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Review

Oscillatory control of Delta-like1 in somitogenesis and neurogenesis: A unified model for different oscillatory dynamics

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ABSTRACT

During somite segmentation, mRNA expression of the mouse Notch ligand Delta-like1 (Dll1) oscillates synchronously in the presomitic mesoderm (PSM). However, the dynamics of Dll1 protein expression were rather controversial, and their functional significance was not known. Recent live-imaging analysis showed that Dll1 protein expression also oscillates synchronously in the PSM. Interestingly, accelerated or delayed Dll1 expression by shortening or elongating the Dll1 gene, respectively, dampens or quenches Dll1 oscillation at intermediate levels, a phenomenon known as "amplitude/oscillation death" of coupled oscillators in mathematical modeling. Under this condition, oscillation of the Notch effector Hes7 is also dampened, leading to severe fusion of somites and their derivatives, such as vertebrae and ribs. Thus, the appropriate timing of Dll1 expression is critical for its oscillatory expression, pointing to the functional significance of Dll1-mediated oscillatory cell–cell interactions in the segmentation clock. In neural stem cells, Dll1 expression is also oscillatory, but non-synchronous, and when Dll1 oscillation is dampened, oscillation of another Notch effector, Hes1, is also dampened, leading to defects of neural development. In this review, we discuss the underlying mechanism for the different oscillatory dynamics (synchronous versus non-synchronous) in the PSM and neural stem cells in a unified manner.

Contents

1. Introduction

A bilateral pair of somites is formed by segmentation of the anterior parts of the presomitic mesoderm (PSM). In mouse embryos, this process is repeated every two hours under the control of the segmentation clock, which involves Hes7, a basic helix-loop-helix factor [1–3]. Hes7 expression oscillates synchronously between PSM cells, and each cycle of Hes7 oscillation leads to the formation of a pair of somites. Both the loss of expression and sustained expression of Hes7 lead to severe somite fusion, suggesting that the oscillatory expression of Hes7 is required for periodic somite segmentation [2,4]. Hes7 oscillation is regulated by negative feedback (Fig. 1A): Notch signaling activates the *Hes7* promoter, generating

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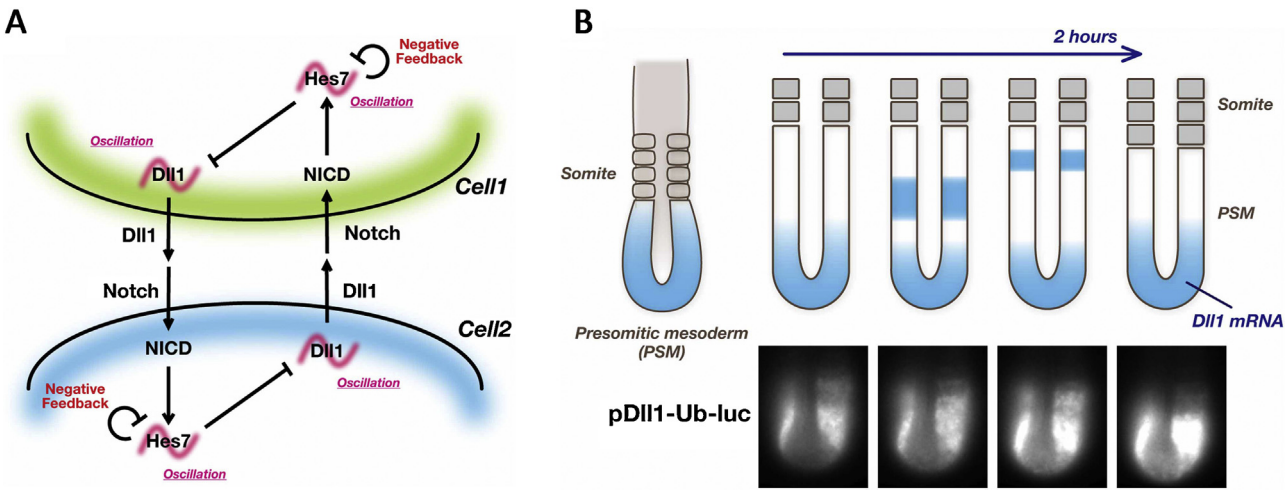

Fig. 1. The oscillatory networks for somitogenesis. (A) The Dll1-Notch-Hes7 pathway in the PSM. Dll1 activates notch signaling in a neighboring cell. The activation of notch signaling generates NICD, and NICD induces Hes7, which probably represses Dll1 expression. Hes7 expression oscillates by negative feedback, and Hes7 oscillation leads to Dll1 oscillation. (B) Dll1 expression patterns in the PSM. *Dll1* mRNA production (blue) is initiated in the posterior PSM (Phase 1), propagates anteriorly (Phase 2), and reaches the S-1 region (Phase 3). After the disappearance of *Dll1* transcription in the S-1 region, a new segmentation event occurs between the S-1 and S0 regions, thereby forming a bilateral pair of somites (the rightmost panel). Now, the S-1 region becomes the new S0 region. Bioluminescence images are shown below.
Adapted from Ref. [39].

Hes7 mRNA and Hes7 protein, while Hes7 protein then represses its own expression at a delayed timing by binding directly to the *Hes7* promoter [5–7]. Repression of the *Hes7* promoter leads to the disappearance of both *Hes7* mRNA and Hes7 protein, because they are extremely unstable, facilitating the next round of expression. Negative feedback with delayed timing is essential for Hes7 oscillation: deletion of all three introns accelerates Hes7 protein expression because the time required to transcribe and then remove the introns by splicing is not necessary, and this accelerated negative feedback leads to steady (non-oscillatory) Hes7 expression and severe somite fusion [4]. Interestingly, deletion of two introns (leaving one intron) from the Hes7 gene moderately accelerates Hes7 protein expression, and this moderate acceleration increases the tempo of Hes7 oscillation. As a result, the tempo of the segmentation clock is also accelerated, forming more somites and vertebrae, although Hes7 oscillation is later dampened [8]. These phenomena can be simulated mathematically [4,8–10], and these data indicate that Hes7 is the central gene of the mouse segmentation clock.

Although the mechanism for such oscillatory expression has been well analyzed, how Hes7 oscillation is synchronized between neighboring PSM cells still remains to be elucidated. In this review, we discuss recent findings about the mechanism underlying the synchronous oscillation of PSM cells. We also discuss the difference and similarity of oscillatory expression in neural stem cells.

2. The role of Notch signaling in synchronous oscillation in the PSM

While oscillation occurs in phase between neighboring PSM cells, it becomes unstable and easily goes out of phase, when the cells are dissociated, suggesting that cell–cell communication is important for stable synchronized oscillation [11,12]. It has been shown that Notch signaling is required for the synchronization of oscillatory expression. In Notch signaling, Notch ligands such as Delta-like1 (Dll1) in mice and DeltaC in zebrafish activate the transmembrane protein Notch in neighboring cells (Fig. 1A). Upon activation, Notch protein is processed at the membrane portion, releasing the Notch intracellular domain (NICD) (Fig. 1A). NICD is then transferred to the nucleus, forms a complex with the mediator Rbpj and the coactivator mastermind-like, and up-regulates the expression of downstream genes such as *Hes7* in mice (Fig. 1A) and *her1* and *her7* in zebrafish [13,14]. In zebrafish lacking Notch signaling genes or treated with γ-secretase inhibitors, which inhibit Notch signaling, oscillatory gene expression is desynchronized between neighboring PSM cells, forming salt-and-pepper expression patterns [15–18]. Wash-out of γ-secretase inhibitor treatment reactivates Notch signaling, and synchronization recovers quickly [16]. These results indicate that Notch signaling regulates synchronization between neighboring PSM cells, which makes the in-phase oscillatory expression resistant to perturbation such as mitosis and cell movement [19]. In zebrafish, expression of the Notch ligand DeltaC protein oscillates under the control of *her* oscillations [20], and DeltaC oscillation drives synchronization by periodic activation of Notch signaling [17,21].

In mice, *Dll1* is required for somitogenesis [22], as in zebrafish. However, although *Dll1* mRNA expression oscillates probably under the control of Hes7 oscillation in the mouse PSM (Fig. 1A) [23], Dll1 protein dynamics were rather controversial; conflicting results have been reported showing that Dll1 protein expression in the mouse PSM is both dynamic and static [24,25]. Instead, it was shown that the expression of Lunatic fringe (Lfng), β1,3-*N*-acetyl-glucosaminyl-transferase, which modulates Notch and Dll1 activity [24,26], oscillates in the mouse and chick PSM [27–31], and that in *Lfng*-null mice, Hes7 oscillation desynchronizes, leading to segmentation defects [32–34]. Furthermore, although the introduction of steady Lfng expression in the PSM only partially rescues the segmentation defects of *Lfng*-null mice [35,36], the introduction of oscillating Lfng expression driven by the *Hes7* promoter completely rescues the defects [37]. Thus, Lfng oscillation is required for complete synchronization between neighboring PSM cells, and it was suggested that Lfng oscillation periodically modulates the activity of Notch signaling, thereby inducing synchronized oscillation.

Despite the significant role of Lfng oscillation in synchronization, Hes7 expression still oscillates loosely in phase between neighboring PSM cells in *Lfng*-null mice, suggesting that another factor is also responsible for synchronization.