Model for RNA granule formation suggests dual function for adaptor molecules.

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Formation of A2 RNA granules is modeled accounting for core molecular components: specific RNA (contain A2RE sequence) and non-specific RNA molecules, A2 proteins that bind specifically (high affinity) to A2RE sequences or nonspecifically (lower affinity) to other RNA sequences, and the heptavalent protein TOG that binds both A2 molecules and RNA. Mathematically, interactions among multivalent components give rise to combinatorial complexity (large number of potential molecular complexes). Results using hybrid modeling approach (deterministic-stochastic-statistical) suggest that A2 either facilitates or inhibits granule formation depending on the concentration regime, and also impacts the selectivity of granule formation for specific RNAs.

***Keywords* —A2RE RNA, hnRNP A2, CKAP5, hybrid model, concentration regime, granule selectivity.**

I. Introduction

RNA granules are protein ensembles that are trafficked to particular subcellular sites for localized translation [1]. We model a well-characterized type of RNA granule, the A2 RNA granule, containing specific A2RE RNA molecules with high affinity binding sites (A2REs) for the adaptor protein hnRNP A2 (A2). A2 protein can also bind to the heptavalent scaffold protein TOG (alternative name CKAP5). Each RNA molecule also contains many (up to 100) non-specific low affinity binding sites for A2 and TOG proteins. Non specific RNA (lacking the A2RE sequence) is also considered. Previous *in vitro* experiments indicate that purified RNA binding proteins (such as hnRNP A2) and RNA molecules can form large aggregates and undergo sol-gel phase transitions [2]. In this study, we explore the parameters that modulate granule formation and serve as determinants of granule composition and selectivity. We use a hybrid modeling approach (deterministic-stochastic-statistical) [3, 4] to overcome the problem of combinatorial complexity.

II. Results

Model results are consistent with previous experimental observations that both A2 and TOG protein are essential for formation of A2 RNA granules [5]. Decreased A2 or TOG expression results in reduced numbers of granules in the distal processes, while RNA remains diffuse in the perikaryon, leading to the interpretation that A2 and TOG are required for traffic of the RNA granules to the dendrites [6]. Our model allowed us to formulate alternative hypotheses. Simulations using *in vitro* affinities between TOG and RNA suggest that at low concentrations of A2, most TOG and RNA molecules are sequestered in large aggregates. We hypothesize that if such affinities translate to the *in vivo* environment, such large complexes might be difficult to transport through the narrow dendritic processes. Therefore the function of A2 protein may be to tune granule size to allow transport to distal dendrites. It is not clear that such large aggregates are formed *in vivo* in these cells. We performed further simulations assuming that the effective *in vivo* affinity between TOG and RNA is reduced. The results reveal that the concentration of the adaptor molecule A2 impacts its function: a minimum concentration of A2 is required for granule formation and selectivity; whereas high concentrations of A2 reduces connectivity and inhibits granule formation.

III. Conclusions

The hybrid method allowed us to: (a) overcome combinatorial complexity and analyze RNA granule formation and compositions as a function of RNA valence and molecular concentrations; (b) better understand granule formation, interpret experimental observations and generate alternative hypotheses.

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