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Short Communication

Does GATA3 act in tissue-specific pathways? A meta-analysis-based approach

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Abstract

The GATA3 transcription factor is expressed in many tissues such as the immune system, kidney, brain, endometrium, and mammary epithelial cells. As such it must co-ordinate a diverse transcriptional program to achieve specific outcomes in different tissues. One of the most interesting questions raised is whether GATA3 will be involved in the same pathways in every tissue or will be involved in distinct regulatory networks within different tissue types? While previous studies may imply the latter, with some known targets of GATA3 perhaps being specific to cell-type or tissue-type, the question has not been systematically addressed until now. With the advent of techniques such as co-expression meta-analysis a better understanding of the pathway partners of GATA3 can be obtained and specifically the partners within different tissue types can be found, yielding leads for future studies. Here, a recent technique of meta-analysis from the Oncomine database has been employed to probe this very question. Data obtained implies that GATA3 is involved in distinct pathways in different tissue types.

Keywords: GATA3, meta-analysis, tissue-specific, transcription, co-expression, p63

Introduction

The GATA3 transcription factor has been studied intensively in the immune system, but has most recently been shown to be important in the context of breast cancer and the estrogen receptor α pathway.[1,2] These and many other studies have shown the power of linking breast cancer co-expressed gene datasets of GATA3 to its ability to play a putative role in the luminal A subtype of breast cancers, while also having a physiological role in normal breast epithelial cells. Recently, it has been proposed that GATA3 might act differently in different tissues.[3] As meta-analysis of GATA3 co-expressed genes in breast cancers, from the Oncomine database, yielded data that was analogous to previously known studies, it was possible that this technique could also be utilized to show tissue-specific (or common) pathways of GATA3.[4]

Consistent co-expression of genes has been shown to link their protein products to the same pathways, although it is impossible to determine the nature of this association (e.g., upstream, downstream, together in a complex) without further study. What this does generate, however, are rich leads into previously unknown or undefined areas for study.

The Oncomine meta-analysis technique[4–6] was employed using various studies of different types (leukemia, lymphoma, brain, kidney, and prostate studies), all of which have been previously observed to show GATA3 expression. Co-expressed genes of GATA3 were then assessed within these cancer/tissue-types and are described below. Finally, the gene lists generated for individual analyses were compared to assess common co-expressed genes over multiple tissues. Tentative results indicate that GATA3 may be involved in distinct pathways in different tissue-types, confirming the initial hypothesis. A prime example of this is the estrogen receptor alpha (ERα) pathway in breast cancer studies,[4] where ERα is the highest co-expressing gene

with GATA3, whereas in the other cancer types investigated, this high level of co-expression was not evident, thereby indicating that the ERα pathway need not play a significant role for GATA3 in every situation.

Co-expression Meta-analysis of Leukemia Studies

GATA3 expression has previously been observed in leukemia cells, however, the role GATA3 may play has not been intensively investigated, leaving a need for new knowledge.[7] The highest co-expressing gene with GATA3 in leukemia meta-analysis was the T-cell receptor (TCR) alpha locus (*TRA@*), in over 60% of studies [Additional File 1]. This is confirmation of a previous report that demonstrated GATA3 binding to the TCR-alpha enhancer.[8] Similar to this, the TCR-delta locus (*TRD@*) was also co-expressed with GATA3 and has also previously shown to be bound by GATA3.[9,10] Both of these results act as initial validation of the meta-analysis technique. As might be expected, there was an abundance of immunological co-expressed genes such as these. Interleukins and their receptors (*IL32*, *IL27RA*, *IL2RB*, *IL10RA*, *IL7R* and *IL15*), other T-cell receptors and associated factors (*TRBC1*, *TRAT1*, *LAT*, *CD3D*, *CD3E*, *CD3G*, *TARP*, *ICOS*, *MAL*, *TRGV9*, *TRGC2* and *PTCRA*), and granzyme proteases (*GZMA*, *GZMB*, *GZMK* and *GZMM*) are just some notable examples of the many immune genes represented.

As GATA3 has been intensively investigated in an immunological context for many years, especially with regard to T-cells, these data may help to shed light on the role GATA3 plays, albeit by implication via these co-expressed genes. For example, the granzyme proteases have been shown to be involved in cell-death pathways, regulated by cytotoxic T-cells and natural killer cells.[11]

Co-expression Meta-analysis of Lymphoma Studies

As lymphomas are also derived from the cells of the immune system, it is no surprise that the co-expressed genes with GATA3 have a significant overlap with those of the leukemias. For example, the interleukins and receptors (*IL15*, *IL15RA*, *IL7R*, *IL2RB*, *IL32*, *IL1R1*, *IL3RA*, *IL1R2*, *IL18R1*, *IL13RA1* and *IL10*) show overlap with 4 of the 6 co-expressed for leukemias [Additional File 2].

Chemokines and receptors are also notably co-expressed with GATA3 in lymphomas (*CXCL10*, *CXCR6*, *CXCL9*, *CXCL11*, *CXCL12* and *CXCL13*) as are the members of the STAT transcription family (*STAT1*, *STAT3*, *STAT4*, *STAT5A* and *STAT5B*). It is of interest that GATA3 has previously been observed to co-operate with STAT5A in naïve CD4 T-cells to prime towards a Th2 phenotype, emphasizing its role in differentiation.[12]

Co-expression Meta-analysis of Brain Studies

GATA3 has been seen to be important in the development of the mammalian brain, with *Gata3 -/-* mice displaying severe brain and nervous system abnormalities.[13] GATA3 was also shown to be downstream of GATA2.[14,15] More recently, however, it was shown that the role of GATA3 in neonatal (i.e. post-development) mouse brain is limited.[16]

It is possible that in conditions such as brain tumors the cancer will be in a de-differentiated state, thus expressing more developmental proteins such as GATA3. The highest co-expressing gene with GATA3 in Oncomine brain studies was the Disco Interacting Protein 2, homolog C (*DIP2C*) [Additional File 3]. While this remains little-studied, it is interesting to note that dip2 is expressed in the mouse nervous-system.[17] Of interest, the neurofibromin 2 (*NF2*) gene is strongly expressed in the developing brain[18] and is involved in schwannomas[19] and is here also co-expressed with GATA3 in Oncomine brain studies. Whether GATA3 plays a role in schwannomas remains to be investigated.

Co-expression Meta-analysis of Kidney Studies

The hypoparathyroidism, sensoneural deafness, and renal abnormality (HDR) syndrome in humans is linked to haploinsufficiency of GATA3.[20–22] GATA3 is also expressed in developing human and mouse kidneys.[23,24] Specifically, GATA3 was shown to be important for the development of the nephric duct.[25] These data show a requirement for GATA3 to be expressed within renal tissues.

For meta-analysis, however, there were a limited number (9) of Oncomine renal studies with co-expressing genes for GATA3. Even so, many highly co-expressing genes were observed such as *KCNJ1 (ROMK),* which is seen with GATA3 in over half of these studies [Additional File 4]. ROMK, as might be expected by its function as a potassium channel, is important to kidney function.[26,27] Furthermore, GATA3 co-expressed with many other transporters (*SLC7A8*, *SLC19A2*, *SLC12A1*, *SLC7A7*, *SLC27A2*, *SLC26A7*, *SLC29A2*, *SLC25A33*, *SCN3A*, *SCN2A*, *KCNK10*, *KCNJ15*, *KCNJ10*, *CLIC5*, *CLCNKA*, *CLCNKB*, *CACNG4*, *ATP1A1*, *ATP6V0A4* and *AQP2*), possibly implying a GATA3 pathway in the kidney. There was also a modest co-expression with renin (*REN*), which as part of the renin-angiotensin system is one of the key genes of the kidney.

Co-expression Meta-analysis of Prostate Studies

The role of GATA3 in the prostate is the least studied of all tissues presented. In contrast, however, there were many (17) Oncomine studies with co-expressed genes for GATA3 [Additional File 5]. In a recent study of candidate prostate cancer genes, GATA3 was identified and confirmed by immunohistochemistry.[28] This report showed that GATA3 expression is normally low in normal prostate, perhaps explaining why it has not yet been studied to any significant degree. However, as Oncomine studies are based on cancer, the data presented here might be most useful in analysis of GATA3 in prostate cancer. GATA sites were also shown to be important for full induction of prostate-specific antigen (PSA) in LNCaP cells,[29] while a different antigen, the prostate stem cell antigen (PSCA) is co-expressed with GATA3 in the meta-analysis.

As GATA3 is co-expressed with keratin 18 in breast cancers,[4] it is of interest that in prostate, GATA3 co-expressed with many other keratins (*KRT5*, *KRT7*, *KRT13*, *KRT14*, *KRT15*, *KRT17*, and *KRT23*). GATA3 was also co-expressed with transcription factors including p63 (*TP63*). The p63 protein is essential for the development of stratified epithelia in tissues such as the prostate and is highly expressed in proliferative epithelial stem cells.[30] GATA3 and p63 appeared to be overexpressed in urothelial cancers in a recent study combining microarrays and histochemistry, although this was not observed in prostate.[31] Other co-expressed transcription factors from the current meta-analysis include *SMARCD3*, *SMAD3*, *PDLIM3*, *PDLIM4*, *NR4A2*, *NR4A3*, *MEIS1*, *ZNF593*, *ZNF516*, *ZNF423*, *ZEB1*, *TFAP2A*, *TCF21*, *KLF6*, *KLF9*, *JUN*, *JUNB*, *ESR2*, *FHL1*, and *FHL2*.

Conversely to p63 the ZEB1 factor is involved in epithelial to mesenchymal transition in carcinogenesis, i.e., the de-differentiation of epithelial cells[32] and is a putative prostate cancer biomarker.[33] It remains to be investigated how GATA3 might interplay in prostate transcriptional networks with the aforementioned co-expressed factors. However, it is of interest that ZEB1 protein can bind *in-vitro* to a GATA3 gene silencer and can repress GATA3 in reporter gene assays, in the context of the Jurkat T-cell line.[34] While this needs to be shown in a more rigorous manner in an *in-vivo* context using, for example, chromatin immunoprecipitation of ZEB1 on the GATA3 regulatory element, whether this can also be shown in prostate is a point of significant interest.

pS2 (*TFF1*) is a co-expressed gene of GATA3 in breast cancers.[4] Interestingly, this was again seen to be the case in prostate cancers. The presence of prostate pS2 has previously been investigated, correlating with prostate hyperplasia and cancer.[35,36] Although it remains to be shown, it is possible that pS2 may then be a common target of GATA3 in both breast and prostate tissues.

However, the most frequent co-expressing gene with GATA3 was *TRIM29* (ATDC) in almost 60% of studies analyzed. ATDC was observed to be downregulated in cancers including prostate cancers,[37] and when transfected into cancer cells, ATDC reduced colony formation in soft agar,[38] which is suggestive of a tumor suppressive role.

Altogether, the genes listed in this meta-analysis may prove to be most useful in future studies of GATA3 in prostate, acting as a "road-map" of putative pathway-partners. For example, GATA3 might act in co-operation with p63 in epithelial cells, as GATA3 itself has been shown to be important for epithelial terminal differentiation, albeit in the context of mammary glands.[39,40]

Common GATA3 Co-expressing Genes

All of the previous meta-analyses were compared for common overlapping genes [Table 1]. As GATA3 co-expressed genes in breast cancer, using an identical technique, have already been reported,[4] the overlaps with these new meta-analyses are shown here in [Additional File 6].

As can be observed, only 10 genes were co-expressed with GATA3 in over 2 tissues (*TRA@*, *PDE4DIP*, *MAL*, *LCK*, *KRT7*, *HLA-DQB1*, *IL32*, *IL15*, *DPYD*, and *CHI3L2*). This low number reflects the concept of tissue-specific pathways of GATA3 regulation, supported by the types of genes co-expressed with GATA3 within the tissues themselves (e.g., immunological genes in leukemias and lymphomas, transporters in the kidney studies). Altogether, the data not only provide evidence that GATA3 may be involved in distinct pathways, but also reveal some of these pathway partners.

Conclusions

While the *in-silico* meta-analysis data presented can do no more than imply pathway partners of GATA3 in various tissues, the data presented can be considered as initial leads into future analysis. While an in-depth meta-analysis yields much data, it can only scratch the surface regarding putative pathways of GATA3. These data also strongly imply tissue-specific functions of GATA3, consistent with mounting evidence from the literature. How GATA3 can act in such a tissue-specific manner is an issue that has not yet been addressed, but likely to involve unique tissue-specific partners and post-translational modifications, controlling the functions of this transcription factor.

Table 1: Common co-expressed genes of GATA3 over different tissues

	Leukemia	Lymphoma	Kidney	Prostate	Brain
TRA@	✓	✓			✓
PDE4DIP	✓	✓	✓		
MAL	✓		✓	✓	
LCK	✓	✓		✓	
KRT7			✓	✓	✓
HLA-DQB1	✓			✓	✓
IL32	✓	✓		✓	
IL15	✓	✓		✓	
DPYD	✓	✓		✓	
CHI3L2	✓		✓	✓	
CCL4	✓	✓			
ZEB1				✓	✓
ZAP70	✓	✓			
WARS	✓	✓			
TSC22D1		✓		✓	
TRO	✓			✓	
TRIM22		✓		✓	
TRD@	✓				✓
TRBC1	✓	✓			
TRAT1	✓	✓			
TPM2		✓		✓	
TPM1		✓		✓	
TOP2A			✓		✓
TNFSF10		✓		✓	
TNFAIP2	✓			✓	
TMEM158	✓			✓	
TGFBR3	✓			✓	
TFAP2A			✓	✓	
TARP	✓	✓			
SVIL	✓				✓
STAT5B	✓	✓			
STAM	✓				✓
SQLE	✓		✓		
SPOCK2	✓	✓			
SORBS2				✓	✓
SH2D1A	✓	✓			
SEMA3C			✓	✓	
RTN1	✓	✓			
RGN			✓	✓	
RAB25			✓	✓	
QPRT	✓		✓		
PTPRF	✓	✓			
PTPRD	✓				✓
PTPN3	✓			✓	
PRSS23	✓			✓	
PRKCB1			✓	✓	
PRF1	✓	✓			
PKIA	✓				✓
PIP4K2A	✓				✓
PELO	✓	✓			
PEG10			✓	✓	
PARD3	✓				✓
NP			✓	✓	
NELL2	✓			✓	
MYCN	✓		✓		
MAST4	✓			✓	
MAP3K8		✓			✓
MAFB	✓	✓			
MAF	✓	✓			
LTBP1		✓		✓	
LEF1	✓	✓			
LAT	✓	✓			
KLRB1	✓	✓			
KLF6				✓	✓
KCNJ15			✓	✓	
JUN		✓		✓	
ITK	✓	✓			
ITGA1	✓			✓	
IL7R	✓	✓			
IL2RB	✓	✓			
IL1RL1			✓		✓
IFITM2	✓			✓	
IER3		✓		✓	
ID2		✓		✓	
HPGD	✓		✓		
HLA-DPA1	✓			✓	
HLA-B		✓		✓	
GZMK	✓	✓			
GZMB	✓	✓			
GZMA	✓	✓			
GSN	✓		✓		
GNPDA1	✓	✓			
GNLY	✓	✓			
GLS		✓	✓		
GBP1	✓	✓			
GAS1				✓	✓
GABARAPL1			✓	✓	
FYN	✓	✓			
FYB		✓	✓		
FLT3LG	✓	✓			
FGL2	✓			✓	
FER1L3				✓	✓
FAS	✓			✓	
EPS8		✓		✓	
EPHX2	✓		✓		
EPHA3				✓	✓
EPB41L3	✓			✓	
ENPP2	✓	✓			
ENG		✓	✓		
DUSP6		✓		✓	
DUSP4		✓		✓	
DMD	✓			✓	
DIP2C	✓				✓
DDR2		✓		✓	
CYP2B6		✓	✓		
CYP27A1		✓		✓	
CTSW	✓	✓			
CTSB		✓		✓	
COL4A3			✓	✓	
CLEC2B		✓		✓	
CG018		✓		✓	
CD8B	✓	✓			
CD8A	✓	✓			
CD7	✓	✓			
CD6	✓	✓			
CD5	✓	✓			
CD3G	✓	✓			
CD3E	✓	✓			
CD3D	✓	✓			
CD28	✓	✓			
CD247	✓	✓			
CD2	✓	✓			
CCR7	✓	✓			
CCND2		✓		✓	
CCND1		✓			✓
CCL5	✓	✓			
CAPN2	✓	✓			
CAMK4	✓		✓		
BCL11B	✓	✓			
ATF3		✓		✓	
ARL4C	✓	✓			
AQP3	✓			✓	
ANXA1	✓			✓	
ANK3	✓				✓
ANGPT1	✓			✓	
AKR1C2	✓				✓
AIF1	✓		✓		

Genes were compared over the different meta-analyses. ✓ shows that this gene is represented.

In conclusion, the data presented reveal many novel findings regarding putative pathways within which GATA3 might act and support the hypothesis that GATA3 acts in a tissue-specific manner, while retaining its common function in differentiation and development.

Additional material on web

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