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Review

A comparative overview of immunoglobulin genes and the generation of their diversity in tetrapods

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ABSTRACT

In the past several decades, immunoglobulin (Ig) genes have been extensively characterized in many tetrapod species. This review focuses on the expressed Ig isotypes and the diversity of Ig genes in mammals, birds, reptiles, and amphibians. With regard to heavy chains, five Ig isotypes – IgM, IgD, IgG, IgA, and IgE – have been reported in mammals. Among these isotypes, IgM, IgD, and IgA (or its analog, IgX) are also found in non-mammalian tetrapods. Birds, reptiles, and amphibians express IgY, which is considered the precursor of IgG and IgE. Some species have developed unique isotypes of Ig, such as IgO in the platypus, IgF in *Xenopus*, and IgY (ΔFc) in ducks and turtles. The κ and λ light chains are both utilized in tetrapods, but the usage frequencies of κ and λ chains differ greatly among species. The diversity of Ig genes depends on several factors, including the germline repertoire and recombinatorial and post-recombinatorial diversity, and different species have evolved distinct mechanisms to generate antibody diversity.

Contents

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1. Introduction

The genomic organization of the tetrapod IgH and IgL loci is in a "translocon" configuration, in which many tandemly duplicated variable (V) genes are localized in a chromatin domain followed by many similarly arranged diversity (D) genes (only for heavy chains) and joining (J) genes. Compared with the cluster configuration of the Ig gene locus in cartilaginous fish, this type of organization both allows for somatic rearrangement among different V, D, and J segments (known as VDJ recombination) to greatly increase combinatorial diversity and further expands this diversity after rearrangement by somatic gene conversion (GC), a mechanism that utilizes upstream V genes to unidirectionally modify a pre-rearranged V gene. In the tetrapod IgH loci, constant (C)-region genes, which encode various Ig isotypes with different effector functions, are also tandemly arranged downstream of the V, D, and J segments. This arrangement of the C-region genes facilitates the production of different IgH isotypes through a class switch recombination (CSR) process while maintaining the same antigen-binding specificity. Therefore, the tetrapod Ig genes have evolved to produce antibodies with highly diversified multiple effector functions. This review will analyze the features of Ig genes in four lineages of tetrapods: mammals, birds, reptiles, and amphibians, focusing on the multiple IgH and IgL isotypes and the mechanisms responsible for generating Ig diversity.

2. Mammals

Mammals (*Mammalia*) are taxonomically divided into two subclasses: the Prototheria and the Theria. *Prototheria* contains only one living order, Monotremata (the monotremes), and the *Theria* consists of the infraclasses Metatheria (including marsupials) and Eutheria (the placentals).

2.1. Placentals

2.1.1. The heavy- and light-chain isotypes

Most of our knowledge of the mammalian Ig genes is based on studies of placental mammals. The structure and/or diversity of IgH and/or IgL genes are described in many species belonging to at least nine orders. With the exception of rabbits, whose δ gene is lost in the genomic IgH loci, most placental mammals express five classes of Igs: IgM, IgD, IgG, IgA, and IgE (Lanning et al., 2003; Ros et al., 2004). A remarkable feature of the placental IgH locus is the large copy number of Cγ and Cα genes, which encode multiple IgG or IgA subclasses. For example, the number of Cγ genes in the haploid genome of the elephant, horse, cattle, mouse, and human are eight, seven, three, four, and four, respectively (Guo et al., 2011; Schroeder, 2006; Wagner et al., 2004; Zhao et al., 2003), and the pig genome also possesses a large number of Cγ genes (Butler et al., 2006). Moreover, the rabbit germline IgH locus contains 13 non-allelic Cα genes (Burnett et al., 1989). Different IgG subclasses have evolved to exert diverse effector functions by interacting with FcγRs and activating the classical complement pathway, and this is well illustrated in the human and in the mouse (Burton and Woof, 1992; Nimmerjahn and Ravetch, 2008; Ravetch and Bolland, 2001). In addition, cattle seem to have a second IgH locus, including a μ-like C-region sequence, on another chromosome (Hayes and Petit, 1993; Tobin-Janzen and Womack, 1992).

To date, two light-chain types, λ and κ, have been found in placental mammals. Usually, the λ locus consists of a few Jλ–Cλ clusters, and the κ locus contains several Jκ segments followed by one Cκ gene. The rabbit genome possesses a duplicated Cκ gene, Cκ2, which is normally expressed at a low level (Heidmann and Rougeon, 1983; Hole et al., 1991).

2.1.2. The germline, recombinatorial, and post-recombinatorial diversity of the heavy and light chains

A large number of germline and rearranged VH and VL genes, as well as cDNAs, have been identified in various placental mammals. According to these sequences, VH elements of placental mammals are classified into three clusters: mammalian clans I, II, and III (Ota and Nei, 1994; Sitnikova and Su, 1998). The germline and rearranged VH repertoires of the mouse and human are diverse. The mouse germline VH repertoire contains nearly 200 VH segments (113 potentially functional, 79 pseudogenes, and six ORF VH segments for C57BL/6), which are grouped into 16 subgroups. Among the VH segments, at least 39 VH segments from nine subgroups participate in rearrangement (Lefranc, 2003). In the human IgH locus, 38–44 potentially functional VH segments, most of which can be rearranged and expressed, belong to seven subgroups (Lefranc, 2003). In addition, the VH repertoires expressed in the mouse and human are distributed across all three mammalian VH clans (Lefranc, 2003; Schroeder et al., 1990). However, a preference for a single VH subgroup in the expressed VH repertoire is demonstrated in the rabbit (only VH1 is preferentially utilized), dog, horse, and several artiodactyl lineages, although a few recent studies indicate that the germline VH repertoires of the sheep and horse are more complex and diverse than previously thought. All of these preferred VH segments belong to either clan II (including the horse, cattle, and sheep) or clan III (including the rabbit, dog, and pig) (Almagro et al., 2006; Bao et al., 2010; Becker and Knight, 1990; Berens et al., 1997; Charlton et al., 2000; Dufour et al., 1996; Sun et al., 1994, 2010).

Mammalian VL genes are grouped into six clans – five containing Vλ sequences and one exclusively containing Vκ genes – which are further divided into 10 subgroups (Sitnikova and Nei, 1998; Sitnikova and Su, 1998). Light chain usage in placental mammals has two characteristics. First, in most species, the overall complexity of the germline Vλ and Vκ repertoire seems to correlate with the preferential use of one light-chain isotype over another (Almagro et al., 1998). Obvious examples include the human and the mouse. The former has numerous and diverse Vλ and Vκ segments and uses both extensively (κ:λ, 60%:40%), and the latter has many Vκ but only three functional Vλ segments; as a result, it primarily uses Vκ (κ:λ, 95%:5%) (Almagro et al., 1998). This rule may also partially explain the predominance of the λ isotype in the horse and the κ isotype in the rabbit (Sun et al., 2010 and our unpublished data). Second, the placental mammals that express relatively restricted VH repertoires also seem to express limited VL repertoires. Horse and cattle, two predominant lambda chain usage species, mainly utilize a single Vλ subgroup in their combinatorial repertoires (Saini et al., 2003; Sun et al., 2010). Pigs show nearly equal usage of κ and λ light chains, and their pre-immune VL repertoire prefers only one Vκ and two Vλ subgroups (Butler et al., 2006, 2004). The rabbit may be one exception. Rabbits predominantly use the κ light chain type, and most of their Vκ genes belong to one subgroup with at least 80% identity (Ros et al., 2005; Sehgal et al., 1999). However, the Vκ–Jκ junctions seem to be diverse mainly because of the heterogeneity of the CDR3 length (Sehgal et al., 1999). In some cases, the diversity of the IgL chain is not necessary for the overall diversity of the antibody in camelids (camels and llamas), which express unique classes of IgG (IgG2 and IgG3) that lack light chains entirely (De Genst et al., 2006).

With regard to the mammals in which V(D)J recombinatorial diversity is limited, two post-rearrangement somatic strategies, somatic hypermutation (SHM) and/or GC, contribute to the generation of a diverse primary antibody repertoire. Unlike GC, SHM can introduce template-independent point mutations into the V regions of Ig genes. In the rabbit, sheep, and cattle and likely in the horse and pig, the gut-associated lymphoid tissue (GALT), especially the appendix in the rabbit and the ileal Peyer's patch