# Chapter 1

# Introduction:

# Groucho – A Multifunctional Regulator of Drosophila Development

## Introduction

The Groucho/TLE (Gro) family of of corepressors play crucial roles in development throughout metazoans. Groucho, the sole *Drosophila melanogaster* member of this protein family, was first discovered in the context of a slight hypomorphic allele which resulted in the formation of extra supraorbital bristles reminiscent of the bushy eyebrows of Groucho Marx {Lindsley, 1968 #3055}. Subsequent research on Gro in *Drosophila* has served to characterize this factor’s central importance to developmental gene regulation in response to a variety of developmental programs and signaling pathways. As a corepressor, Groucho has no documented direct ability to bind DNA in a sequence-specific manner, instead relying on recruitment to genomic loci through interaction with a diverse array of transcriptional repressors. Groucho is essential to the correct patterning and development of *Drosophila* and is required for viability. Similar roles have been identified in vertebrates {Paroush, 1994 #172}.

Groucho consists of five domains, two of which are highly conserved {Turki-Judeh, 2012 #2385}. The N-terminal Q (glutamine rich) domain is one of the two conserved domains. The Q-domain is responsible for the formation of tetramers, and possibly higher-order oligomers of Gro {Chen, 1998 #267}. Additionally, the Q-domain mediates a subset of interactions with transcriptional repressors, including the TCF/Lef family of proteins {Brantjes, 2001 #3058}. Assays involving Grg3, a mouse homolog of Gro, on *in vitro* chromatin arrays showed that Q-domain mediated tetramerization is not required for recruitment of Gro to chromatin, but is required for subsequent aggregation of chromatinized fragments. However, assays in cell culture revealed that oligomerization-deficient mutants of Gro exhibited similar binding peak widths as wild-type Gro {Kaul, 2014 #2204}. The structure of the Q-domain of TLE1, a human homologue of Gro, was recently solved, revealing the domain to form a dimer of dimers {Chodaparambil, 2014 #3057}. Though this explains the observation that *Drosophila* Gro forms a tetramer, the current model of oligomerization fails to account for the observation of higher-order oligomerization.

The WD-domain is the second conserved domain of Gro and comprises the C-terminus of the protein. The WD-domain consists of a seven-bladed β-propeller domain, and is responsible for the majority of Groucho interactions with DNA-binding repressors. The majority of these interactions are mediated through binding of the WD-domain to short peptide motifs {Jennings, 2006 #3059}, the most well-characterized of which are the Engrailed homology domain (Eh1) and WRPW motifs.

The central region of Groucho is divided into three domains, the GP, CcN, and SP domains. The GP domain binds to a histone deacetylase (HDAC1/Rpd3), which is involved with some but not all Groucho-repressive activity {Chen, 1999 #3061}. The CcN domain is involved in Gorucho regulation, containing multiple Ck2 and Cdc2 phosphorylation sites {Nuthall, 2002 #3062}. The SP domain contains multiple sites phosphorylated in response to MAPK signaling, resulting in down-regulation of Groucho activity via nuclear export {Hasson, 2005 #3064}. This down-regulation of Groucho repressive activity can persist following relief of signaling, which has been hypothesized to function as a cellular memory, ensuring gene activation even after signaling has weakened or ceased {Helman, 2011 #2938}. There is evidence that the central regions of Groucho are intrinsically disordered {Turki-Judeh, 2012 #2966}, which has emerged as a common strategy among eukaryotic protein domains participating in extensive protein-protein interactions, exposing signaling motifs, and/or accepting posttranslational modifications {Dunker, 2008 #3091}.

Groucho interacts with numerous transcriptional repressors, and through these interactions, is capable of participating in diverse variety of developmental patterning determinations, as well as the reception and interpretation of multiple signaling pathways.

## Figures

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| **Interacting Protein** | **Biological Role** | **Citation** |
| Capicua | RTK signaling; embryonic terminal gene expression | {Jimenez, 2000 #3093} |
| Huckebein | Embryonic terminal gene expression | {Goldstein, 1999 #3094} |
| Hairy | Segmentation/ Anterior-posterior patterning | {Paroush, 1994 #3090} |
| Runt | Segmentation/ Anterior-posterior patterning | {Aronson, 1997 #3095} |
| Even-skipped | Segmentation/ Anterior-posterior patterning | {Kobayashi, 2001 #3076} |
| Odd-skipped | Segmentation/ Anterior-posterior patterning | {Goldstein, 2005 #3096} |
| Sloppy-paired 1 | Segmentation/ Anterior-posterior patterning | {Andrioli, 2004 #3097} |
| Engrailed | Segmentation/ Anterior-posterior patterning | {Jimenez, 1997 #3075} |
| Knirps | Segmentation/ Anterior-posterior patterning | {Payankaulam, 2009 #2955} |
| Goosecoid | Segmentation/ Anterior-posterior patterning | {Jimenez, 1999 #3092} |
| Dorsal | Dorsal-ventral patterning | {Dubnicoff, 1997 #2366} |
| Brinker | Dorsal-ventral patterning | {Zhang, 2001 #3099} |
| Ind | Dorsal-ventral patterning | {Von Ohlen, 2007 #3101} |
| Vnd | Dorsal-ventral patterning | {Cowden, 2003 #3102} |
| Su(H) | Notch signaling | {Barolo, 2002 #3072} |

## References