Review

Stochastic gene expression in mammals: lessons from olfaction

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One of the remarkable characteristics of higher organisms is the enormous assortment of cell types that emerge from a common genome. The immune system, with the daunting duty of detecting an astounding number of pathogens, and the nervous system with the equally bewildering task of perceiving and interpreting the external world, are the quintessence of cellular diversity. As we began to appreciate decades ago, achieving distinct expression programs among similar cell types cannot be accomplished solely by deterministic regulatory systems, but by the involvement of some type of stochasticity. In the last few years our understanding of these non-deterministic mechanisms is advancing, and this review will provide a brief summary of the current view of stochastic gene expression with focus on olfactory receptor (OR) gene choice, the epigenetic underpinnings of which recently began to emerge.

Stochastic decisions in gene expression

Stochasticity in gene expression refers to the random mechanisms that govern transcription and translation resulting in variable levels of mRNA and proteins across cells of the same population. Stochastic gene expression has been studied mainly in prokaryotic organisms and lower metazoans, where it provides the means for genetically identical populations to obtain phenotypic diversity and develop subpopulations with adaptive advantages that can be used for their survival in varying environments [1]. One would expect that stochastic gene expression would not be tolerated in higher eukaryotes, where complex regulatory circuits control reproducible differentiation patterns that have prevailed evolutionarily [2]. Nonetheless, a new wave of studies revealed that stochastic choices are often found at the basis of central developmental programs dictating important cell-fate decisions or inducible transcriptional choices [3,4]. Several excellent reviews have addressed the stochastic mechanisms of cell-fate specification in various organisms and the principles that connect stochastic gene expression with the biological functions it enables [5–8].

In this review we use the regulation of the OR genes as a paradigm of stochastic, but irreversible, gene expression decision. The selection of a single OR allele in each olfactory sensory neuron (OSN) in the mouse olfactory epithelium (OE) is probably the longest-studied example of stochastic choice in the mammalian nervous system. We provide an overview of models proposed to explain OR stochastic expression and we describe newly identified aspects of OR gene complex regulation that highlight the critical role of epigenetic mechanisms, locus repositioning, and nuclear architecture as contributing factors.

The olfactory system is often paralleled to the immune system because they share several characteristics including monoallelic (see Glossary) receptor expression. As a matter of fact, allelic exclusion of the antigen receptor genes is one of the first and most thoroughly studied cases of stochastic choice. Therefore, we begin this review by summarizing key findings on the monoallelic expression of

Glossary

Allelic exclusion: the expression of a single allele from a specific gene locus and silencing of the other allele. In lymphocytes this phenomenon leads to the expression of one type of antigen receptor per cell.
Asynchronous replication: a phenomenon frequently observed with autosomal monoallelically expressed genes, imprinted genes, and X-linked genes where one allele is replicated earlier than the other. In most genes both alleles are replicated at the same time at a specific point in S phase.
Gene switching: a process where neurons that have selected a non-functional (and sometimes functional) OR gene re-choose a different OR allele.
Glomerulus: a specific structure in the olfactory bulb to which all the olfactory sensory neurons that express the same olfactory receptor project their axons. The glomeruli consist of the synapses of the OSN axons with the mitral cells and they form an olfactory topographic map that makes possible the interpretation of transmitted chemical signals to the brain as different odorants.
Locus control regions (LCRs): are 'defined by their ability to enhance the expression of linked genes to physiological levels in a tissue-specific and copy number-dependent manner at ectopic chromatin sites. The components of an LCR commonly colocalize to sites of DNase I hypersensitivity (HS) in the chromatin of expressing cells. The core determinants at individual HSs are composed of arrays of multiple ubiquitous and lineage-specific transcription factor-binding sites' [48].
Monoallelic expression: usually both alleles of a gene are actively transcribed (bi-allelic expression). In some cases, only one allele of a gene is expressed (monoallelism), for example several X-linked genes in females due to X chromosome inactivation. Recent studies have revealed that many autosomal genes display random monoallelic pattern of expression [8].
Monogenic expression: refers to the expression of a single gene or a pair of allelic genes. In the case of the OR family, only one (allele of a) gene is expressed in each neuron.
Olfactory receptor (OR) cluster: the vast majority of OR genes in mouse are found in groups (clusters) of two to several dozens of genes scattered throughout the genome.
Pericentromeric and subtelomeric repeats: highly repetitive DNA regions found adjacent to the centromere and telomeres of chromosomes. They are associated with DNA hypermethylation and the histone modifications H3K9me3 and H4K20me3.

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Box 1. Recombination in antigen receptor loci

There are seven distinct and structurally unique antigen receptor loci: the heavy chain locus (IgH), the light chain loci (Igκ and Igλ), and the T cell receptor-α (TCRα), -β (TCRβ), -γ (TCRγ), and -δ (TCRδ) loci. They are composed of multiple variable (V), diversity (D) and joining (J) gene segments as well as of the constant (C) exons. An example of the organization of an antigen receptor locus is shown in Figure I. The mouse Igh locus covers ~3 MB and consists of ~150 V_H, 9–12 D_H and 4 J_H gene segments. Cμ and Cα are the constant exons (locus not drawn to scale). The V(D)J recombination process involves the random rearrangement of the homonymous gene segments to generate the variable part of the immunoglobulin and T cell receptor genes. This process is cell lineage-restricted and developmentally dependent. In the B lineage, the IgH locus is the first to be rearranged with a D segment joining a J segment (pre pro-B cells) followed by V to DJ recombination (pro-B cells; Figure I). Light chain gene (Igκ or Igλ) rearrangement occurs in the next developmental stage of pre-B cells. The Igκ and Igλ loci do not contain D segments and recombination occurs only between the V and J segments (Figure I). Similarly, in the T lineage, the TCR gene segments undergo the same sequence of ordered recombination events. The TCRβ locus is first rearranged through D-to-J recombination, followed by V-to-DJ rearrangement (double-negative thymocytes). In the next stage of T cell maturation (double-positive thymocytes) the rearrangement of the TCRα locus occurs through joining of V to J segments.

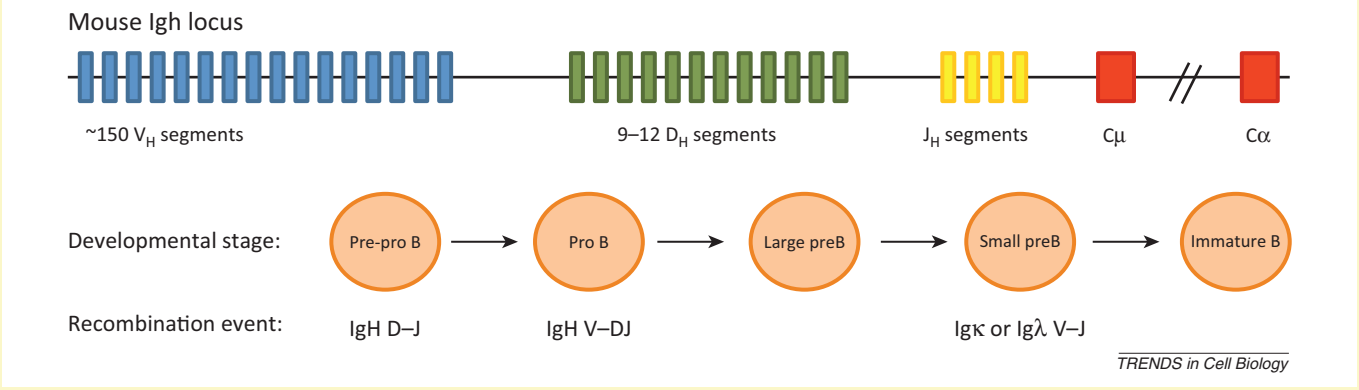

Figure I. Genomic organization and recombination in the immunoglobulin family.

antigen receptors in lymphocytes; we proceed to describe in detail the mechanisms that mediate stochastic choices in OR expression, and discuss analogies between the two systems. Finally, we present recent developments in the expression of clustered protocadherins that confirm the importance of epigenetic silencing and long-range DNA interactions in stochastic processes.

Stochasticity in the immune system: allelic exclusion of antigen receptor genes

As early as in the mid-60s there was evidence of the monoallelic nature of antigen receptor expression [9]. Later studies established that allelic exclusion occurs during the V(D)J [variable–(diversity)–joining] recombination process (Box 1) wherein only one allele is successfully rearranged and expressed. Even though the nature of allelic exclusion, probabilistic versus deterministic, remains a matter of debate, it is notable that both schools of thought evoke stochastic choices to account for this phenomenon [10]. The probabilistic model describes the monoallelic rearrangement as the result of random choice between two equivalent alleles and as the consequence of the low probability of simultaneous efficient recombination. Experimental support for this model was provided by the observation that both alleles of the T cell receptor TCRβ locus were distributed frequently and stochastically within the nuclear lamina and pericentromeric heterochromatin foci [11]. Notably, these alleles were less likely to undergo V_β-to-$D_\beta J_\beta$ recombination in double-negative thymocytes [11]. Therefore, it was proposed that stochastic interactions with repressive nuclear compartments could reduce the likelihood of simultaneous VDJ recombination [12]. The deterministic (instructive) model favors an initial stochastic marking of one allele at an early developmental stage; this marking is clonally maintained and ultimately dictates (instructs) the successful rearrangement and activation of the associated locus. A hallmark of monoallelic expression, asynchronous replication, was determined to set the mark for the subsequent allelic exclusion of antigen receptor genes [13]. A recent study has shed more light into this mechanism [14]. Using the Igκ locus as a model system, the authors showed that commitment to a chosen allele occurs in early lymphoid lineage cells, is accompanied by changes in asynchronous replication, is clonally maintained, and it predetermines monoallelic rearrangement in B cells [14]. This model has gained wider acceptance and describes allelic exclusion as a phenomenon that evolves in two phases, initiation and maintenance. The initiation phase, apart from the stochastic asynchronous replication, involves additional layers of regulation that ensure only one productive recombination will occur at each antigen receptor locus. Such mechanisms include the preferential association of the late-replicating antigen allele with pericentromeric heterochromatin and monoallelic contraction by chromosome looping that leads to the juxtaposition of the V and D–J segments [15], as well as changes in the DNA methylation and the histone modification status of the replicating allele that allow it to be accessible to recombination enzymes [16–18] (Figure 1A). In the maintenance phase, once an in-frame rearrangement takes place, a feedback mechanism is elicited that inhibits further recombination and is associated with epigenetic and locus conformation changes. For example, the non-functional IgH allele becomes recruited to pericentromeric heterochromatin and adopts a closed chromatin state [19] (Figure 1B). These changes could inhibit recombination by preventing the binding of recombinases to

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