Diversification of the bovine primary immunoglobulin heavy chain repertoire: Ontological and hypermutational analyses in fetal and neonatal animals

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Abstract

The objective of this dissertation was to identify and characterize diversity within the expressed primary immunoglobulin heavy chain (IgH) repertoire in cattle. Determinations relied heavily upon different comparative analysis strategies focussing on both germline and expressed IgH gene segment sequences. We determined that the early fetal expressed IgH repertoire is constituted by as few as 2–3 VH genes and a single JH gene (multiple D). VH gene use increases with age, though IgH expression is restricted to members of a single VH family and primarily one JH gene (>300 sequences analyzed). All isolated germline VH genes also belong to a single VH family, corresponding to that in the expressed repertoire. Therefore, germline-encoded VH (and JH) sequence polymorphism is low, making limited contributions to overall IgH sequence diversity. In sharp contrast, bovine CDR3 regions exhibit extremely high levels of heterogeneity both in terms o f sequence and hypervariable lengths. ^ A major fraction of IgH diversification occurs after rearrangement, most likely via untemplated somatic hypermutation. Nucleotide substitutions within the JH-Cμ intron, which does not support gene conversion due to a lack of known donor sequences, were consistent with USH on multiple levels, including hotspot targeting, the ratio of transitions to transversions, preferential nucleotide substitutions and potential strand bias. ^ Sequence diversity levels varied with time among immunologically relevant

tissues. Early fetal spleen and late fetal ileum appear to be two important sites of B cell diversification during their respective developmental stages. Patterns of IgH expression suggest that spleen is the early site of substantial gene rearrangement, and source of B cell emigrants, which subsequently populate other peripheral tissues including liver, ileum, and bone marrow. ^

Subject Area

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