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Multiomics approach to interrogate translational regulation to GPCR signaling and its spatial bias

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Ligand activation of G protein-coupled receptors (GPCRs) induces a plethora of cellular responses that ultimately culminate in changes in protein expression. Our lab and others have demonstrated that certain GPCR-dependent responses that feed into protein expression changes are biased by receptor localization. Specifically, we have shown that gene transcription is stimulated downstream of endosomal receptors. However, transcription represents only one layer of gene expression regulation, and therefore analysis of steady-state RNA abundance alone does not adequately capture the full breadth of changes that underlie protein expression. To address this, we apply a multiomics approach to interrogate the comprehensive landscape of transcriptional and post-transcriptional changes in cellular responsiveness to receptor activation, and assess their dependence on GPCR localization. We pair RNA-seq and Ribo-seq and identify hundreds of target genes downstream of the prototypical beta-2-adrenergic receptor (B2AR) to be regulated exclusively at the transcriptional or translational level. Strikingly, none of the translational targets identified here have been previously linked to GPCR signaling. In addition, we find distinct functional categories over-represented across each set of targets (transcriptional vs translational), suggesting that unique cellular processes downstream of B2AR activation are subject to discrete regulatory mechanisms. In further studies, we show that the vast majority of these genes likely represent conserved translational targets downstream of Gas-coupled receptors. Lastly, we are probing the spatial dependence of the novel translational targets. In follow-up work, we have identified genes encoding ribosomal subunits are exclusive translational targets of B2AR signaling. Using reporters for cap-dependent translation, we have identified that B2AR-cAMP signaling induces the expression of translation machinery through a novel PKA-dependent mechanism. This work is extending our understanding of the cellular processes dependent on compartmentalized receptor signaling and their underlying regulation.