The evolution and functional diversification of two CD83 homologs in the monocyte-macrophage lineage in ginbuna crucian carp, Carassius auratus langsdorfii

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Title　：The evolution and functional diversification of two CD83 homologs in the monocyte-macrophage lineage in ginbuna crucian carp, *Carassius auratus langsdorfii*

（ギンブナ(*Carassius auratus langsdorfii*) の単球マクロファージ系細胞における 2 つの CD83 ホモログの進化と機能的多様性）

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Thesis Summary

[Introduction]

CD83 is a well-known co-stimulatory molecule predominantly expressed on the surface of mature dendritic cells, B cells, and activated T cells. It plays a crucial role in the regulation of the immune response, particularly in antigen presentation. The CD83 molecule enhances the capacity of antigen-presenting cells (APCs) to stimulate T cells, thereby modulating both innate and adaptive immunity. The monocyte-macrophage lineage is an essential component of the innate immune system. Monocytes, which originate from bone marrow progenitors, circulate in the bloodstream and can differentiate into macrophages or dendritic cells upon entering tissues. Macrophages are key players in the immune response, responsible for phagocytosis, cytokine production, and antigen presentation. They are also involved in tissue repair and homeostasis. Dendritic cells are specialized APCs that capture antigens and present them to T cells, initiating and regulating immune responses. Microglial cells of the central nervous system play a vital role in maintaining brain homeostasis and responding to injury and disease. They are involved in immune surveillance, phagocytosis of cellular debris, and modulation of neuroinflammatory process. Given the critical roles of CD83 in immune cell function and the importance of the monocyte-macrophage lineage in immunity, understanding the evolution and functional diversification of CD83 homologs is paramount. This study focuses on characterizing and analyzing two CD83 homologs in the ginbuna crucian carp, a teleost model, to uncover evolutionary pathways and functional roles of these genes in the immune system.

[Objective]

The primary objective of this study was to clone and characterize two homologs of the CD83 gene in the ginbuna crucian carp, a fish model, and to investigate the evolution of the CD83 gene across species. This evolutionary perspective aims to uncover pathways through which the two CD83 homologs have evolved, paving the way for a comprehensive functional analysis in teleosts. Given the importance of CD83 in immune cells, particularly within the monocyte-macrophage lineage, this research seeks to deepen our understanding of CD83 function in immune defense, with potential applications in vaccine development and immunotherapy.

[Results]

Identification of CD83 homologs

Two CD83 homologs, designated as CD83 and CD83-L (CD83-like), were successfully identified in ginbuna crucian carp with the DNA length are 621bp and 561bp, respectively.

The evolution of CD83 homologs

The phylogenetic analysis and genomic studies revealed that CD83 and CD83-L genes are present in a wide range of vertebrates, including sharks, spotted gar, teleosts, coelacanths, lungfish, and reptiles. However, amphibians, birds, and mammals possess only the CD83 gene, lacking CD83-L. This pattern suggests that the presence of only one CD83 gene in these groups is likely due to lineage-specific gene loss events that occurred after the initial gene duplication. Such losses might have been driven by changes in selective pressures, functional redundancy, or other evolutionary factors. The phylogenetic tree suggests that CD83 and CD83-L genes are paralogs, derived from a common ancestral gene through a duplication event. Following gene duplication, evolution processes may lead to divergence between homologous genes. It may result in major variations in genetic context and function.

Functional analysis

Both CD83 homologs are significantly expressed in spleen, thymus. There are differences in tissue distribution of these two homologs. *CD83* is highly expressed in spleen, thymus, and kidney, while *CD83-L* is profoundly expressed in brain, spleen, and thymus.

The two CD83 homologs exhibit differential expression during monocyte differentiation. CD83 is highly expressed in monocytes, while CD83-L is significantly expressed at later stages, potentially in monocyte-derived dendritic cells.

CD83 and CD83-L expressions were also studied in kidney-resident macrophages (KRMs) and microglial cells (brain macrophages) *in vitro*. CD83-L protein is predominantly expressed in KRMs and microglia.

Under lipopolysaccharide (LPS) stimulation, both *CD83* and *CD83-L* genes were significantly upregulated after 24 hours, indicating their roles in immune response. These findings suggest that CD83 can serve as a marker for the monocyte-macrophage lineage and a potential molecule for adjuvant vaccines.

[Conclusion]

This study provides significant insights into the presence and evolution of two CD83 homologs in teleost, revealing their distinct evolutionary paths post-gene duplication. The disappearance of CD83-L in amphibians, birds, and mammals highlights the role of evolutionary pressures in shaping gene retention and loss across species. Functionally, the differential expression of CD83 homologs in monocytes, macrophages, and microglial cells underscores their specialized roles in the immune response. Furthermore, *CD83* homologs exhibited the upregulation post-24-hour LPS stimulation *in vitro*. The findings suggest that CD83 could be a valuable marker for the monocyte-macrophage lineage and a potential immunomodulator. This research holds promise for future applications in vaccine development and immunotherapy, leveraging the unique functions of CD83 homologs.