Notch Signalling and Cellular Fate Choices: A Short Review

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Summary. During mammalian central nervous system (CNS) development, an enormous variety of cell types are generated. This cell diversity is due in part to asymmetrical cell division. Asymmetrical segregation of Numb, a cell-determinant protein, can result in the differential activation of the Notch pathway. The Notch pathway defines one of the few fundamental signalling pathways that govern metazoan development. Notch signals link the fate decisions of one cell to those of its neighbours. Notch activation has a profound effect on many aspects of nervous system development. Here we present a brief overview of Notch signalling and reiterate some relevant questions relating to the Notch pathway.

1 Cell Diversity

The mammalian central nervous system (CNS) contains an enormous variety of cell types each with a unique morphology, physiology and function (Lein et al., 2006). Understanding how neuroepithelial cells (stem cells) of the developing CNS choose between alternative cell fates to generate cell diversity is a challenge (Cayouette and Raff, 2002). During development, cell-fate diversity is brought about, in part, by asymmetric cell divisions (Gho and Schweisguth, 1998). Asymmetric segregation of cell determinants, such as Numb can result in the differential activation of the Notch pathway, which can generate cell diversity (Fichelson and Gho, 2004). In invertebrates, asymmetric segregation of cell-fate determining proteins or mRNAs to the two daughter cells during precursor cell division plays a crucial part in cell diversification. There is increasing evidence that this mechanism also operates in vertebrate neural development and that the Numb protein, which function as cell-fate determinant during Drosophila development, may also function in this way during vertebrate development (Cayouette and Raff, 2002). A very clear illustration of symmetric and asymmetric segregation of a cell fate-determining protein can be found in Figure 2 of Cayouette and Raff (2002).

2 Notch Pathway

Cells that receive Numb antagonize Notch activity. Those cells that do not receive numb will adopt the fate associated with Notch activation. Despite the complexity of the action of Notch, some general principles underlying the action of this fundamental cell-interaction mechanism have become known. During development, animals use Notch signalling to amplify molecular differences between neighbouring cells. The implementation of a particular developmental program modulated by Notch depends, however, on how Notch integrates its activity with other cellular factors (Artavanis-Tsakonas et al., 1999), and is dependent on cellular context (Bray, 2006). The Notch cell interaction mechanism defines one of the few fundamental signalling pathways that govern metazoan development. Notch signals link the fate decisions of one cell to those of its neighbours and have been shown to have a profound effect on many aspects of nervous system development (Louvi and Artavanis-Tsakonas, 2006). Delta-Notch signalling is involved in cell fate decisions in developing vertebrates.

3 Notch Activation

Notch, a transmembrane protein, is activated by the ligands Delta and Jagged, which are also transmembrane proteins expressed by neighbouring cells. Notch activation is described in detail in Kageyama et al. (2005), which we now summarise. Upon activation, the intracellular domain of Notch is transferred into the nucleus and forms a complex with RBP-J. This complex induces Hes1 and Hes5 expression. Hes1 and Hes5 inhibit the expression of activator-type bHLH. In a differentiating neuron, Notch is not activated, and RBP-J represses Hes1 and Hes5 expression. The activator-type bHLH genes are expressed. The activator-type bHLH factors induce expression of Hes6, which inhibits Hes1 functions and reinforces the neurogenic process. The activator-type bHLH factors also induce neuronal specific genes. One of them includes the Notch ligand Delta, which activates Notch signalling in neighbouring cells. An excellent illustration of Delta-Notch signalling is found in Kageyama et al. (2005): Figure 1, entitled "Regulation of neural development by the repressor-type and activator-type bHLH genes". Put simply, Delta ligands bind and activate Notch receptors on a neighbouring cell, this Delta-Notch signalling can dictate the fate of the neighbouring cells (by influencing intracellular gene expression).

4 Notch Pathway: Questions

Notch signals affect specific cell fates in a context-specific manner, a schematic summarising the effects of Notch signalling and its affect on cell fate decisions can be found in Louvi and Artavanis-Tsakonas (2006), Figure 3. Understanding how and why different target genes are activated according to cell type and time is a very important question, in other words: how and why is Notch activation context dependant (Bray, 2006)? This and other important questions are posed in Bray (2006). The response to Notch differs greatly between cell types, for example Notch promotes cell proliferation in some contexts and apoptosis in others. What is the reason for this? Bray also states that recent data reveals that the precise location of the Notch ligand and the receptor in the cell can have profound effects on signalling. How does the different ligand locations exactly impact on Notch activity? All of these questions are extremely important in untangling the role of Notch during diverse developmental and physiological processes.

5 Modelling

Modelling biological processes can be a fruitful undertaking (Fussengger et al., 2000). As stated in Fisher and Henzinger (2007) computational and mathematical modelling of biological systems is becoming increasingly important in efforts to better understand complex biological behaviours. Over the years, diagrammatic models have been used to summarise and understand experimental data. Despite the many benefits of such models, as well as their simplicity, they give a stationary picture of cellular processes. Therefore, translating these models into more dynamic forms may be very useful (Fisher and Henzinger, 2007). Fussengger et al. (2000) believe "The model represents a flexible yet rigorous method to store, visualise and interact with current and newly emerging biological information." A modelling approach that permits rigorous tests of mutual consistency between experimental data and mechanistic hypotheses and can identify specific conflicting results can provide a useful tool to developmental biology (Kam et al., 2008).

The Notch pathway is a fundamental pathway in metazoan development and the design and implementation of a good dynamic model of this pathway, and of crosstalk between Notch and other signalling pathways, may be beneficial to developmental biologists.

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