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Review

The MHC class I genes of zebrafish

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ABSTRACT

Major histocompatibility complex (MHC) molecules play a central role in the immune response and in the recognition of non-self. Found in all jawed vertebrate species, including zebrafish and other teleosts, MHC genes are considered the most polymorphic of all genes. In this review we focus on the multi-faceted diversity of zebrafish MHC class I genes, which are classified into three sequence lineages: U, Z, and L. We examine the polygenic, polymorphic, and haplotypic diversity of the zebrafish MHC class I genes, discussing known and postulated functional differences between the different class I lineages. In addition, we provide the first comprehensive nomenclature for the L lineage genes in zebrafish, encompassing at least 15 genes, and characterize their sequence properties. Finally, we discuss how recent findings have shed new light on the remarkably diverse MHC loci of this species.

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1. Introduction

Originally identified as a genetic locus responsible for transplant rejection between congenic mouse strains (Klein, 2001; Snell and Higgins, 1951), major histocompatibility complex (MHC) loci have been well studied in many species. With a high gene density, the MHC locus is one of the most polymorphic regions in mammalian genomes (Klein, 2001; Kumanovics et al., 2003; Takada et al., 2003). The human MHC locus comprises a 4 Mb section of chromosome 6 containing hundreds of genes (MHC Sequencing Consortium, 1999; Shiina et al., 2009) including the MHC class I and class II genes, which encode molecules that present peptide antigens to T cells and play a central role in distinguishing between self and non-self (Chaplin, 2010). These transmembrane proteins have been found in all jawed vertebrate species examined including cartilaginous fishes (Kulski et al., 2002; Okamura et al., 1997; Trowsdale, 1995).

Levels of sequence diversity found between MHC genes and their alleles are considered the highest of any genes in the vertebrate genome (Vandiedonck and Knight, 2009). Evidence for overdominance has been found within MHC loci favoring heterozygosity and is likely associated with response to diverse pathogens (Hughes and Nei, 1988). MHC genes also play a fundamental role in allograft recognition (Thorsby, 2009), and matching at MHC loci between donors and recipients is important to ensure successful transplant outcomes by minimizing acute graft rejection and/or graft-versus-host disease after bone marrow transplantation (reviewed by Groth et al., 2000). Human donor and recipient matching at the most polymorphic classical MHC genes may have a disproportionate impact on transplantation success (Horan et al., 2012). MHC loci are also considered model regions for genomics research in large part due to the association of the MHC with a number of different diseases (Trowsdale and Knight, 2013; Vandiedonck and Knight, 2009).

As a vertebrate model species, the zebrafish (*Danio rerio*) has several advantages over the more traditional mouse model including higher fecundity, smaller size, more rapid development, external fertilization, and optical clarity at the embryonic and larval stages. Because of these advantages, zebrafish are routinely employed for studies of in vivo immune function (van der Vaart et al., 2012), host-pathogen interactions (Kanther and Rawls, 2010; Tobin et al., 2012), and cell migration (Ignatius and Langenau, 2011; Renaud et al., 2011), as well as transplantation assays, particularly for the study of hematopoietic stem cells (de Jong et al., 2011; Li et al., 2011; Taylor and Zon, 2009). However their use in this type of assay highlights a current limitation: attempts at generating inbred zebrafish lines met with only limited success (Shinya and Sakai, 2011), resulting in standard laboratory "lines" of zebrafish harboring a multitude of polymorphisms as well as haplotypic variation especially at immune loci (Howe et al., 2013; Patowary et al., 2013). As immunologically compatible zebrafish donors and recipients are not readily available, genotyping strategies have been and are being developed for identifying MHC-matched zebrafish. However, the number of described MHC class I loci in the zebrafish genome is growing (Dirscherl and Yoder, 2014; McConnell et al., 2014). In this review we will summarize the current knowledge on the polygenic, polymorphic and haplotypic nature of the zebrafish MHC class I gene families. We will also provide an overview on the data implicating zebrafish MHC class I genes in immune function.

2. Classical and nonclassical MHC class I molecules

Classical function of MHC class I molecules is defined as presentation of peptide antigens to $CD8^+$ T cells in order to initiate an immune response. In mammals, only a subset of MHC class I genes is associated with classical function, as some MHC molecules interact with other immune cells, present non-peptide antigens, or have non-immune functions (Parham, 2005; Rodgers and Cook, 2005). Classical MHC class I genes have extremely high levels of polymorphism, often found as specific patterns of substitutions in the MHC molecules particularly among residues associated with the peptide binding site (Bjorkman et al., 1987). Additional characteristics of classical MHC molecules include conservation of peptide anchor residues, conserved structural residues and conserved surface residues associated with binding sites with other molecules such as beta-2-microglobulin (β2M) and CD8 (Hee et al., 2013). Presentation of diverse processed intracellular peptides by classical MHC class I molecules at the cell surface allows their interrogation by the immune system, and thus T cells become activated upon recognizing these MHC-presented allo-antigens to help initiate an immune response (Bjorkman and Parham, 1990; reviewed in Klein and Sato, 2000).

The nonclassical MHC genes are frequently at least an order of magnitude less polymorphic than their classical counterparts and are often expressed in limited tissues (Shiina et al., 2009). Interestingly, some MHC molecules considered classical, such as HLA-C, also have nonclassical characteristics, and are thus capable of initiating an immune response by more than one mechanism (Colonna et al., 1993). It has been hypothesized that classical MHC genes are periodically duplicated within the genome (Klein et al., 2007; Nei and Rooney, 2005) and thus over time may be free to be selected upon to acquire diverse roles (Flajnik and Kasahara, 2001). Of note, a large fraction of the nonclassical MHC genes are not found within the core MHC locus but are instead scattered on additional chromosomes in humans (Horton et al., 2004) and many other vertebrate species. This scattering of class I genes outside of the core MHC locus also applies to zebrafish (Dirscherl and Yoder, 2014; McConnell et al., 2014;Sambrook et al., 2005).

In zebrafish, three MHC class I lineages have been described: U, Z and L. The U lineage genes function as classical MHC class I genes in zebrafish whereas the L lineage genes likely represent nonclassical MHC class I genes. The zebrafish Z lineage genes cannot be currently classified as either classical or nonclassical MHC class I genes. A phylogenetic analysis of all identified zebrafish MHC class I proteins (α1–α3 domains) illustrates their classification into these three lineages and highlights their subgrouping based on chromosomal location (Fig. 1). The evidence supporting the classification of these genes is discussed below.

3. Nomenclature and history of MHC class I lineages

Based on guidelines proposed for all species (Klein et al., 1990), the current zebrafish MHC class I gene nomenclature reflects the nomenclature system in Atlantic salmon (*Salmo salar*; Lukacs

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