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Immunology Notes and Resources

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Nomenclature of Toso, Fas Apoptosis Inhibitory Molecule 3, and IgM FcR

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Hiromi Kubagawa and John E. Coligan coordinated an online meeting to define an appropriate nomenclature for the cell surface glycoprotein presently designated by different names: Toso, Fas apoptosis inhibitory molecule 3 (FAIM3), and IgM FcR (FcμR). *FAIM3* and *Faim3* are the currently approved symbols for the human and mouse genes, respectively, in the National Center for Biotechnology Information, Ensembl, and other databases. However, recent functional results reported by several groups of investigators strongly support a recommendation for renaming *FAIM3/Faim3* as *FCMR/Fcmr,* a name better reflecting its physiological function as the FcR for IgM. Participants included 12 investigators involved in studying Toso/FAIM3(Faim3)/FμR, representatives from the Human Genome Nomenclature Committee (Ruth Seal) and the Mouse Genome Nomenclature Committee (Monica McAndrews), and an observer from the IgM research field (Michael Carroll). In this article, we provide a brief background of the key research on the Toso/FAIM3(Faim3)/FcμR proteins, focusing on the ligand specificity and functional activity, followed by a brief summary of discussion about adopting a single name for this molecule and its gene and a resulting recommendation for genome nomenclature committees. *The Journal of Immunology*, 2015, 194: 4055–4057.

In 1998, Hitoshi et al. (1) in Nolan's laboratory first identified a cDNA encoding a potent inhibitor of Fas-induced apoptosis by functional assay and designated it Toso, after a Japanese liquor used on New Year's Day to celebrate long life and eternal youth. They used an agonistic IgM anti-human Fas mAb (clone CH11) to induce Fas-mediated apoptosis in an apoptosis-prone human T cell line, Jurkat. Toso-bearing Jurkat cells were resistant to such IgM mAb-induced apoptosis, whereas control Jurkat cells were susceptible.

In 2005, Song and Jacob (2) cloned the mouse ortholog and found that colocalization of Fas and mouse Toso was observed in Fas^+ HEK 293 cells transiently transfected with a mouse Toso cDNA, ectopic expression of mouse Toso protected Jurkat cells from apoptosis induced by FasL and TNF-α but not TRAIL, and primary T cells isolated from *Toso*-transgenic mice (under the *Lck* promoter) were resistant to apoptosis induced by FasL or an IgG2 agonistic anti-mouse Fas mAb (clone JO2). The Human Genome Nomenclature Committee approved naming Toso as *FAIM3* (Fas apoptosis inhibitory molecule 3) for the human gene, and the Mouse Genome Nomenclature Committee approved *Faim3* for the mouse gene.

In 2009, Richter et al. (3) showed that small interfering RNA–mediated downmodulation of FAIM3/Toso increased the susceptibility of blood T cells activated with anti-CD3 mAb plus IL-2 to FasL-induced apoptosis. Also in 2009,

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Abbreviations used in this article: CLL, chronic lymphocytic leukemia; FAIM3, Fas apoptosis inhibitory molecule 3; FcμR, IgM FcR.

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Kubagawa et al. (4) cloned a cDNA encoding an IgM FcR (FcμR) based on an IgM-binding screening strategy from two cDNA libraries generated from human B-lineage cells, including chronic lymphocytic leukemia (CLL) cells. The nucleotide sequence of the FcμR cDNA was identical to that of Toso/FAIM3. They confirmed the finding of Fas inhibitory activity of Toso/FAIM3/FcμR reported by Hitoshi et al. (1), but this was only observed when Fas was ligated by an agonistic IgM mAb. Apoptosis was induced in both Toso/FAIM3/FcμR-bearing and control Jurkat cells when Fas was ligated by an agonistic IgG3 mAb (2R2). Consistent with previous findings of Kubagawa et al. and other investigators, enhanced FcμR expression, as well as IgM binding, was observed on CLL B cells. *FCMR* is a single-copy gene located on human chromosome 1q32.2 adjacent to two other IgM-binding receptor genes: *PIGR* and *FCAMR* (4).

In 2010, Shima et al. (5) in Ohno's laboratory showed that a HeLa cell line transiently expressing mouse Toso/Faim3 exhibited weak binding to IgM and that the clustering of *Toso/Faim3* with *Pigr* and *Fcamr* also was conserved in the mouse genome.

In 2011, Nguyen et al. (6) in Lee's laboratory showed that FasL-induced apoptosis of the human B cell line BJAB and anti-CD3/anti-CD28–activated blood T cells and Jurkat cells correlated inversely with cell surface expression levels of Toso/FAIM3, which were modulated by Toso miRNA-mediated knockdown and Toso cDNA transduction; no IgM binding was observed with BJAB or Jurkat cells overexpressing Toso/FAIM3; A38, but not A36, anti-Toso mAb specifically blocked the antiapoptotic function of Toso/FAIM3 in FasL-induced apoptosis assays; and *Toso/Faim3*-deficient mice were protected from TNF-α–induced liver damage. Vire et al. (7) in Wiestner's laboratory demonstrated that Toso/FcμR was highly expressed on CLL B cells, was internalized upon IgM binding and shuttled to the lysosomes for degradation, and was downmodulated in response to TLR7 and TLR9 activation.

In 2012, Honjo et al. (8) in Kubagawa's laboratory disputed the findings reported by Nguyen et al. (6) and provided data showing that FcμR/Toso bound to IgM and did not affect Fas-mediated apoptosis by an agonistic IgG mAb or native FasL. Nguyen et al. (9) replied that they could not confirm IgM binding by Toso in their hands and cited experimental data from their group and other investigators to support a role for Toso as a general regulator of death receptor signaling via FasL, TNF-α, and TRAIL. Murakami et al. (10) in Coligan's laboratory demonstrated that Toso/FAIM3-bearing Jurkat cells and the human NK cell line YTS, as well as Toso on blood NK cells, bound IgM; IgM binding to NK cells correlated with cell surface expression of Toso/FcμR; and overexpression of Toso/FcμR on Jurkat T cells or on blood NK cells expanded in vitro with IL-2 did not rescue them from Fas-mediated apoptosis induced by an agonistic IgG mAb or FasL. They also demonstrated the resistance of such Toso/FcμR-bearing cells to agonistic IgM anti-Fas mAb-induced apoptosis (10).

Two laboratories (Ohno and Mak) had generated *Fcmr*/*Toso*-deficient mice, and from 2012 to 2015 four groups of investigators independently characterized their phenotypes (11–19). Clear differences in the reported phenotypes, in addition to the cellular distribution of FcμR/Toso, were evident but are not discussed in this article because they are not directly related to the topic of this meeting.

In 2013, Ouchida et al. (20) in Wang's laboratory showed that FcμR was not involved in Fas-mediated cell death in thymocytes or in splenic T and B cells before and after activation, because there were no differences in FasL- or agonistic IgG mAb-induced apoptosis between wild-type and *Fcmr*-deficient mice. Also in 2013, Ding et al. (21) in Heyman's laboratory, in collaboration with Ohno and Wang, showed that mouse FcμR/Faim3, ectopically expressed on BW5147 cells, bound equally well to serum IgM isolated from wild-type and Cμ13 mice, although the latter mice produce IgM that cannot activate the classical complement pathway because of a point mutation in position 436 in the μ H chain. This confirmed direct binding of IgM to the FcμR, rather than indirect binding through a complement receptor.

In 2014, Kubagawa et al. (22) demonstrated that human FcμR-bearing cells exhibited IgM ligand binding, irrespective of the growth phase in cell culture (constitutive ligand binding activity), whereas mouse FcμR-bearing cells bound to IgM during the early phase, prior to the exponential growth phase (transient ligand-binding activity). The cell surface FcμR levels in FcμR-bearing mouse cells, as determined by receptor-specific mAbs, were not significantly changed during the entire period of culture. Kubagawa et al. (23) showed that preincubation of membrane lysates of FcμR/FAIM3-bearing cells with receptor-specific mAbs completely removed the ∼60-kDa IgM-reactive protein, and addition of FcμR-blocking mAb (HM7) in apoptosis assays with an agonistic IgM anti-Fas mAb inhibited the interaction of the Fc portion of IgM mAb with FcμR in a dose-dependent manner, thereby promoting apoptosis of FcμR-bearing Jurkat cells.

In 2015, Honjo et al. (24) demonstrated that, although FcμR/FAIM3 binds soluble pentameric IgM with a relatively high avidity of ∼10 nM (4), FcμR/FAIM3 interacted more efficiently with the Fc portion of IgM Ab when it was bound to the plasma membrane via its Ag-binding Fab regions; this interaction occurred in *cis* on the same cell surface but not in *trans* between neighboring cells.

Conclusions

Nolan initially questioned the wisdom of a constant renaming of genes because the literature has often been confused by investigators making premature name changes for proteins to fit their latest published function; several other investigators (Richter, Jacob, Lang, Lee) supported his opinion. Toso was originally renamed by a nomenclature committee to FAIM3. Morse argued against the nomenclature committee's naming based on strong evidence that Toso is an IgM-binding receptor and on its chromosomal localization, which is conserved in both species, adjacent to two other IgM-binding receptors (pIgR and Fcα/μR). He proposed naming the gene *FCMR* for human and *Fcmr* for mouse. Wiestner and Ohno supported the FcμR nomenclature. Lee also raised a concern that studies describing the IgM-binding activity mainly dealt with human Toso/FAIM3/FcμR. Kubagawa responded to this concern by providing data showing that mouse FcμR/Faim3 indeed binds IgM, but it does so only transiently, unlike the constitutive IgM binding by the human receptor. A recent article by Ding et al. (21) supporting this observation

was cited. In the end, Nolan agreed that he would be amenable to a name change recommended by the consensus. Although Wang agreed to rename Toso/Faim3 as FcμR, he raised the possibility of a survival-enhancing function of FcμR in murine B cells. In conclusion, based on all of the correspondence during the meeting, we highly recommend renaming the genes *FAIM3* (for humans) and *Faim3* (for mice) as *FCMR* and *Fcmr*, respectively.

Disclosures

The authors have no financial conflicts of interest.

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