

## Homeostatic functions of a CD46-like membrane bound complement regulatory protein (Tecrem) in teleost

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<https://hdl.handle.net/2324/4496113>

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出版情報 : Kyushu University, 2021, 博士 (農学), 課程博士  
バージョン :  
権利関係 :

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論文題名 : Homeostatic functions of a CD46-like membrane bound complement regulatory protein (Tecrem) in teleost  
(硬骨魚類における CD46 様膜型補体制御タンパク質 (Tecrem) の恒常性維持機能)

区 分 : 甲

### 論 文 内 容 の 要 旨

Mammalian CD46 have been reported as a multitasking immune modulator, which regulates complement activation on host cells, T cell-mediated adaptive responses, and wound repair by involving epithelial cells. It is of particular interest to explore the evolutionary path of such versatile functions of CD46. Previous studies have identified a CD46-like molecule, termed teleost complement regulatory membrane protein or Tecrem, in a few cyprinid fish species and has shown its regulatory function on complement activation at the protein level. In the present study, we have explored a homeostatic role of Tecrem in maintaining the fish epithelium, by analyzing expression behavior of Tecrem on two epithelial cell lines (KF-1 and CFS) derived from carp fin. Flow cytometric analysis of Tecrem expression on KF-1 using anti-carp Tecrem monoclonal antibody (mAb) (1F12) suggested that epithelial cell aggregation and adhesion is affected by Tecrem expression. Fluorescent microscopic observation and an ELISA-based assay also indicated a role of Tecrem in the adhesion of KF-1 to the surface of culture media. Furthermore, 1F12 mAb deposited on the culture plate significantly enhanced an early stage of cell adhesion process of KF-1.

We have also prepared recombinant Tecrem proteins in the bacterial expression system for functional analysis of Tecrem. Among the four short consensus repeat (SCR) modules making up the extracellular domains of Tecrem, the N-terminal two SCRs (rSCR1-2) and the C-terminal two SCRs (rSCR3-4) were separately expressed as 6xHis-tagged soluble protein using pCold-I vector and Origami B strain. Cell adhesion and wound-healing assays done on KF-1 cells showed that the cell adhesion and wound healing is enhanced when the cells were incubated with anti-SCR1-2 and anti-SCR3-4 polyclonal antibodies and with 1F12 mAb. Increased cell proliferation and wound healing of KF-1 cells upon cTecrem activation suggests that the normal functional role of cTecrem on epithelial cells can be homeostatic via the induction of surface barrier repair upon pathogen entry or any other injury. This could be due to the signaling events followed by the regulation of tight junction proteins. Considering the natural conditions, the C3b, C4b or any pathogen could be acting as a ligand which initiate this process. This homeostatic function of Tecrem on epithelial cells shows its importance in the first line defense of the carp fishes and suggests a possibility that Tecrem may be targeted by many pathogens to enter the fish body.