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REVIEW
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The GIMAP Family Proteins: An Incomplete Puzzle

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Overview: Long-term survival of T lymphocytes in quiescent state is essential to maintain their cell numbers in secondary lymphoid organs and in peripheral circulation. In the BioBreeding diabetes-prone strain of rats (BB-DP), loss of functional GIMAP5 (GTPase of the immune associated nucleotide binding protein 5) results in profound peripheral T lymphopenia. This discovery heralded the identification of a new family of proteins initially called Immune-associated nucleotide binding protein (IAN) family. In this review we will use 'GIMAP' to refer to this family of proteins. Recent studies suggest that GIMAP proteins may interact with each other and also be involved in the movement of the cellular cargo along the cytoskeletal network. Here we will summarize the current knowledge on the characteristics and functions of GIMAP family of proteins.

Keywords: GIMAP5, gimap, lymphopenia, AIG domain, T lymphocyte, B cells

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INTRODUCTION

In the BioBreeding diabetes-prone strain of rats (BB-DP), the recessive *lyp* mutation causes a profound loss of T lymphocytes in secondary lymphoid organs (1). Positional cloning of the gene responsible for the lymphopenic phenotype in the BB-DP rats independently by two groups led to the discovery of a family of proteins that are conserved in vertebrates (2, 3). The *lyp* allele arises from a frame shift mutation within the GTPase domain of the immune associated nucleotide binding protein 5 (*Gimap5*) gene, resulting in a truncated protein lacking 223 amino acids at the C-terminus (2, 3). GIMAP5 is a member of the GIMAP family that are implicated in immune functions in mammals (4). Initially this family of proteins was named IAN, for 'immune associated nucleotide binding' proteins, as they were predominantly expressed in the cells of the hematopoietic system and contained domains that can bind to GDP/GTP. In this review we will summarize our current knowledge of the structure and functions of GIMAP proteins, many of which are implicated in the development and maintenance of lymphocytes (**Table 1**). All *Gimap* genes are clustered within a short locus in the genome. The human *GIMAP* cluster, spanning about 500kb on

Abbreviations: BB-DP, Biobreeding diabetes prone; CRAC, Ca^{2+} release activated Ca^{2+} channel; GIMAP, GTPase of the immune associated nucleotide binding protein; GPN, Gly-Phe β-naphthylamide; HSC, hematopoietic stem cell; MHC:p, MHC peptide complex; RTE, recent thymic emigrants; T1D, Type 1 diabetes.

TABLE 1 | Phenotype of deficiency in *GIMAP* genes.

Gene/Protein localization	mice/rats	Humans	References
Gimap5 Lysosomes, vesicles	**Rats:** Normal T cell development; reduced T cell export; peripheral T lymphopenia; Survival defects in naïve resting T cells; normal B and NK cells; T cell-mediated autoimmunity dependent on the genetic background; Normal life span; spontaneous activation of the AKT signaling pathway **Mice:** Deficiency in T, B and NK cells; survival defects in lymphocytes; exhaustion of HSC; hepatic extramedullary hematopoiesis; reduced life span; spontaneous activation of AKT signaling In another independent knockout mouse line, no defect was observed	T and NK defects; splenomegaly and lymphadenopathy; spontaneous activation of the AKT pathway; responsive to rapamycin treatment; replicative senescence in T cells.	Rats: (1–3, 5–34). Mice: (35–41). Humans: (40, 42).
Gimap1 Golgi apparatus	Reduced survival of T and B cells; loss of mitochondrial potential and oxygen consumption	GIMAP1 expression is increased in DLBCL lymphomas	(33, 43)
Gimap2 Lipid droplets	absent	Not known	(44–46)
Gimap3 Endoplasmic reticulum	Pseudogene in rats In mice GIMAP3 regulates the segregation of mitochondrial DNA	Pseudogene in humans	(47, 48)
Gimap4 Cytosolic	Required for the transition of T cells from apoptotic to dead cells	Associated with cytoskeleton, movement of vesicles and secretion of cytokines	(49, 50)
Gimap6 Autophagosomes	Reduced T and B cell numbers; Increased sensitivity to apoptosis	Increased sensitivity to apoptosis	Mice: (51–53). Humans: (54).
Gimap7 Cytosolic	Not known	Not known	(44–46)
Gimap8	Reduction in recirculating B cells		(55)

[1]Among the GIMAP genes, only GIMAP5 appears to affect the longevity of mice and possibly, humans.

chromosome 7, contains seven functional genes and one pseudogene (4). In mice and rats the *Gimap* genes are present as a tight cluster within a 150kb region on chromosome 6 and 4, respectively (2, 3). *Gimap*-like genes have been identified in angiosperms, corals, nematodes and in snails wherein they are implicated in protection from infections (56–59). The observed homology between GIMAP proteins and the plant avrRpt2 induced gene 1 (AIG1) might have resulted from convergent evolution of the AIG1 domain (4, 60). In fact, initial homology searches identified *Arpt1* in *Arabhdiposis thaliana* (61) as the closest homolog of the mammalian *Gimap* family proteins.

The GIMAP family consists of putative small GTP-or/and ATP binding proteins that are conserved among vertebrates (**Figure 1**). Among the GIMAP family proteins, sequence similarity is restricted to the N-terminus, which contains a guanine nucleotide-binding domain (4, 62). All GIMAP family members harbor the AIG1 domain containing a GTP-binding motif, that is referred to as GIMAP GTPase domain comprised of the five G motifs G1, G2, G3, G4, and G5, which are involved in nucleotide binding. It is thought that the GIMAP GTPase domains may be functional and that their activity may be controlled by homo/hetero dimerization (44–46, 63). However, only some GIMAPs have been shown to bind GDP/GTP or to hydrolyze GTP. GIMAP4 is the first member reported to bind GDP and GTP and exhibit GTPase activity (63). Further studies have shown that GIMAP2 and GIMAP5 can bind GTP with high affinity but cannot hydrolyze it on their own (44). GIMAP7 can stimulate its own GTPase activity and promote GTP hydrolysis by GIMAP2 (44). Besides the GTPase domain, all GIMAP proteins contain a helical segment that folds back on to the GTPase domain and may mediate interaction with partner proteins. In addition, GIMAP1, GIMAP3, and GIMAP5 contain a transmembrane hydrophobic domain at the C-terminus that have been shown to mediate membrane anchoring and target them to intracellular organelles (64). In the next sections each of the GIMAP family member is discussed in detail, starting with the founding member GIMAP5.

GIMAP5

Mutation in *Gimap5* Is Associated With T Lymphopenia

A spontaneous mutation in an outbred colony of Wistar rats was associated with the development of autoimmune type 1 diabetes (T1D) (5). Incidentally these rats were also lymphopenic. Further inbreeding resulted in the establishment of the strain of BB-DP rats (1, 6–8). Genetic studies mapped the lymphopenia phenotype to the *lyp* locus on chromosome 4 (9). In 2002, two groups independently identified a frameshift mutation within the *Gimap5* gene as being responsible for this lymphopenic phenotype (2, 3). In BB-DP rats, lymphopenia is restricted to the T cell compartment with a 5-10 fold reduction in the number of mature T cells in secondary lymphoid organs (10). This lymphopenia is more severe in the $CD8^+$ T cell

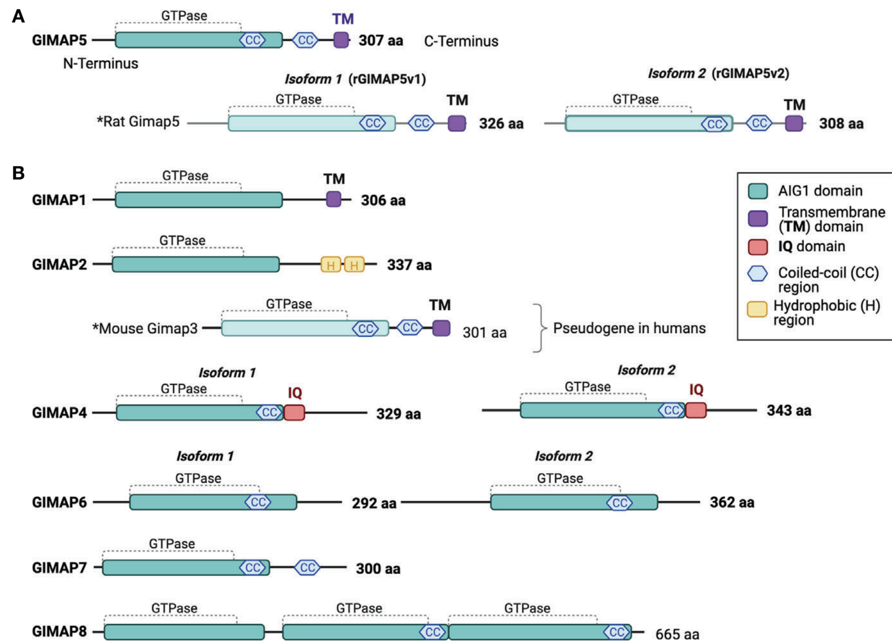

FIGURE 1 | Human GIMAP family protein structure. Predicted structural domains of human GIMAP family members. **(A)** The 307-amino acid long human GIMAP5 protein contains the GIMAP GTPase domain, coiled-coil (CC) regions and a C-terminal transmembrane (TM) domain. Rat GIMAP5 protein is found in two isoforms that differ in length (GIMAP5v1 and GIMAP5v2). Both retain the CC regions and the TM domain. **(B)** Predicted structures of other human GIMAP family proteins and mouse GIMAP3, as the latter is a pseudogene in humans. The calmodulin interaction domain (IQ) is unique to both GIMAP4 isoforms. The drawings are not to scale.

compartment than in the CD4$^+$ T cell compartment (11, 12). Thus, most studies characterizing the function of GIMAP5 in T cells have been carried out on the CD4$^+$ T cell subset. Mature CD4$^+$ T cells, characterized by the expression of the RT6 marker in the rats, were almost completely absent in the secondary lymphoid organs of BB-DP rats (13, 14). *In vitro* studies have shown that the few surviving T cells in BB-DP rats are not fully functional. Purified BB-DP rat CD4$^+$ T cells stimulated with mitogens or anti-CD3/CD8 antibodies displayed impaired proliferative response (15). *In vivo*, the decreased functionality of the BB-DP rat T cells was attributed to the increased nitric oxide (NO) production by macrophages (16). Bone-marrow chimeras showed that the increased NO production by macrophages of the BB-DP rats was secondary to the T lymphopenia, as correcting the latter decreased NO production (15). In addition, the *lyp* mutation affects the development of regulatory T cells, γδ T cells and intra-epithelial lymphocytes (iIELs) in the intestinal mucosa (17, 18). The development and survival of NK cells and B lymphocytes are not affected by the *lyp* mutation in BB-DP rats (genotype: $Gimap5^{lyp/lyp}$) (1). An important paradox in BB-DP rats that aroused much scientific investigation in the 80s and 90s was the T cell dependency of autoimmune T1D development despite severe lymphopenia. Depletion of the few CD4$^+$ or CD8$^+$ T cells, but not NK cells, prevented T1D development in BB-DP rats (19, 20), indicating that the remaining lymphocytes are the crucial mediators of disease.

Phenotype of T Cells in the Absence of Functional GIMAP5

During T cell development, hematopoietic precursors with restricted multipotency enter the thymic cortex from the bone marrow and undergo a series of developmental changes that are demarcated by specific phenotypic characteristics associated with their commitment towards the T cell lineage (65). Until the rearrangement of the T cell antigen receptor (TCR) genes, thymocytes do not express CD4 or CD8 co-receptors and are referred to as double negative (DN) thymocytes. TCR rearrangement upregulates the expression of both CD4 and CD8 co-receptors, allowing these double positive (DP) cells to undergo positive selection (66, 67). Subsequent to TCR signaling, DP cells lose one of the two co-receptors, depending on their ability to recognize MHC class I or class II molecules, and become CD4 or CD8 single positive (SP) cells that transit to the thymic medulla where T cells with high affinity to self-antigens are deleted by the negative selection process. The surviving SP thymocytes undergo further maturation before exiting to the periphery as recent thymic emigrants (RTE). RTE undergo additional maturation in the periphery to become long-lived naïve T cells. Naïve T cell survival is maintained in the periphery by constant low-level interactions with the self MHC:peptide complexes (MHC:p) (68). Upon encounter with the cognate antigen, the TCR-stimulated T cell clones undergo proliferative expansion and initiate the adaptive immune response. Some of the antigen-specific T cells undergo

reprogramming to become long-lived memory T cells that constantly patrol the tissues. Both naïve and memory T cells rely on cues from TCR- MHC:p interactions and cytokines such as IL-7 and IL-15 for their survival and homeostasis in the periphery.

Even though the proportion of DN, DP and SP subsets are comparable between control and BB-DP rats, the reduced thymic output in BB-DP rats (1, 21, 22) suggested that the lymphopenic phenotype caused by *Gimap5$^{lyp/lyp}$* genotype manifests during the later stages of T cell development in the thymus. In line with this observation, transcripts for *Gimap5* are detected at higher levels starting from DP stage of T cell development in normal rats (23). Some groups have observed a decrease in the frequency of immature $CD8^+$ SP thymocytes (24–26). Nevertheless, SP thymocytes from *Gimap5$^{lyp/lyp}$* rats undergo accelerated apoptosis *in vitro* (1, 25–27).

Homeostatic expansion of T cells present in the periphery can compensate for reduced thymic export and can almost fully restore the T cell numbers under conditions of lymphopenia (69). However, the peripheral T lymphopenia in the *Gimap5$^{lyp/lyp}$* rats suggests that the homeostatic expansion may also be compromised by GIMAP5 deficiency or, alternately, that the expanding cells are unable to survive and persist in the secondary lymphoid organs. To address this issue, we thymectomized control and *Gimap5$^{lyp/lyp}$* rats and labeled the cycling cells with bromodeoxyuridine (27). Whereas only 5-10% T cells incorporated the label in control rats with a full T cell compartment, almost 100% of the T cells in *Gimap5$^{lyp/lyp}$* rats had incorporated BrDU during the same period. Despite this increased T cell cycling in the periphery, *Gimap5$^{lyp/lyp}$* rats fail to restore their T cells numbers in the periphery. Follow up of the BrDU-labeled cells during the chase period suggested that most of them were lost from the secondary lymphoid organs in *Gimap5$^{lyp/lyp}$* rats while they were present in control rats. The complete loss of the BrDU-labeled cells from the secondary lymphoid organs of *Gimap5$^{lyp/lyp}$* rats indicated that the progeny of the cycling cells was unable to persist and survive and that the homeostatic pressure maintains the few surviving cells in a perpetual cycling phase. Reconstitution of the lymphopenic BB-DP rats with splenocytes from syngenic, diabetes-resistant (BB-DR) rats that carry the wildtype *Gimap5* allele eliminated the cycling of endogenous BB-DP T cells that were eventually lost from the periphery.

Paradoxically, the few cells that persist in the secondary organs of *Gimap5$^{lyp/lyp}$* rats have been shown to be activated by their cognate antigen and incorporated into the pool of recycling cells (27). As there are no TCR transgenics available for rats, the antigen specificity of the peripheral T cell pool was assessed using allogenic T cells from Wistar Furth (WF) background as lymphopenic BB-DP rats could reject allogenic T cells (27). To determine whether antigen-reactive cells were inducted into the pool of recirculating cells, the BB-DP rats were thymectomized following the rejection of WF T cells. One month after thymectomy, the antigen-exposed rats were still capable of rejecting the allogenic T cells. However, in the absence of prior exposure, thymectomized rats were unable to eliminate the allogenic cells. Additional experiments showed that RTEs had a narrow window of one week after thymic exit in order to be 'rescued' by TCR stimulation. These experiments helped resolve the paradox of T cell mediated autoimmunity in BB-DP rats. In an appropriate genetic background these cycling *Gimap5$^{lyp/lyp}$* T cells recognize self-antigens and induce autoimmune diseases. For example, in the BB-DP rats these cycling T cells recognize islet antigens and induce T1D. In the PVG background the *lyp* mutation contribute to eosinophilic inflammatory bowel disease (70) whereas in Lewis rats experimental autoimmune encephalomyelitis (EAE) becomes aggravated (71).

In humans, transcripts for *GIMAP5* can be detected in peripheral blood T cells but not in B cells (62). Human *GIMAP5* was initially identified in 2001 as the Oar-2 clone from a Jurkat-derived cDNA library that could confer resistance to gamma-radiation and okadaic acid (OA)-induced apoptosis (72). In 2003, the protein was identified as Irod (inhibitor of radiation- and OA- induced death) (73). Overexpression of Oar-2 conferred protection in a CaMKII dependent manner in Jurkat cells (73). Regulation of sensitivity to OA may be species-specific, as no significant alterations in protein phosphatase activity was observed in *Gimap5$^{lyp/lyp}$* rat T cells (28).

To better understand the functions of *Gimap5*, three groups generated mice with inactivating mutations in *Gimap5* (35–37). Two lines of *Gimap5*-deficient mice generated by the groups of H. Weiler and K. Hoebe exhibited comparable phenotype (35, 36). The Weiler laboratory generated *Gimap5$^{-/-}$* mice by replacing the *Gimap5* exon 2 and a part of exon 3 with the neomycin cassette (36). The Hoebe group inactivated *Gimap5* through ENU mediated mutagenesis to generate the *Sphinx* (*Gimap5$^{sph/sph}$*) line of mice (35). The latter carried a point mutation G38C that can abrogate the binding of GTP/GDP to a site that is conserved in RAS family of GTPases. Unlike in rats, where the defect caused by the *lyp* allele is restricted to T cells, absence of functional GIMAP5 leads to a paucity of peripheral T, B and NK cells in *Gimap5$^{-/-}$* and in *Gimap5$^{sph/sph}$* mice. However, positive and negative selection of T cells was not altered by the absence of GIMAP5 (35). In addition to T and B lymphopenia, both lines of mice show exhaustion of hematopoietic stem cells (HSC) and hepatic extramedullary hematopoiesis that is independent of T and B lymphocytes, as *Rag1$^{-/-}$Gimap5$^{-/-}$* mice also show the same phenotype (35, 38). In contrast to the above two mouse strains, *Gimap5$^{-/-}$* mice developed by the Takahama group did not exhibit any T cell survival defects (37). Reasons for this discrepancy remains unclear. The *Sphinx* mice have also been reported to develop intestinal inflammation (35, 39).

Mutation in the *Gimap5* Gene Disrupts Signaling Pathways in T Cells

Homeostatic survival of naive T cells requires two essential signals, one provided by the cytokine interleukin-7 (IL-7) and the other by MHC:self-peptide complexes that engage the TCR (74). Signals delivered *via* the IL-7 receptor and the TCR impact the classical pathway that maintains quiescence in most cell types involving LKB1 and AMPK (75, 76). AMPK, the energy sensor

activated by an elevated AMP/ATP ratio, inhibits the mTORC1 complex by activating its suppressor, the TSC1/2 complex (77, 78). TCR engagement triggers the activation of LCK and ZAP70 that phosphorylate many substrates including the scaffolding protein LAT, resulting in the formation of multi-molecular signaling complex at the plasma membrane (79) (**Figure 2**). Activation of the PI3K/AKT signaling pathway downstream of TCR signaling phosphorylates TSC1/2 complex thereby releasing RHEB GTPase from suppression to activate the mTORC1 complex (80). mTORC1 promotes translation and protein synthesis by activating 70-kDa ribosomal S6 kinase (S6K1) and releasing the repressor protein 4E-BP1 from the translation initiation factor eIF-E4. Thus, in the absence of functional LKB1, AMPK or the TSC1/2 complex, T cell quiescence is lost (75–78). We observed that *Gimap5*-deficient T cells showed normal AMPK activation and mitochondrial respiration but displayed defects in IL-7 signaling, proximal TCR signaling manifested as reduced phosphorylation of ZAP70 and LAT, T cell calcium response and constitutive activation of AKT and the mTORC1 pathway (28–31) (**Figure 2**). Molecular mechanisms by which GIMAP5 impacts TCR and IL-7R signaling pathways remain to be elucidated.

Rat GIMAP5 Regulates Cellular Calcium Homeostasis

The TCR signalosome recruits and activates phospholipase Cγ (PLCγ), which hydrolyzes the membrane bound phosphatidylinositol 4,5 bisphosphate (PIP_2) to generate inositol 1,4,5-triphosphate (IP_3) and diacyl glycerol (DAG) (**Figure 2**). IP_3 binds to its receptor IP_3R on the endoplasmic reticulum (ER) and triggers Ca^{2+} release from the ER store, resulting in a conformational change in the ER-localized STIM1 protein (81, 82) (**Figure 3**). This event relays a signal to open the Ca^{2+} release-activated Ca^{2+} channel (CRAC) on the plasma membrane, inducing the capacitative Ca^{2+} entry from the extracellular milieu (83, 84). CRAC channels consisting of the ORAI proteins are the major store-operated channels in T lymphocytes (85, 86). TCR stimulation by antigen induces sustained Ca^{2+} influx *via* CRAC channels leading to T cell proliferation (87).

We observed that TCR-induced Ca^{2+} flux is reduced in T cells from BB-DP rats, which lack a functional GIMAP5 protein (30). The IP_3-mediated Ca^{2+} release from the ER stores into the cytosol (88), can be mimicked by blocking the sarco/endoplasmic reticulum Ca^{2+} ATPases (SERCA) pump that refills the ER Ca^{2+} reserve, using thapsigargin (89) (**Figure 3**). We observed that GIMAP5 deficiency does not affect Ca^{2+} release from the ER in primary rat T cells (30). Similarly, overexpression of rGIMAP5 did not influence the emptying of the ER Ca^{2+} stores (31). However, Ca^{2+} influx from the extracellular milieu which occurs mainly *via* the CRAC channels, was reduced in *Gimap5*-deficient rat T cells (28, 30).

Following sustained Ca^{2+} entry *via* the CRAC channels, the rising concentration of cytosolic Ca^{2+} ($[Ca^{2+}]_c$) activates the Ca^{2+} uniporter on the mitochondrial membrane. This induces a slow, membrane potential-driven uptake of Ca^{2+}, which is released later *via* the Na^+/Ca^{2+} exchanger (90) (**Figure 3**). This process

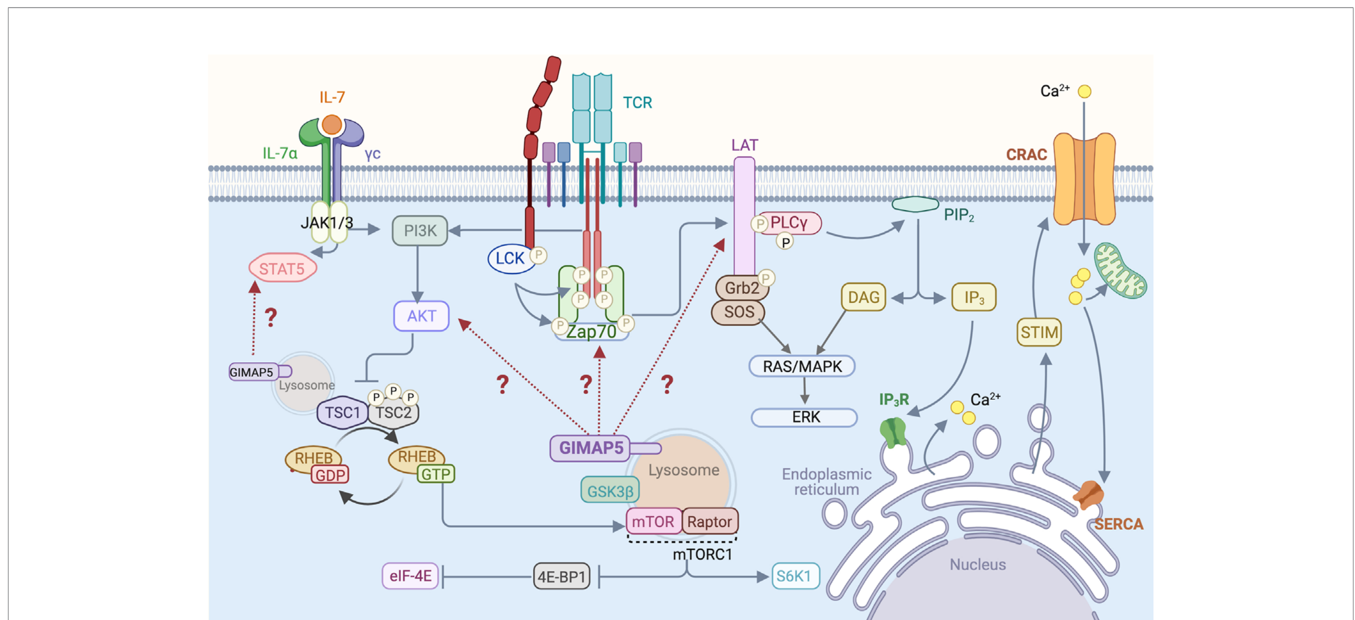

FIGURE 2 | T cell signaling pathways that are influenced by GIMAP5. Following TCR stimulation by MHC:peptide complex or by Ab-mediated TCR cross-linking, LCK phosphorylates CD3 zeta chains and ZAP70, resulting in the phosphorylation of LAT that acts as a scaffold for downstream signaling molecules such as PLCγ. Activation of the PI3K/AKT signaling pathway downstream of TCR phosphorylates and inhibits the TSC1/2 complex, relieving repression of the mTORC1 kinase and leading to activation of downstream signaling events. IL-7 signaling stimulates STAT5 and also activates the PI3K/AKT pathway. GIMAP5 deficiency in rat and mouse T cells compromises proximal TCR signaling characterized by reduced Tyr phosphorylation of ZAP70 and LAT, but results in constitutive activation of AKT and mTORC1. GIMAP5 deficient T cells also display reduced IL-7-induced STAT5 phosphorylation. It is unclear how GIMAP5 impacts the TCR and IL-7R signaling pathways and regulates AKT activity (29, 34, 40–42).

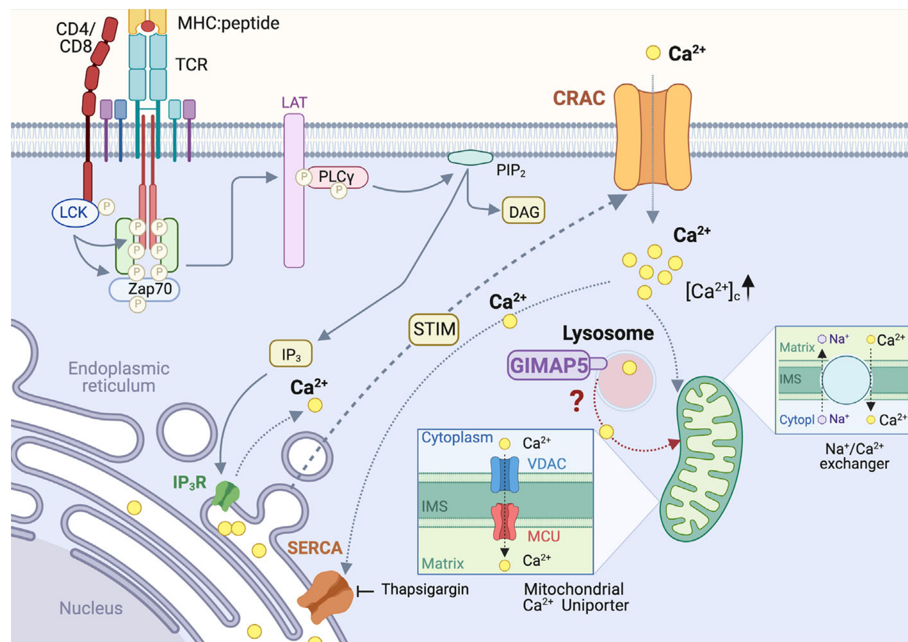

FIGURE 3 | Regulation of Calcium homeostasis in rat T cells by GIMAP5. TCR-induced PLCγ activation leads to cleavage of plasma membrane-associated phosphatidylinositol 4,5 bisphosphate (PIP_2) to generate inositol 1,4,5-triphosphate (IP_3). IP_3 binds to its receptor IP_3R on the endoplasmic reticulum (ER) and triggers Ca^{2+} release from the ER store, resulting in a conformational change in the ER-localized STIM1 protein. This event relays a signal to open the Ca^{2+} release-activated Ca^{2+} channel (CRAC) on the plasma membrane, inducing the capacitative Ca^{2+} entry. The rising concentration of cytosolic calcium ($[Ca^{2+}]_c$) activates the Ca^{2+} uniporter on the mitochondrial membrane to uptake Ca^{2+}, which is released later *via* the Na^+/Ca^{2+} exchanger. In addition to ER, lysosomes also release a significant amount of Ca^{2+} following cell activation. Loss of GIMAP5 does not affect TCR- or thapsigargin- induced Ca^{2+} release from the ER stores but reduces Ca^{2+}entry from extracellular milieu. GIMAP5 resides on lysosomes and the loss of GIMAP5 reduces lysosomal and mitochondrial Ca^{2+} content, presumably leading to feedback inhibition of the CRAC channels by cytosolic Ca^{2+}. How GIMAP5 integrates TCR signaling to regulate lysosomal and mitochondrial Ca^{2+} to promote T cell survival and functions remains to be elucidated (28, 30, 31).

ensures that Ca^{2+} entering *via* the CRAC channel does not cause a feedback inhibition of the CRAC channel activity (91, 92). Thus, mitochondria act like a slow, non-saturable, non-linear buffer for intracellular Ca^{2+}, as they sequester $[Ca^{2+}]_c$ during periods of rapid Ca^{2+} entry and sustain the $[Ca^{2+}]_c$ level by releasing it slowly even after the cessation of Ca^{2+} influx (91) (**Figure 3**). We observed that the reduced Ca^{2+} influx in *Gimap5*-deficient T cells is associated with the inability of their mitochondria to sequester Ca^{2+} ($[Ca^{2+}]_m$) following capacitative entry (28). This reduced mitochondrial Ca^{2+} was also observed following stimulation of the ryanodine receptors that are present on ER membrane (28) and are implicated in T cell functions (93–95). As a corollary, overexpression of rGIMAP5 in HEK293 cells resulted in increased Ca^{2+} accumulation within the mitochondria (28). As a consequence, Ca^{2+} influx from extracellular milieu is reduced in cells expressing GIMAP5, probably due to early saturation of the mitochondrial Ca^{2+} store (28).

Even though the ER is the major intracellular Ca^{2+} store, and mitochondria uptake Ca^{2+} to prevent feedback inhibition of the CRAC channels, a significant amount of Ca^{2+} can be released from the Golgi complex, lysosomes, nucleus and secretory granules (96). As GIMAP5 does not directly interact with mitochondria but is present on lysosomes and certain endocytic vesicles (31–33, 40), we postulated that GIMAP5 might regulate the Ca^{2+} content of lysosomes (**Figure 3**). Ca^{2+} was released from lysosomes by Gly-Phe β-naphthylamide (GPN) whose hydrolysis by cathepsin C results in osmotic lysis of the acidic compartment (97). We observed that GPN-mediated Ca^{2+} release was increased in T cells from *Gimap5$^{lyp/lyp}$* rats, and the Ca^{2+} influx from the extracellular milieu was also higher than that of T cells from control rats (31). These observations suggest that the intracellular partitioning of Ca^{2+} in *Gimap5$^{lyp/lyp}$* rat T cells is different from that of normal rat T cells. These observations were reflected in stable transfectants of full-length GIMAP5 in HEK293T cells, which displayed reduced GPN-induced Ca^{2+} release. Regulation of Ca^{2+} homeostasis was dependent on the full-length GIMAP5 protein as C-terminal or N-terminal deletion mutants were unable to do so. Further analyses of the truncated GIMAP5 proteins indicated that the GIMAP5 is anchored to lysosomal membranes and certain vesicles through the C-terminal anchor while the N-terminal regions interacted with the microtubules (31, 33) (**Figure 4**). Thus, the presence of GIMAP5 appears to decrease Ca^{2+} release from lysosomes. For the first time, our results suggest that lysosomal Ca^{2+} homeostasis regulates the survival of T cells and that this process requires GIMAP5. We also observed that that the lysosomal Ca^{2+} content was altered by signaling through

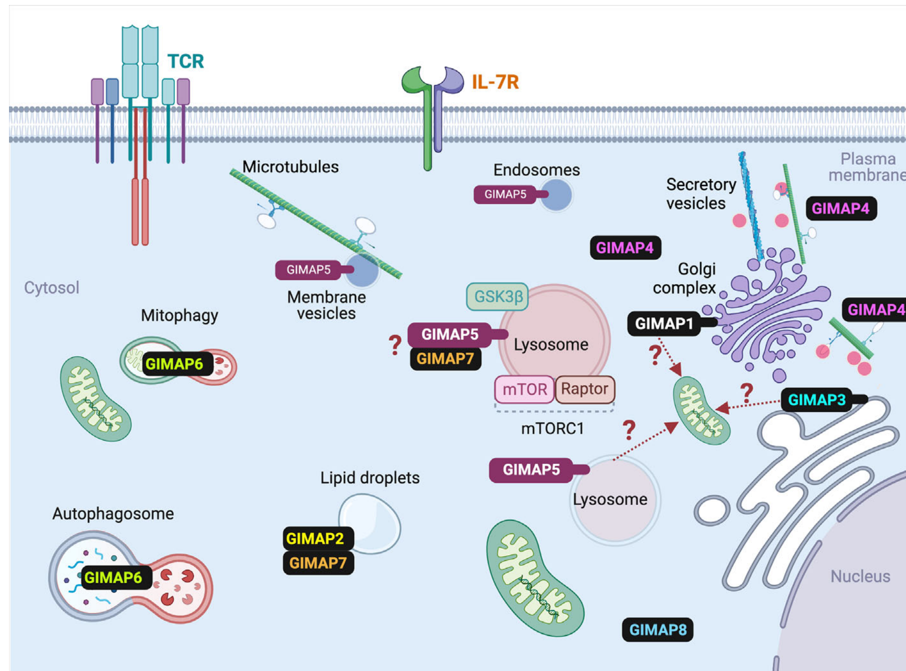

FIGURE 4 | Subcellular localization of various GIMAP proteins in T cells. The known subcellular localization of mammalian GIMAP proteins in T lymphocytes is indicated. For the sake of simplicity, species-specific expression pattern of some GIMAP proteins are omitted. Details are given in the text and **Table 1**. Events that are predicted but require experimental confirmation are indicated by question marks. Ref- GIMAP5: (31–33); GIMAP1: (33); GIMAP2: (45); GIMAP3: (47); GIMAP4: (49); GIMAP6: (51); GIMAP7: (45); GIMAP8: (55).

the TCR in murine and human T cells (31). Whether and how GIMAP5 integrates TCR signaling to regulate lysosomal Ca^{2+} in order to promote T cell survival and functions remain to be elucidated (**Figure 3**).

Signaling Pathways Affected in T Cells in the Absence of GIMAP5

Defective Ca^{2+} signaling in BB-DP rat T cells is evident within 30 minutes of TCR signaling induced by CD3 cross-linking (30). However, T cells from *Gimap5*$^{Sph/Sph}$ mice do not display any defect in Ca^{2+} influx induced by TCR signaling (40). Nonetheless, the TCR proximal signaling events showed similar impairments in *Gimap5* mutant T cells in both the species (29, 34, 40, 41) (**Figure 2**). Rat T cells were activated by cross-linking CD3/CD28, and T cells from OT-II TCR transgenic control and *Gimap5*$^{sph/sph}$ mice were activated using anti-CD3/CD28 antibodies or dendritic cells pulsed with the cognate OVA-peptide. *Gimap5* mutant rat and mouse T cells displayed reduced phosphorylation of LCK and the scaffold protein LAT following anti-CD3 stimulation (29). Notably, T cells from the *Gimap5* mutant mice and rats exhibited constitutive phosphorylation of ATK at the basal level (34). This constitutive phosphorylation of AKT was inhibited by PI3K inhibitors. While aberrant activation of the PI3K/AKT pathway results in malignant growth in most cell types (98), it causes cell death in non-transformed T lymphocytes, leading to immunodeficiency (99–101). Spontaneous activating mutations of PI3K that results in constitutively active PI3K/AKT pathway in T cells has been observed in a new class of patients with primary immunodeficiency (99–101). T cells from these patients do not proliferate in response to mitogenic signals. These published reports and our observation indicate that aberrant activation of the PI3K/AKT pathway in the absence of TCR engagement may result in T cell death. The constitutive phosphorylation of AKT can also explain the reduced phosphorylation of STAT5 that we have observed following IL-7 stimulation (29), as pAKT can suppress the phosphorylation of STAT5 (102).

Spontaneous AKT activation observed in *Gimap5* deficient T cells is reflected in the phosphorylation of downstream substrates including mTORC1 and FOXO1 (34). In fact, FOXO1 proteins are depleted progressively with age in *Gimap5*$^{Sph/Sph}$ mice (41). It is possible that the persistent phosphorylation of FOXO1 can lead to their degradation by proteasomes (103, 104). The Hoebe group recently showed that GIMAP5, which is localized on lysosomes and in certain vesicles, is required for+ the inactivation of GSK3β (40). GSK3β is a serine threonine kinase that is constitutively active in all cell types (105). Phosphorylation on Ser-9 and Ser-389 is required to inactivate GSK3β and promote T cell proliferation (106–108). Absence of GIMAP5 in T cells prevented CD3/CD28-induced inactivation of GSK3β as its inhibition by lithium chloride permitted the survival of T cells in *Gimap5*$^{Sph/Sph}$ mice (40). As GIMAP5 is present in certain vesicles, GIMAP5-mediated sequestration of GSK3β may play a role inhibiting its activity and promote cell proliferation (40).

GIMAP5 in Hematopoietic Stem Cells

GIMAP5 is essential to maintain the hematopoietic stem cell (HSC) niche as HSC numbers diminish with age in mice carrying mutant GIMAP5 (38), although this is not the case in rats. The absolute numbers of HSCs as defined by $Lin^-IL\text{-}7R^-cKit^+Sca^+$ (LSK) cells, was comparable between wildtype and *Gimap5*$^{-/-}$ mice (38, 41). However, *Gimap5*-deficient HSCs have intrinsic defects in long-term engrafting capacity (38). The exhaustion of HSC in *Gimap5*$^{-/-}$ mice may be the consequence of their inability to stay in the quiescent state. In line with these observations, *Gimap5* expression is observed in murine HSC (38). Interaction of GIMAP5 with MCL1 and HSC70 appears to contribute to quiescence, however the underlying mechanisms are not yet known (38, 40). Simultaneous deletion of the two pro-apoptotic proteins, BAX and BAK, which rescues survival in the absence of MCL1, did not alter the survival of T cells in *Gimap5*$^{Sph/Sph}$ mice (40). It is possible that GSK3β, activated in the absence of GIMAP5 (40), might accelerate the degradation of MCL1 (109). These *in vivo* observations stand in contrast to over-expression studies *in vitro* where GIMAP5 was shown to interact with BCL-2 and BCL-xL (110). The requirement of GIMAP5 to maintain quiescence in HSCs is further supported by the observation that extramedullary hematopoiesis and reduced lifespan are still observed *Gimap5*$^{-/-}$*Rag2*$^{-/-}$ mice (36).

Polymorphisms in human *GIMAP5* gene locus has been shown to be associated with autoimmune T1D and lupus in independent studies (111–114). Recently, mutations in GIMAP5 have been described in human primary immunodeficiency. The Hoebe group (40) described one patient who had mild lymphopenia with impaired T cell proliferation *in vitro* that was rescued by GSK3β inhibition. Lenardo's group (42) identified 4 different family clusters with mutations in *GIMAP5* gene. Similar to what was reported in rats (31), GIMAP5 exists as 2 distinct isoforms in humans (42). GIMAP5 expression was observed in NK and T cells but not in B cells or monocytes. Nonetheless, frequency of T lymphocytes was reduced in all the patients studied while some of them also showed reduction in B lymphocytes and neutrophils. These patients exhibit splenomegaly and lymphadenopathy with abnormal liver and were susceptible to recurrent infections. T cells from the patients recapitulate the spontaneous mTORC1 activation observed in GIMAP5 mutant T cells from rats and mice (34). Similar to the *in vitro* findings (34), *Gimap5*$^{Sph/Sph}$ mice that received rapamycin, showed reduced activation of the mTORC1 pathway (42). Treatment of one of the patients with rapamycin for over 6 years diminished splenomegaly and lymphadenopathy, suggesting aberrant activation of the AKT/mTORC1 pathway *in vivo* in humans in the absence of functional GIMAP5. The abnormal activation of T cells in these patients is accompanied by replicative senescence in T cells as seen from reduced telomere length. These observations indicate that mutations in *Gimap5* profoundly compromises the survival of T cells. In rats only one of the two isoforms was shown to regulate calcium homeostasis (31). While the abundantly expressed GIMAP5v2 regulates lysosomal calcium, GIMAP5v1 that is expressed at a lower level did not. It appears that the GIMAP5v1 homolog is functional in mice and in humans but not in rats.

GIMAP1

GIMAP1 was initially identified as *Imap38* that was induced in the spleen following *Plasmodium chaboudi* infection (115). However later studies carried out with anti-GIMAP1 antibody in infected tissues was unable to confirm these findings (116). GIMAP1, which is located in the Golgi complex (33), is expressed during all the stages of thymocyte development and in mature T, B cells and NK cells but minimally in macrophages (116). In humans, GIMAP1 is upregulated following Th1, but not Th2 differentiation *in vitro* (117). Constitutive and induced deletion of *Gimap1* in T cells compromised their survival in the periphery (43, 118). Following T cell activation *via* the TCR, *Gimap1*$^{-/-}$ $CD4^+$ T cells upregulate markers of activation such as CD25 but fail to proliferate and expand (43). *In vitro*, *Gimap1*$^{-/-}$ $CD4^+$ T cells showed accelerated loss of mitochondrial potential with a concomitant reduction in oxygen consumption. GIMAP1 is also essential for the survival and functioning of mature B cells (119). Transgenic expression of BCL-2 did not rescue the loss of *Gimap1*$^{-/-}$ B cells. Deletion of GIMAP1 in germinal center B cells prevented the generation of efficient T-dependent antibody responses. GIMAP1 expression is increased in diffuse large B-cell lymphoma (DLBCL) due to hypomethylation of the *GIMAP* locus (120). Additional studies are needed to understand the role of GIMAP1 in cell survival and leukemia.

GIMAP2 AND GIMAP7

Functional GIMAP2 is present in humans but is absent in mice and rats (3, 4). The functions of GIMAP2 have not been characterized. The C-terminal double hydrophobic domain, which is unique to GIMAP2, localizes it with the lipid droplets marker BIODIPY following overexpression in JURKAT cells (45). Structural studies of GTP-bound and unbound GIMAP2 indicate that the nucleotide binding domains of GIMAPs are related to those found in dynamin, chloroplast proteins Toc and septin-GTPases (45, 46). GTP binding induces the formation of dimers of GIMAP2 and presumably, of GIMAP5. It has been proposed that the membrane bound GIMAPs such as GIMAP5 and GIMAP2 may form scaffolds in the GTP associated forms (121). GTP hydrolysis may be initiated by dimerization-dependent mechanisms involving GIMAP7 and GIMAP4 that do not have a membrane anchor, to promote GTP catalysis (44, 63). If this hypothesis is supported by experimental evidence, it is possible that GTP-bound GIMAP5 scaffolds may inhibit apoptosis, whereas heterodimerization with GIMAP4 and consequent GTP hydrolysis may antagonize the pro-survival functions of GIMAP5 (44, 49). These studies may also help in identifying other associated proteins and delineating their functional contributions.

GIMAP3

GIMAP3 is a pseudogene in humans and in rats (4). Mouse *Gimap3* is present in the ER (47) and influences the segregation of mitochondrial DNA in hematopoietic tissues (48). Mammalian mitochondrial DNA (mtDNA) is inherited from the mother. When

all the cells in an organism carry the same haplotype of mtDNA it is referred to as homoplasmy (122, 123). In the case of mtDNA mutations, the cell carries two different haplotypes of mtDNA, referred to as heteroplasmy. Many of these mutations are associated with maternally inherited disorders in humans (122, 123). The two mitochondrial haplotypes are not inherited by daughter somatic cells in a stochastic manner (124). Additionally, mtDNA segregation in tissues and cell types are regulated by distinct mechanisms in an age-dependent manner (125). In inbred strains of *Mus musculus domesticus* mtDNA exists in two distinct haplotypes namely, BALB and NZB, which are transmitted in a random manner in the germline, but show segregation in the post-natal stage (126). For example, the BALB haplotype is enriched in hematopoietic cells while NZB is enriched in the liver and kidneys (127). While nuclear factors are implicated in tissue-specific segregation of mtDNA, the identity of proteins/RNA that could influence mtDNA segregation and the underlying mechanisms are not yet fully characterized (128, 129).

The group of Battersby showed that GIMAP3 is involved in regulating mtDNA segregation in hematopoietic cells (48). A mutation in the splice acceptor site of *Gimap3* in *Mus musculus castaneus* (CAST/Ei), results in *Gimap3* mRNA that codes for an additional 58 amino acids at the N-terminus (47). However, the longer N-terminus interferes with efficient translation, rendering CAST *Gimap3* a functional null mutant (47). Absence of functional *Gimap3* (CAST/Ei allele) resulted in equivalent representation of NZB mtDNA haplotype in hematopoietic tissues and in neutral tissues (where there is no haplotype selection), whereas mice expressing the wildtype *Giamp3* allele showed enrichment of BALB mtDNA haplotype in hematopoietic tissues (48). Analysis of segregation of BALB mtDNA in *Gimap5* heterozygous mice generated by the Weiler's group (36) indicated that the abundance of GIMAP5 protein influenced that of GIMAP3 protein and was accompanied by differential segregation of BALB mtDNA in hematopoietic cells (47). In this context, it is interesting to note that Yano et al. (37), observed that T cell survival was significantly affected in *Gimap5/Gimap3* double knock out mice indicating as yet unknown interactions between these GIMAP members in hematopoietic cells.

GIMAP4

Gimap4 is expressed in developing T lymphocytes at the DN4 stage in response to pre-TCR signaling, is transiently downregulated in the DP stage and re-expressed in SP thymocytes, peripheral T cells as well as in B cells, NK cells and to a lesser extent in macrophages (49). The absence of GIMAP4 expression in RAG1-deficient thymocytes indicates that it is not expressed in DN 1-3 stages (49). Of the GIMAP proteins, interacting partners have been characterized in detail for GIMAP4 (49). GIMAP4 lacks a membrane anchor and is expressed in the cytosol (**Figure 4**). The C-terminal IQ domain, that is unique to the GIMAP4 (**Figure 1**) binds calmodulin. GIMAP4 harbours four PKC phosphorylation sites that are phosphorylated following T cell activation. Absence of GIMAP4 did not affect the generation or survival of T cells in the periphery. However, the frequency of apoptotic cells was increased in *Gimap4*-deficient T cells following exposure to gamma-irradiation, etoposide or dexamethasone, suggesting that GIMAP4 may be involved in promoting cell death following induction of apoptosis. In support of this notion, wildtype T cells undergoing apoptotic death display increased phosphorylation of GIMAP4 (49). The mitochondrial membrane potential and cytochrome c levels were comparable between the wildtype and *Gimap4*-deficient T cells indicating that GIMAP4 modulates apoptosis downstream of mitochondria. Furthermore, the apoptotic phenotype was inhibited by effector-caspase inhibitor in *Gimap4*-deficient T cells (49). Similar to other GIMAP proteins, GIMAP4 shows association with cytoskeletal elements and is implicated in membrane trafficking, movement of vesicles and cytokine secretion in T cells (31, 33, 47, 50, 130). Polymorphisms in *GIMAP4* was shown to be associated with asthma and allergy, although the underlying mechanisms remain to be elucidated (111).

GIMAP6

Human GIMAP6 has been shown to be involved in autophagy (51). Mass spectrometry analysis identified GABARAPL2, the mammalian homolog of yeast ATG8, as the binding partner for GIMAP6. GIMAP6 is localized to the punctate structures along with GABARAPL2 and MAP1LC3B, an autophagosome marker. Knockdown of GIMAP6 in JURKAT T cells resulted in reduced levels of GABARAPL2, suggesting that GIMAP6 may regulate the expression of the latter (51). Knockdown of GIMAP6 in JURKAT cells also increased their sensitivity to apoptosis inducing agents (52). Similar to human GIMAP6, mouse GIMAP6 is also implicated in autophagy. CD2-Cre mediated deletion of *Gimap6* in mice caused in a significant reduction in T and B cell numbers in the periphery even though antigen-specific responses of *Gimap6*$^{-/-}$ T and B cells remained unaffected (53). The half-life of T cells lacking GIMAP6 was estimated to be around 4-5 days based on 4-hydroxytamoxifen mediated deletion in *Gimap6*$^{fl/fl}$*ERT2Cre* mice. Recently, genetic loss of GIMAP6 protein was reported in humans, but with different degrees of clinical manifestations, presumably influenced by additional genetic and environmental factors, as one sibling exhibited lymphopenia while the other was asymptomatic even though both of them were homozygous for the mutant allele (54). Lymphocytes from these patients exhibited accelerated apoptosis, while maintaining normal activation, proliferation and cytokine secretion *in vitro*. Given the lymphocyte-specific expression of GIMAP proteins, it is possible that GIMAP6 may confer additional level of control over apoptotic and autophagic pathways in T cells.

GIMAP8

In contrast to other GIMAP proteins, GIMAP8 possesses three GTPase domains and it is expressed in DN1, DN2 and mature thymocytes and T cells similar to GIMAP5 (23, 55). *Gimap8*-deficient mice show normal T cell development but show a

reduction of recirculating B cells in the bone marrow (55). Nonetheless, the responses of B cells to a T-dependent antigen appear to be normal in these mice.

GIMAP GENES IN LEUKEMOGENESIS

The importance of GIMAP proteins in cell survival and their regulation during the ontogeny of different HSC-derived cell populations suggest that their deregulation may contribute to oncogenesis. The *GIMAP* locus has been implicated in T acute lymphoblastic leukemia (T-ALL) as a target of NOTCH signaling. During T cell development in the thymus, transition through DN1 to DN4 stages is accompanied by a progressive increase in NOTCH1 signaling (131). The DN3 to DN4 transition is a critical checkpoint that selects for productive rearrangement of the *TCRB* locus. Subsequent pre-TCR signaling induces NOTCH1 activation, which is required to expand the pool of cells that rearrange the *TCRA* locus, become $CD4^+CD8^+$ DP thymocytes and undergo positive and negative selection processes to generate SP $CD4^+$ or $CD8^+$ naïve T cells. A majority of thymocytes die due to the lack of survival signals in the absence of productively rearranged *TCR* genes (131, 132). Aberrant oncogenic signaling arising from faulty TCR rearrangement is often implicated in the pathogenesis of T-ALL. Aberrant NOTCH1 activation plays a key oncogenic role in T-ALL (133). In addition to NOTCH1, T-ALL development is associated with oncogenic activation of transcription factors such as TAL1, LYL1, LMO2, TLX1, TLX3 etc., which interfere with progression through T cell developmental stages (134–141).

GIMAP5 was identified as one of the NOTCH1 targets that contributed to the survival of leukemic T cell lines (142, 143). Many GIMAP genes are expressed in T-ALL cell lines (144, 145). The expression of *GIMAP5* occurs in many T cell leukemic cell lines and in anaplastic large cell lymphoma (ALCL) cell lines while the expression of GIMAP1, GIMAP2, GIMAP6 and GIMAP7 were down-regulated in ALCLs (44, 146). KMT2A/GIMAP8 rearrangements were detected in a patient with acute undifferentiated leukemia (147). *Gimap1* is upregulated in a murine leukemic cell line during p53-induced apoptosis (148). Most of the *Gimap* genes are expressed in HSC and/or in mature T cells but not in DN thymocytes in zebrafish (145). The *GIMAP* super-enhancer region was shown to be activated by the oncogenic transcription factor TAL1 and is repressed by E- proteins. Knocking out the TAL1 binding domain in JURKAT cells abrogated the expression of *GIMAP* genes. Ectopic expression of human *GIMAP5* and *GIMAP7* under the *Rag2* promoter did not induce leukemia but was capable of accelerating T-ALL induced by *MYC* in the zebrafish (145). As knockdown of *GIMAP* in T-ALL cells reduced their survival, it is possible that GIMAP proteins play an important role in maintaining the survival of transformed cells.

CONCLUSIONS AND FUTURE DIRECTIONS

GTPases with similarities to mammalian GIMAPs appear to have evolved independently in different species (56, 58, 59, 149–152). Proteins containing the AIG domain are present in angiosperms (flowering plants) and are induced by infections and stress (57, 61). *Gimap* genes are upregulated in certain invertebrates and zebrafish in response to infections (58, 59, 149, 151). Future studies aimed at understanding the functions of the related genes in the context of stress and infections in different species will further our knowledge on GIMAP proteins.

The data available to date overwhelmingly indicate that the GIMAP proteins have important and non-redundant functions in the survival of lymphocytes and in the maintenance of quiescence (GIMAP5) in HSCs. While some GIMAP proteins may interact with proteins involved in classical pathways of cell survival such as BCL2 family members and caspases, they also appear to promote survival by distinct mechanisms. GIMAP proteins are distinctly related to septins and share structural similarities with dynamins, Toc and other TRAnslation FACtor (TRAFAC) proteins (153). Structural analyses of GIMAP2 and GIAMP7 suggest that their GTPase activity is regulated by dimerization (44). GIMAP1, GIMAP2, GIMAP3 and GIMAP5 are membrane-associated while the rest of the GIMAP proteins do not have membrane anchor domains (**Figures 1**, **4**). Overexpressed GIMAP2 increases the formation of lipid droplets in JURKAT cells and can dimerize with GIMAP7 (44–46, 121). It is possible that the homo- and hetero-oligomers can form membrane scaffolds that recruit additional interacting proteins (121). Many of these interactions can be presumed to be dynamic and temporal, making it difficult to identify the interacting partners by classical methods (53). GIMAP5 and GIMAP4 have been observed to be associated with microtubules and actin (31, 50), implicating them in the transport of cellular cargo. Given the implication of GIMAP proteins in the survival of T lymphocytes, it is not surprising that GIMAPs have been associated with different types of leukemias. Unravelling the functions of GIMAP proteins will predicate a better understanding of their role in T cell survival and their contribution to the development of leukemias.

AUTHOR CONTRIBUTIONS

SR and M-AL designed the content and wrote the manuscript. SI, MC, and MN contributed to the discussions and specific subtitles in the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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