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Previews

Giving translation a hand

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A cell's identity is commonly regarded as its transcriptomic profile. In this issue of *Developmental Cell*, Fujii et al. (2021) show that a global translation factor subunit acts differentially on transcripts to modulate morphogen signaling levels, revealing a global mechanism of transcript-specific translational control in development.

Development is a dynamic process that requires spatial and temporal coordination of different signaling pathways and gene expression to shape cell fate specification and morphogenesis. While extensive work has been done to understand how the genome, epigenome, and transcriptome modulate cell fate, less attention has been focused on translational control.

In this issue of *Developmental Cell*, Fujii et al. (2021) look at how global housekeeping translation factors fine-tune protein output for individual genes across different tissues. The authors focus on the *extra-toes spotting* mouse mutant, which gives rise to a specific posteriorization of distal limbs and neural tube defects caused by a reduction in *eIF3c* (eukaryotic initiation factor 3c) dosage and aberrant Sonic Hedgehog (SHH) signaling (Gildea et al., 2011). Using heterozygous mutations in *eIF3c*, they show that *eIF3c* modulates the selective translation of components of the SHH pathway required for normal patterning during development (Figure 1A).

eIF3c is one of 13 subunits in the eIF3 complex, a potent regulator of translation initiation and early elongation. eIF3 facilitates small ribosomal subunit recruitment to and scanning of the 5′ untranslated region (UTR) (Hinnebusch 2014). To explain how loss of function of the *eIF3c* subunit leads to distal limb and neural tube defects, Fujii et al. (2021) hypothesized that *eIF3c* could regulate the translation of specific transcripts within the SHH pathway. The authors generated a double heterozygous mutant mouse for *Patched 1* (*Ptch1*), a SHH receptor, and *eIF3c*. They observed a striking increase in patterning defects in double mutant mice, suggesting a genetic interaction between *Eif3c* (and possibly other eIF3 components) and *Ptch1*. While it is unclear whether *Ptch1* translation itself is altered in developing limbs, the authors show a significant decrease in PTCH1 protein in the developing neural tube. To understand how eIF3c is recruited to mRNA transcripts, the authors used eCLIP demonstrating that the distribution of eIF3c is not uniform across 5′ UTRs. Interestingly, they observed two different patterns of eIF3c recruitment: uniform and heterogeneous. They attribute the uniform distribution to the scanning 43S small ribosomal subunit. Sharp eIF3c peaks, in contrast, may reflect transcript-specific recruitment, and these transcripts showed reduced translation efficiency in the mutant.

Next, the authors identified a pyrimidine-rich motif specific to 5′ UTRs for which eIF3c is distributed unevenly. They find that many 5′ UTR components of key signaling pathways, including *Ptch1 and Gli3*, contain this pyrimidine-rich motif; deletion of these motifs suppresses the translation of reporter mRNAs, though it remains unclear whether this effect depends on eIF3c function. The authors propose a model that favors the specific recruitment of eIF3c through a UC-rich motif to regulate translation of the target genes. While this is certainly possible, alternatively, the enrichment of eIF3c could be caused by pausing of the scanning subunit of the ribosome in different structures or sequences in the 5′ UTR. It is also worth considering that the motifs highlighted are absent in alternative transcript isoforms of *Ptch1*, indicating that tissue-specific splice isoforms could determine different mechanisms of translation regulation. Similarly, it is interesting that four members of the eIF3 complex (*c*, *a*, *m*, and *k*) include regulatory motifs for *eIF3c*, suggesting potential feedback regulatory mechanisms for translation of these subunits.

While the prospect of gene-specific regulation by eukaryotic initiation factors is very exciting and has the potential to reshape how we conceive 5′ UTR-mediated translational control, cell-type-specific regulation of eIF3c-mediated translational control remains unclear. Over 1,300 genes have sharp eIF3c peaks and as a group show lower translation in eIF3c mutants. Based on our understanding of the field, we are left to speculate whether the genetic relationship between eIF3c and the SHH pathway is the product of transcript-specific translational control (Figure 1B) or the consequence of a broad change in translation for many of the bound genes where some of the affected genes have a potent dosage effect in development and therefore elicit a specific phenotype (Figure 1C). Genes have different thresholds for the protein output required to maintain function. These thresholds may provide a different contribution of each target to the overall phenotype, especially in the most dose-sensitive signals (including potent morphogens such as SHH). Further, the cis-regulatory elements encoded in transcripts define the buffering capabilities for different genes to shape protein output. Indeed, the fact that the phenotype is only present in about half of animals indicates that, even in the case of SHH pathway, there

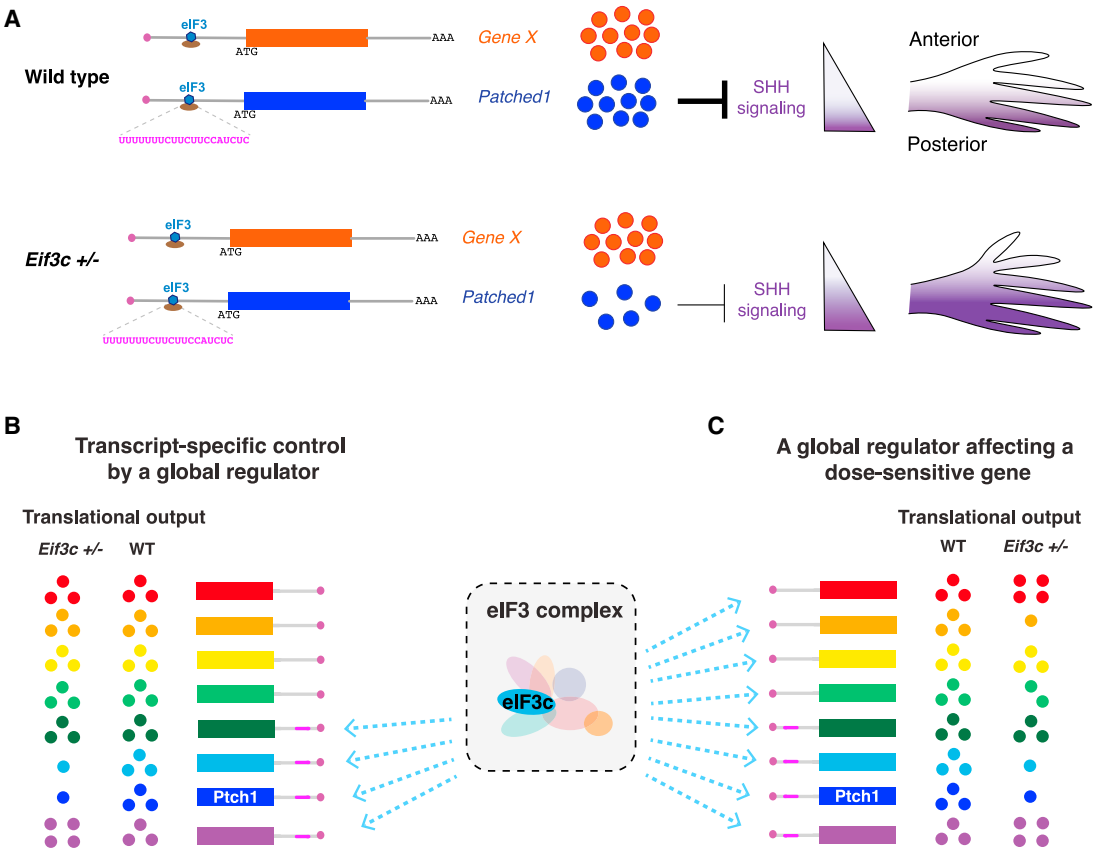

Figure 1. Possible molecular mechanism for transcript-specific regulation by eIF3c

(A) Hypothesized mechanism of *Eif3c* mutant mouse anterior polydactyly phenotype, based on Fujii et al. (2021). A housekeeping (orange) or *Patched1* (blue) transcript, with the eIF3 complex with small ribosomal subunit, being translated in wild-type (top) or *Eif3c* heterozygous mutant (bottom) mice. Magenta sequence is the pyrimidine-rich sequence identified in the *Ptch1* 5′ UTR. The authors propose that *Eif3c* binds to UC-rich motifs in the *Ptch1* 5′ UTR as part of the eIF3 complex; heterozygous *Eif3c* mutants show reduced PTCH1 translation, leading to reduced inhibition of SHH signaling (purple gradient) and subsequent posteriorization of a developing hand.

(B and C) We envision two possible models: one where eIF3c specifically controls translation of different SHH pathway components, partly through UC-rich motifs (magenta) (B), and an alternative model where the phenotypes observed are caused by a broader change in translation of many genes where some of the affected genes have a prominent dosage effect in development causing a specific phenotype (C).

are buffering capabilities to this *eif3c* mutation.

Lastly, this study highlights an unappreciated layer of translational regulation embedded in untranslated regions, including alternative 5′ UTRs, for developmental and evolutionary novelties (Resch et al., 2009). In fact, the 5′ UTR of *Ptch1* has tissue-specific splice isoforms; understanding these isoforms may further inform tissue-specific phenotypes and translational regulatory mechanisms. In this context, it is intriguing to consider the evolutionary playground of the noncoding genome and its interplay between transcriptional control, mRNA stability, and translational output along with *trans*-acting factors.

It is interesting that specific effects of global regulators are observed in translation and other areas of gene regulation. For example, ribosomopathies present pleiotropic yet distinct phenotypes across tissues for different ribosomal proteins (Farley-Barnes et al., 2019). These phenotypes are attributed to either the reduction of ribosome function across different tissues, which affects different groups of genes, or the preferential regulation of specific mRNAs by different ribosomal proteins. Interestingly, expansion segments of the ribosome seem to regulate distinct mRNAs for translation (Leppek et al., 2020). Similarly, reducing the function of general regulators of splicing can affect distinct groups of genes based on the limiting step that is more sensitive to that particular factor during splicing (Papasaikas et al., 2015). Moreover, genes with different codon optimality or uORF content might be differentially regulated by tRNA levels and differential expression of translation initiation factors across different tissues during development (Johnstone et al., 2016; Bazzini et al., 2016). Future studies will be needed to illuminate the complex interplay between untranslated regions and global regulators of translation.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Girl power: NORTIA polarization seals pollen tube fate

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How protein dynamics contribute to developmental processes is a critical biological question. In this issue of *Developmental Cell*, Ju et al. show that subcellular localization of NORTIA in the female gametophyte is required for pollen reception. NORTIA redistribution boosts cues that drive pollen tube bursting, thus promoting male gamete release and fertilization.

During pollination, cells from genetically distinct individuals must communicate in order to direct the cellular processes that lead to fertilization. In flowering plants, fertilization involves the delivery of two sperm cells to the female gametophyte (reviewed by Johnson et al., 2019). The two sperm cells are carried by a pollen tube (PT) that grows through floral tissues, guided by female cues toward a target ovule where it ultimately enters an aperture called the "micropyle." After arrival and reception, the PT stops growing and bursts at one of two specialized cells of the female gametophyte, which are called "synergid cells," and the receptive synergid cell then undergoes programmed cell death. PT burst releases the sperm cells, one fuses with the egg cell to generate the embryo, and the other fuses with the central cell to form the nutritive endosperm.

Synergid cells are reproductive accessory cells with a central role in PT guidance, reception, and bursting (reviewed by Johnson et al., 2019 and others). Evidence that links synergid cells to early events in the intercellular communication in pollination comes from mutants in the receptor-like kinase FERONIA (FER) and a glycosylphosphatidylinositol (GPI)-anchored protein, LORELEI (LRE), which exhibit similar PT reception phenotypes (Capron et al., 2008). In *fer* and *lre*, PTs are attracted to ovules, but they are not properly received, and so they fail to stop growing; this results in one or more PTs curling around inside the ovule. In these mutants, PTs do not rupture, and male gametes are not released (Huck et al., 2003; Escobar-Restrepo et al., 2007). FER and LRE proteins accumulate asymmetrically within synergid cells, localizing at a highly invaginated plasma-membrane-rich region, called the filiform apparatus (FA), that is covered by a thickened cell wall (Rotman et al., 2003; Escobar-Restrepo et al., 2007). Before PT arrival, LRE functions as a FER chaperone to enable FER movement from the endoplasmic reticulum to the FA (Li et al., 2015), where together, LRE and FER function in PT reception.

Mutants in another synergid-specific protein, the mildew resistance locus O (MLO)-like protein NORTIA (NTA), exhibit *fer* and/or *lre*-like phenotypes (Kessler et al., 2010). Prior to PT arrival, NTA fused to green fluorescent protein (NTA-GFP) is homogeneously distributed in synergid cells in a compartment that colocalizes with a *cis*-Golgi marker (Jones et al., 2017; Ju et al., 2021). After PT arrival, NTA-GFP is only detected at the FA plasma membrane. In *fer* and *lre* mutants, NTA-GFP is not re-distributed to the FA,