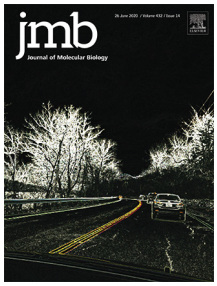

RNA Polymerase and the Ribosome: In Touch or out of Touch?

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It has been known for decades that the rates of transcription elongation by the *Escherichia coli* RNA polymerase and translation elongation by the *E. coli* ribosome are matched [1]. A prevailing mechanistic model in the field suggests that such kinetic coordination of transcription and translation in bacteria, and perhaps all prokaryotes, is mediated through a direct, physical coupling of RNA polymerase to the first translating ribosome (i.e., the "lead ribosome") [2]. Indeed, several investigations have shown that such a physical coupling may be mediated by the NusG/RfaH family of transcription factors through their ability to simultaneously interact with RNA polymerase and the ribosome [3–8]. Nonetheless, several recent studies highlight mechanistic discrepancies in the field, and either present challenges to the physical coupling model or provide evidence that physical coupling is not strictly required for kinetic coordination of transcription and translation [9–15]. Perhaps the most prominent of these at the moment are a set of recent cryogenic electron microscopy studies that have provided near-atomic resolution structures of RNA polymerase–ribosome complexes [9–11]. The structure of one of these complexes, formed by physically colliding a ribosome into an RNA polymerase that had been artificially stalled during an *in vitro* transcription–translation reaction, places the mRNA entry channel of the ribosome right up against the mRNA exit channel of the RNA polymerase [9]. Although this relative positioning makes structural sense, the functional relevance of this structure has nonetheless been questioned due to the fact that it represents an artificially collided complex and that it sterically precludes NusG from simultaneously interacting with the RNA polymerase and the ribosome [5–7]. A second structure, this time of a complex formed between RNA polymerase and just the small ribosomal subunit, juxtaposes the mRNA exit channel of the small ribosomal subunit against the mRNA exit channel of the RNA polymerase [11]. Such a relative positioning is challenging to functionally rationalize, is inconsistent with the structure of the collided complex [9], and, because the NusG binding sites on RNA polymerase and the ribosome are now too far away from each other, is also incompatible with a role for NusG. In the most recent study, three structures of RNA polymerase–ribosome complexes were solved, one compatible with the collided complex [9], one compatible with NusG-dependent coupling of RNA polymerase and the ribosome, and one compatible with NusG-independent coupling of RNA polymerase and the ribosome [10]. Collectively, these structural studies highlight some of the mechanistic discrepancies in the field and challenges to the physical coupling model.

In a very timely and provocative new Perspective published in this issue, Chen and Fredrick evaluate the previous and recent literature and present a new view of how and why transcription and translation may be coordinated in *E. coli* and other prokaryotes [16]. The Perspective begins by briefly reviewing the relevant previous literature and quickly arriving at a discussion of the most recent genetic, biochemical, and structural studies, highlighting the emerging discrepancies across these studies and the challenges some of these studies pose to the physical coupling model. Chen and Fredrick then review emerging results from their laboratory and others suggesting that, rather than a direct physical coupling of RNA polymerase to the lead ribosome, the coordination of transcription and translation is instead mediated through indirect effects. Chen and Fredrick conclude their Perspective by proposing a unifying model in which features on the mRNA being synthesized and translated dictate whether, when, and how translation by the lead ribosome may aid

transcription by RNA polymerase. Specifically, their model focuses on the effect that "ribosome traffic" (i.e., the number of ribosomes that can simultaneously translate a particular mRNA) has on transcription and how artificially altering ribosome traffic (e.g., *via* perturbations that slow down or block translation) might impact transcription. Given the intensity of ongoing research currently aimed at elucidating the mechanism through which transcription and translation in prokaryotes are coordinated as well as how such a mechanism might be used to regulate gene expression and, possibly, develop novel antibiotic therapeutics, there is no doubt that Chen and Fredrick's Perspective will inspire new studies aimed at testing their proposed model.

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