Exploring if Wnt7B is part of the Canonical Wnt Signaling Pathway

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Abstract

The scientific community has yet to fully understand the pathway and function of a multitude of genes. One of which being Wnt7b. It is important that the scientific community strives to uncover programmed functions and pathways of genes like Wnt7b because in understanding basic biological systems more can be discovered about how genetic diseases and cancers work. Treatments for these can be made after understanding a gene's functions and pathways it's involved in. By looking for co-expression of genes closely linked to Wnt7b and genes known to be part of the Wnt canonical signaling pathway, I was able to find evidence that supports Wnt7b being part of the canonical signaling pathway. The most significant findings I revealed were a strong connection between beta catenin and Wnt7b suggesting dependency and co-expression of Wnt7b with genes known to be a part of canonical Wnt signaling pathway.

Introduction

The Wnt family of genes is one of the most essential families in the genome. The Wnt genes all play an important role in the Wnt signaling pathway. With proper regulation life will proceed in a healthy manner for multiple organisms: flies, mice, zebra fish, humans etc. The list goes on because the Wnt signaling pathway has been a crucial part of the evolution of multicellular organisms (Holstein, 2012). There are 19 known Wnt genes. The exact function and pathway of each one of the Wnt genes isn't fully known. Generally the Wnt genes play an important role in embryonic development (Ng, 2019), but there's limited information about specific family members function and role in Wnt signaling.
Understanding how a gene interacts with other genes and chemicals in a pathway gives major insights about how the gene functions. Wnt7b is one of the family member that lacks a distinct pathway. However, the scientific community has been able to identify a probable function for Wnt7b gene. Wnt7b is protein coding gene located on chromosome 15 (UCSC) responsible for cell death, differentiation, population proliferation; establishment of localization, immune system process, response to stimulus, signaling, and system development (MGI). Wnt7b's regulator gene is FoxB2 (Koch, 2021). It is well known that the Wnt genes can only signal through three pathways (Schubert, 2013), one canonical and two non-canonical. For clarification, there are two types of Wnt signaling pathways: canonical and non-canonical. In summary, the canonical pathway is beta catenin dependent and the non-canonical functions dependent of beta catenin (Ng, 2019). There is currently no conclusive knowledge or pathway mapped out showing Wnt7b's exact interactions and thus function. There are only 'maybes'. Using R we can make inferences about the pathway Wnt7b is involved in. This means that by looking at Wnt7b's interactions with other genes and it's levels of co-expression with genes confirmed to play well known roles in canonical Wnt signaling, Wnt7b can be confirmed to be part of the canonical Wnt signaling pathway.

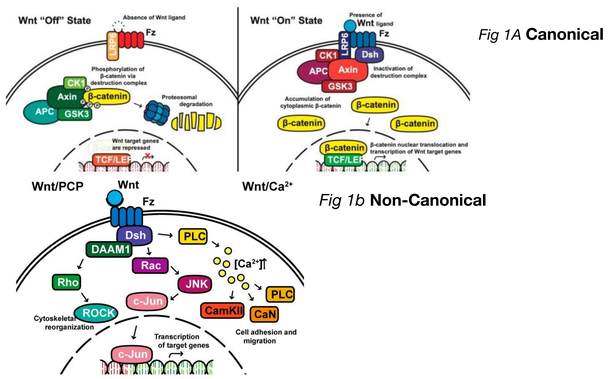


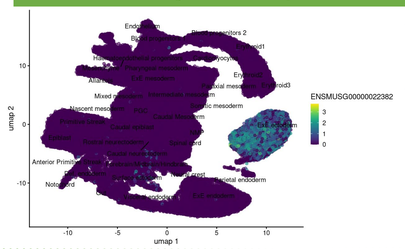
Fig 1A **Canonical**

Fig 1b **Non-Canonical**

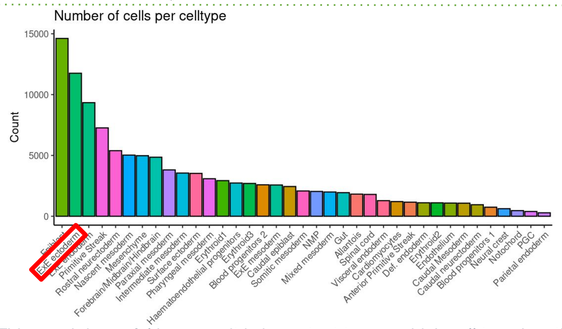
Methods

FlyBase and MGI were used to find a Wnt family gene of interest. Once found a literature search was conducted. Simultaneously, a mouse gastrulation dataset in RStudiio was used to generate several graphs using R. Other databases like UCSC Genome Browser, KEGG Pathways, String Network, and CellXGene were used at various time points.

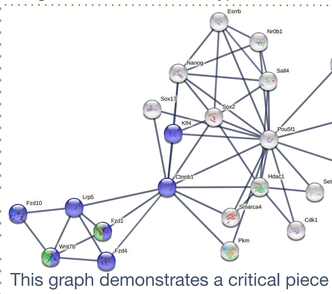
Evidence on why Wnt7B is part of the canonical pathway.



This graph show us the enrichment of Wnt7B in ExE ectoderm cell type. This is significant because ExE ectoderm cell types are important for embryo development.



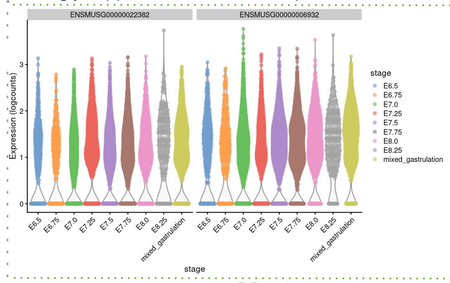
This graph is useful because it is important to see which cell type has the highest number of cells of all the various cell types in embryonic development. Knowing this is important because it can give important insights about which cell types are most crucial to embryonic development.



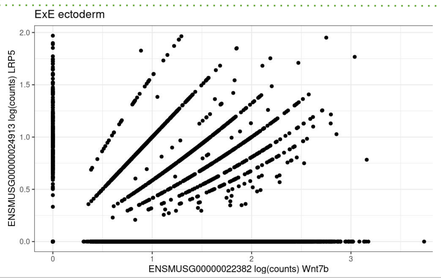
Blue-Canonical Wnt signaling pathway, this is significant because it suggests that Wnt7B is part of the canonical Wnt signaling pathway.

Green-Wnt signaling pathway, planar cell polarity pathway

This graph demonstrates a critical piece of information: a connection between Wnt7b and Ctnnb1, aka beta catenin. This is significant because it suggests that Wnt7b is dependent on beta catenin. If dependent on beta catenin, that'd strongly support that Wnt7b takes part in a canonical Wnt signaling pathway.

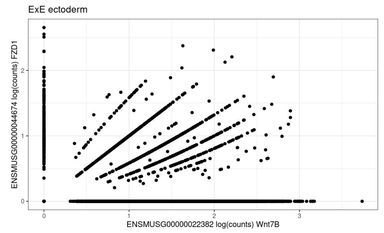


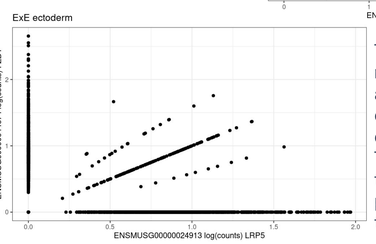
This graph shows relationship between Ctnnb1(beta catenin) and Wnt7B. Significant because shows high co-expression between both genes and might suggest that Wnt7b is dependent on beta catenin.



This 2D scatter plot shows an adequate relationship between LRP5 and Wnt7b. Important because may signify Wnt7b is working with LRP5 in the Wnt "On" state when the 2 genes bind along with an FZD gene.

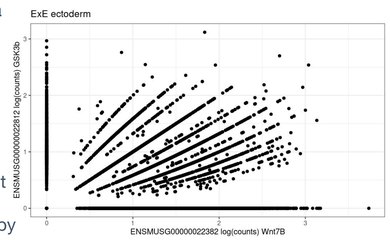
This 2D plot shows a decent relationship between FZD1 and Wnt7b. This is important because, as previously mentioned, it may serve as an indication that Wnt7b binds to LRP6 and an FZD gene.

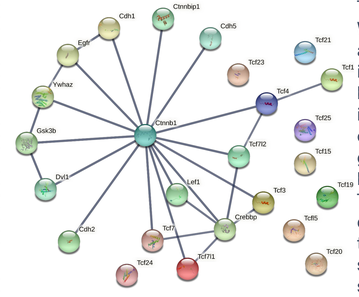




This 2D plot displays the relationship between FZD1 and LRP5. The plot demonstrates reasonable co-expression of the 2 genes. This is significant because these two genes can potentially act as a receptor to the signaling molecule, Wnt7b.

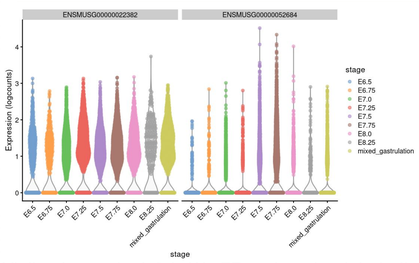
This 2D graph demonstrates a strong relationship between Wnt7b and GSK3b. GSK3b is part of the 'destruction complex' in Wnt canonical signaling that aims to phosphorylate beta catenin in the absence of the Wnt7B ligand. When Wnt7b is present and binded to the destruction complex, which is supported by this graph, Axin can inhibit GSK3b from phosphorylating beta catenin.





TCF that interacts closest with Wnt7B and Ctnnb1 is not specified anywhere in the literature. It's important that Ctnnb1 is examined because out of the 3 beta catenins it has the most similar count expression with Wnt7B. This string graph demonstrates connections between all 14 TCF's and Ctnnb1. There was no significant co-expression because TCF is typically upregulated until later stages that this data set doesn't show (MGI).

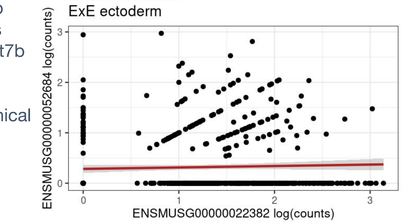
Evidence Wnt7b isn't part of the non-canonical pathway.



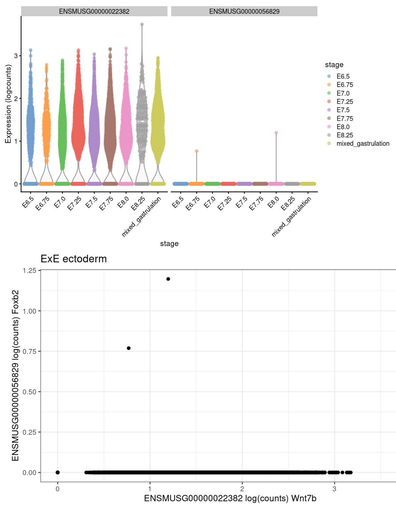
Violin plot on the left is Wnt7B and on the right is C-Jun. C-jun is a protein coding gene that is crucial to the non-canonical planar cell polarity pathway. In comparing these graphs it's notable that they don't demonstrate co-expression very well. This is significant because it supports the idea that Wnt7B is part of the canonical signaling pathway. If it was part of the non-canonical signaling pathway then, in theory it would have similar expression to c-jun.

The correlation coefficient above and the 2D graph on the right don't demonstrate any significant relationship between the 2 genes. This supports the idea that Wnt7b isn't part of the canonical pathway because c-jun is essential to the non-canonical PCP pathway.

rho	p.value
<dbl>	<dbl>
0.0287771	0.464261



Future: Differential Expression of FoxB2 important for ""Off" Wnt Signaling State



These three figures are significant because they show differential expression between Wnt7b and FoxB2. One key detail about the information being presented is the correlation coefficient, it's negative. Insights about "Off" state of canonical signaling can potentially be seen if removing FoxB2 later in the organism's life. Changing the expression of FoxB2 may prevent the Wnt7b ligand from functioning. The absence of Wnt7b ligand would in turn lead to the proteasomal degradation of beta-catenin.

rho	p.value
<dbl>	<dbl>
-0.0008412458	0.9273255

Conclusions

The purpose of this project was to find if there was evidence to support if Wnt7b is part of the canonical Wnt signaling pathway. One of the most significant findings was a potential dependency of beta catenin to Wnt7b. This piece of information was crucial because the biggest indicator of a type of pathway a gene is involved is it's catenin dependency. Another crucial finding was no novel link of Wnt7b to c-jun, a gene important in the non-canonical Wnt signaling pathway. C-jun is one of the most important genes to non-canonical signaling. It was important to hypothesis that there be no link between Wnt7b and c-jun.The biggest limitation this project had was determining a significant link between Wnt7b and Ctnnb1 with TCF genes. Access to another data set and a longer research time frame are two contributors that could've helped combat this problem. The findings of this project help to propose a trajectory for the role that Wnt7b may have in a canonical Wnt signaling pathway.

References

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