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Mini-review

Immunoglobulin gene conversion: Synthesizing antibody diversification and DNA repair

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ABSTRACT

Recent developments in the field of antibody (Ab) diversification have rapidly advanced our understanding of the molecular mechanism underlying these events. Key to these developments was the identification of activation-induced cytidine deaminase (AID) as the central regulator of secondary Ab diversification, and the elucidation of its primary function as a DNA deaminase. Incredibly, current literature suggests the existence of a shared pathway, common to all secondary diversification processes, from which the separate outcomes branch outwards at various points. Immunoglobulin gene conversion (IGC) is one of these mechanisms and is used by a number of vertebrate species in both the development of the pre-immune repertoire and in affinity maturation. In a manner similar to other Ab diversification mechanisms, IGC has managed to co-opt a normal DNA repair pathway for the generation of receptor diversity. In the case of IGC specifically, that pathway is homologous recombination (HR). A burgeoning wealth of genetic, biochemical and structural data has clarified the roles of many key HR factors, allowing new insight into its molecular mechanism. These insights, combined with those from the common mechanism of AID action, synergize to develop an emerging picture of the mechanism underlying IGC.

Contents

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1. Introduction

That an effective humoral response is vital for protective immunity is undisputed. Through the production of antibodies (Ab), the humoral response serves to enhance non-specific responses and neutralize pathogens and toxins. Key to the effectiveness of this response is the generation of receptor diversity. It has only been in recent years, however, that an appreciation has been gained for the assortment of mechanisms employed by vertebrate species to achieve this goal. In primates and rodents, the immunoglobulin (Ig) locus is organized to promote the role of VDJ recombination as the focus of Ab diversification (Fig. 1A). In contrast, the Ig locus of *Gallus Gallus* (chicken) contains only a single copy of the V and J segment at both the heavy and the light chain loci [1], and though the heavy chain has 15 D segments, these are all nearly identical [2]. Chicken B-cells also exhibit limited junctional diversity [3], begging the question of how chickens can generate a full pre-immune repertoire in the face of such limited primary diversification.

It has become apparent that the primary role of VDJ recombination in the chicken is to generate an assembled V-region that is used as the basis for a second diversification mechanism, namely, immunoglobulin gene conversion (IGC) [4]. IGC is a secondary Ab diversification mechanism that produces templated changes in the sequence of the Ig V-region (Fig. 1D), changes that share much in common with the gene conversion (GC) products of homologous recombination (HR). The GC pathway is involved in repairing DSBs [5], transferring alleles in meiosis [6], and mating type switching in yeast [7]. GC can be described as the non-reciprocal exchange of sequence between a donor and recipient locus to produce a continuous tract of sequence that is donor derived, and ranging in length from several to 200 nucleotides (Fig. 1D) [5]. In the chicken, this mechanism has been co-opted to serve as a means of diversifying the specificity of the antigen receptor (Fig. 1D) [4]. In this review, the mechanism of IGC will be discussed in the context of recent development in the fields of DNA repair and antibody diversification. The focus will be primarily on the events that take place after the action of the master regulator, activation-induced cytidine deaminase (AID) since many recent reviews have covered the function of AID and its role in other mechanisms of secondary diversification.

2. Antibody diversification in the chicken

B-cell development in the chicken immune system begins with VDJ recombination in the yolk sac followed by B-cell precursor colonization of the bursa, regardless of whether productive VDJ recombination has occurred [8]. Bursal B-cells that successfully express Ig are then able to oligo-clonally seed follicles [9], beginning a program of extensive Ig diversification [1]. Through rounds of IGC, bursal B-cells extensively diversify their V-regions to generate a pool of naïve B-cells with a wide range of receptor specificities [10]. In contrast to the Bursa, diversification in the chicken germinal center occurs through both IGC and somatic hypermutation (SHM, see Section 4 and Fig. 1B), especially in the early stages of the reaction, while late germinal centers are believed to favor SHM [11]. This observation coincides with the fundamental nature of each mechanism. Specifically, IGCs capacity to make multiple changes in a single event [4] could facilitate rapid diversification of Ig receptors, an advantage in the low affinity environment of the early germinal center. As Ab affinities increase, point mutations generated by SHM would be more appropriate for fine-tuning the specificity of the improved Abs characteristic late in the reaction [12].

3. Overview of immunoglobulin gene conversion

The information encoding the potential modifications of IGC is stored in a series of ψV genes, 5′ of the heavy and light chain V-regions (Fig. 1D) [4]. The chicken λ locus contains 25 ψV genes, numbered in order with increasing distance from the V-region [4]. These pseudo-genes lack recombination signal sequences, promoters/enhancers, and they frequently harbor 5′ and/or 3′ truncations [4]. IGC events can be derived from any of the pseudo-genes, and subsequent events frequently overlap and/or overwrite pre-existing ones [4]. Heterology between the V-region and pseudo-genes varies from 10 to 20%, with the majority of sequence divergence localized to the CDRs