Structural Switch of Lysyl-tRNA Synthetase between Translation and Transcription

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Results and Discussion

Lysyl-tRNA synthetase (LysRS), a component of the translation apparatus, is released from the cytoplasmic multi-tRNA synthetase complex (MSC) to activate the transcription factor MITF in stimulated mast cells through undefined mechanisms. Here we show that Ser207-phosphorylation provokes a new conformer of LysRS that inactivates its translational, but activates its transcriptional function. The crystal structure of an MSC subcomplex established that LysRS is held in the MSC by binding to the Nterminus of the scaffold protein p38/AIMP2. Phosphorylation-created steric clashes at the LysRS domain interface disrupt its binding grooves for p38/AIMP2, releasing LysRS and provoking its nuclear translocation. This alteration also exposes the C-terminal domain of LysRS to bind to MITF and triggers LysRS-directed production of the second messenger Ap4A that activates MITF. Thus our results establish that a single conformational change triggered by phosphorylation leads to multiple effects driving an exclusive switch of LysRS function from translation to transcription.

In quiescent mast cells, LysRS is associated with p38 in a closed form and is retained in the cytoplasmic MSC. Antigen activation phosphorylates Ser207 and triggers an open form of LysRS. By opening up the structure, phosphorylated LysRS is released from the MSC, translocates from cytoplasm to the nucleus, binds to MITF and generates Ap4A to activate MITF transcription functions. Thus, by selecting two distinct conformers, phosphorylation could switch the functional of LysRS between translation and transcription.

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References

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