discrete in the growing brain (Riechman and Sablitzky, 1995). Id3 is only found in the telencephalon's

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posterior wall, which is where the hippocampus develops, and Id4 is limited to the telencephalic vesicle's frontal and parietal cortex. Mysteriously, neurons of certain sensory organs and some of the peripheral nervous system produce Id2 and Id4 (Riechman and Sablitzky, 1995; Jen et al., 1997). Id4 may modulate the multiplication and differentiation of neural stem cells to be necessary for appropriate brain mass and side-wise extension of the mitotic area in the embryonic cortical and hippocampal areas (Yun et al., 2004).

Id proteins are distinguished by the presence of a dimerization domain consisting of a helix-loop-helix (HLH) structure. The domain sticks to the basic HLH (bHLH) region, which is found widely in TFs. In general, bHLH TFs form complex with tissue-specific bHLH TFs. They ultimately bind to promoters possessing E-box and enhance their gene transcription. The absence of the fundamental DNA-binding region makes the Id proteins contrast from bHLH TFs. Thus they bind to widespread bHLH TFs, preventing them from engaging in transcription. Neuronal NeuroD and neurogenin as well as Muscle MyoD, are examples of tissue-specific bHLH TFs. Id proteins hamper the transcription of these genes by binding to their specific bHLH TFs leading to the repression of neurogenesis and myogenesis. These studies imply that Id proteins may be a potential mediator by which various biological functions of BMPs are elicited (Miyazawa et al., 2002).

When precursor cells of oligodendrocytes were induced to divide rapidly by removing PDGF, there was an astounding interdependence between the amount of Id4 reduction and the degree of oligodendrocyte growth. The transcription process regulates the amount of Id4 protein since Id4 mRNA and protein quantities decline concurrently in these proliferating cells and both diminish fastly at 33°C (Kondo and Raff, 2000). Through a negative feedback loop, Mash1, one of the bHLH proteins binds to the several E-box found in the promoter sequence of the ID4 gene and thereby increases transcription (Pagliuca et al., 1998; Kondo and Raff, 2000). An additional study reported the downregulation of ID4 to promoter HMN. This substantial relationship was linked since the upstream region of the ID4 promoter was formerly charted and has a thick 5' CpG zone spanning it. HMN in the ID4 promoter was demonstrated in 30% of original tumors and majorly in the cell lines of gastric cancer. Moreover, these circumstances were associated with a drop in Id4 synthesis. It was made clear how closely ID4 and HMN were related in the hMLH1 promoter. In tandem with it, one of the genes that the tumor-promoting CpG area HMN signal may be focusing on is ID4 (Chan et al., 2003).

Colorectal adenocarcinoma has significant concentrations of Cdc42, which suppresses ID4 with an epigenetic approach (Gómez del Pulgar et al., 2008). In prostate cancer, consistent downregulation and moderate HMN of ID4 were examined (Vinarskaja et al., 2012). Further research is being done on reduced Id4 synthesis in ER+ BCs. Gene expression, epigenetic regulation, and clinical information from the TCGA are viewed and analyzed using MEXPRESS, an insilico tool. When BCs turn ER+, the methylation frequencies rise, indicating that methylation in the CpG zone of the ID4 promoter interrupts its expression. This depicts that ID4 downregulation upsets the usual homeostasis of crucial ER signaling genes (Nasif et al., 2018). In BC cell lines namely MDA-MB-231 and MCF-7/Adr, decreased Id4 dramatically reduced cell growth and migration, but elevated adriamycin vulnerability. Id4 operates in that way by activating over the CBF1-MRP1 pathway, coupled with MyoD1 (Zhang et al., 2020).

Id4 is reported to be needed further for both the regeneration of SSC (Oatley et al.,

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2011) and the p38MAPK-mediated formation of the mammary gland (Dong et al., 2011). During the formation of the postnatal testis, GLIS3, a key regulator is only produced in gonocytes and immature spermatogonial cells of mice. Most notably, GLIS3 defective animals have severely compromised spermatogenesis. ID4, the marker gene of SSC is less produced. The movement of FOXO1 TF into the nucleus which is crucial for self-renewal of SSC and the gonocyte to SSC transition is blocked. This suppresses the conversion of gonocytes to SSC. All of these facts point to GLIS3 being essential for spermatogenesis to occur normally (Kang et al., 2016). Continuously more, an investigation showed that GLIS3 in mouse embryos is involved in the generation of male sex-type germ cells. In the limited period before the start of piRNA-mediated retrotransposon monitoring, the regulator is produced in male germ cells. Its dysfunction resulted in a drastic loss of retrotransposon-silencing factors, abnormal retrotransposon production, and substantial germ cell destruction. Thus, GLIS3 plays a significant function in the development of the fetal testis due to the specific pattern of production it exhibits in embryonic testis (Ungewitter et al., 2018). In our findings, GLIS3 has been annotated as one of the TF for ID4, whose downregulation might be evident from the aforesaid experiments because of its dysfunction.

Conclusion

According to the findings, gastric cancer, colorectal adenocarcinoma, prostate cancer, and BC are among the malignancies related to CRIP1 and ID4 downregulation. In addition, decreased ID4 expression and GLIS3 malfunction inhibits spermatogenesis and embryonic testis in mice models. On the one hand, the appropriate lead molecules that can optimize the synthesis of these DRGs must be developed to optimize the activity of the male propagative apparatus and to decrease the occurrence of certain cancers. On the other hand, the incidence of malignancies as a comorbidity in psoriasis patients must be recognized and treated appropriately based on gender.

Abbreviations

BC – breast cancer, BMPs – bone morphogenetic proteins, DEGs – differentially expressed genes, DRGs – downregulated genes, ER+ – estrogen receptor-positive, HMN – hypermethylation, PDGF – platelet-derived growth factor, SSC – spermatogonial stem cells, TGF – transforming growth factor, TF – transcription factor, URGs – upregulated genes.

Conflict of Interest

None.

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