

Multiscale modeling to understand robustness of stem cell maintenance

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The mechanisms regulating the robustness of multicellular development are often multilayered, with underlying processes occurring at different spatio-temporal scales. Pluripotent stem cells are stably maintained in shoot apical meristems (SAMs) despite periodic differentiation of stem cell progeny into all above-ground organs and variable environmental conditions. In *Arabidopsis thaliana*, the stem cell-promoting homeodomain transcription factor (TF)-WUSCHEL (WUS) diffuses between cells through microscopic pores, the plasmodesmata (PD), to form a concentration gradient critical for stem cell homeostasis. WUS regulates itself by transcribing *CLAVATA3* (*CLV3*), which encodes a secreted peptide that activates receptor kinase signaling, through a novel concentration-dependent activation-repression switching mechanism. My talk will focus on integrating multiple mechanisms that contribute to robustness. They include i) Analysis of the determinants of cooperative interaction among cis-elements within the 3 cis-regulatory modules (CRMs) and interaction among different CRMs in stable *CLV3* regulation, explored through stochastic modeling. ii) The action of *CLV3* signaling and plant hormones in regulating the WUS concentration gradient at multiple levels: its transcription, subcellular partitioning, and diffusion between cells explored by employing deterministic modeling. iii) Development of a hybrid model coupling both the stochastic and deterministic models to study simultaneous control of processes regulating robustness of the *CLV*-WUS feedback system in stem cell homeostasis. Specifically, I will present new insights that have obtained into the architecture of CRMs, *CLV3* signal-dependent shadowing of cis-elements in *CLV3* regulation, and the simultaneous negative and positive regulation of *CLV3* signaling on *WUS* transcription and *WUS* protein regulation, respectively, in the robust maintenance of the WUS protein gradient.

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(Science and Agricultural Build.)



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