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KLRG1—more than a marker for T cell senescence

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Abstract The co-inhibitory receptor killer-cell lectin like receptor G1 (KLRG1) is expressed on NK cells and antigen-experienced T cells and has been postulated to be a marker of senescence. Whilst KLRG1 has frequently been used as a marker of cellular differentiation, data are emerging indicating that KLRG1 plays an inhibitory role. In this review we examine evidence highlighting this view of KLRG1 with emphasis on the functional defects that arise during T cell differentiation with age that may, in part, be actively maintained by inhibitory receptor signalling.

Keywords KLRG1 · Inhibitory · ITIM
Highly differentiated T cell

Introduction

The immune system undergoes a dramatic restructuring with age, leading to a decline in immune responses and an increased vulnerability of old individuals. The incidence and severity of infectious diseases, such as pneumonia (LaCroix et al. 1989), meningitis (Gorse et al. 1984), sepsis (Chattopadhyay and Al-Zahawi 1983), urinary tract infections (Ackermann and Monroe 1996), infection with respiratory syncytial virus (Barker and Mullooly 1980) or influenza (Sprenger et al. 1993) all increase with age. Indeed the mortality rate of older adults suffering urinary tract infections or tuberculosis is ten-fold higher than that of young adults (Yoshikawa 1997). This waning immunity in old age results from defects in numerous different leukocyte populations with the dysfunction being most pronounced in T cells. This T cell immune decline is marked by a dramatic decline in the number of naïve T cells as a result of a thymic atrophy (Douek et al. 1998; Linton and Dorshkind 2004). This reduced thymic output leads to the peripheral expansion of naïve and memory T cells to regenerate the T cell pool, which in turn leads to the accumulation of oligoclonally expanded, functionally impaired T cells (Akbar and Fletcher 2005; Messaoudi et al. 2004). These age-associated changes contribute to the inability of the aged immune system to respond to new antigenic challenge and mount optimum responses to vaccination (Goronzy et al. 2001).

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Phenotypic changes to T cells during aging

There are numerous reports cataloging the phenotypic and functional changes to human T cells that occur

during ageing (Table 1). Old individuals show an increased proportion of T cells that are highly differentiated, with similar phenotypic changes occurring in both $CD4^+$ and $CD8^+$ T cells during differentiation. However, the rate at which these changes happen varies within each subset, with age-related changes being more pronounced on $CD8^+$ T cells due to a greater homeostatic stability of $CD4^+$ T cells (Effros et al. 1994; Czesnikiewicz-Guzik et al. 2008; Goronzy et al. 2007). These highly differentiated cells have functional defects that may explain the decreased efficiency of the immune system in older individuals (Fletcher et al. 2005). Highly differentiated T cells are characterised by the loss of the cell surface co-stimulatory molecules CD27 and CD28, $CD8^+$ T cells losing CD28 first followed by CD27 with the converse being true for $CD4^+$ T cells (Appay et al. 2002; Amyes et al. 2003; Fletcher et al. 2005; Plunkett et al. 2005). Initially, it was thought that the loss of CD28 was a major factor in the reduced activation and function of these cells (Champagne et al. 2001; Effros et al. 2005). However, subsequent studies have suggested a greater plasticity with regard to co-stimulatory receptor expression and usage among T cells. For example, co-stimulation through ICOS, a CD28 family member, and CD137 and CD134, members of the TNF family, have all been shown to enhance the proliferation (Bukczynski et al. 2003; Serghides et al. 2005; Plunkett et al. 2007; Waller et al. 2007) and telomerase activity in $CD8^+CD28^-$ T cells (Plunkett et al. 2007). This redundancy in co-stimulatory receptor usage suggests that changes in addition to the loss of co-stimulatory receptors are involved in T cell dysfunction during ageing. One such change may be a rise in co-inhibitory receptors, in particular the co-inhibitory receptor killer-cell lectin like receptor G1 (KLRG1).

KLRG1—more than a marker for T cell memory

In both mice and humans, KLRG1 expression is found on NK cells and antigen-experienced T cells (Blaser et al. 1998; Hanke et al. 1998; Voehringer et al. 2002). Human KLRG1 is also found on a subset of γδ T cells (Eberl et al. 2005) and in a large proportion of $CD4^+$ and $CD8^+$ T cells found in cord blood (Marcolino et al. 2004). In young adults, the expression of KLRG1 is about 40% on $CD8^+$ T cells and 20% on $CD4^+$ T cells (Voehringer et al. 2002).

Table 1 Phenotypic and functional characteristics of human T cell subsets[a]

Phenotype	Naïve	Central memory	Effector memory	CD45RA memory	References
CD45RA	+++	-	-	+++	(Akbar et al. 1988; Sallusto et al. 2004)
CD45RO	-	+++	+++	-	(Akbar et al. 1988; Sallusto et al. 2004)
CD28	+++	++	+/-	+/-	(Hamann et al. 1997; Sallusto et al. 2004)
CD27	+++	++	+/-	+/-	(Akbar et al. 1988; Sallusto et al. 2004)
CCR7	+++	++	-	-	(Sallusto et al. 2004)
CD62L	+++	+++	+	+	(Sallusto et al. 2004)
CD11c	-	+++	+++	+++	(Faint et al. 2001)
CD57	-	+	++	+++	(Appay et al. 2007; Koch et al. 2008)
KLRG1	+	++	++	+++	(Voehringer et al. 2001; Ouyang et al. 2003)
Telomere length	+++	++	+	++	(Faint et al. 2001; Plunkett et al. 2005)

[a] Activation of T cells results in phenotypic and functional changes. Using relative telomere length and cell surface phenotype as combined criteria, a scheme for identifying T cells at different stages of differentiation can be constructed. Following antigen stimulation, naïve T cells lose expression of CD45RA and become $CD45RO^+$ memory cells. Upon differentiation to an effector memory population, T cells lose CCR7, CD62L, CD28 and CD27, while expression of CD11c, CD57 and KLRG1 increase. In general, similar phenotypic changes occur in both $CD4^+$ and $CD8^+$ T cells during differentiation; however, the rate at which these changes occur can vary within each subset (Appay et al. 2002). The balance of naïve and memory cells is altered during aging, with older adults showing significantly increased levels of highly differentiated effector memory and primed $CD45RA^+$ T cells and a concomitant loss of naïve cells (Pawelec et al. 2004). These highly differentiated T cells have short telomeres and consequently function poorly, suggesting that, during the course of aging, these populations are eventually driven to end-stage differentiation

The expression of KLRG1 rises dramatically with age, with greater than 90% expression of KLRG1 being seen on $CD8^+$ T cells in individuals over 65 years of age (Ouyang et al. 2003; Ito et al. 2006; Henson et al. 2009). The expression of KLRG1 increases not only with age but also with differentiation, with the highest percentage of expression being seen on memory cells and highly differentiated end stage cells (Voehringer et al. 2002; Thimme et al. 2005). In mice, KLRG1 has been used to identify memory precursor cells from effector T cells. Through the use of acute viral infection models it has been shown that KLRG1 can be used to distinguish short-lived effector $CD8^+$ T cells ($KLRG1^{high}$) and memory precursor effector $CD8^+$ T cells ($KLRG1^{low}$) (Joshi et al. 2007; Mousavi et al. 2008).

Despite the extensive use of KLRG1 as a marker of differentiation, KLRG1 possesses an immune receptor tyrosine-based inhibitory motif (ITIM) in its cytoplasmic domain, suggesting that it may play a functional role in the immune system. An inhibitory role for KLRG1 has been demonstrated in mice, with antibody-mediated cross-linking of KLRG1 being shown to inhibit cytolytic activity and IFNγ production in NK cells (Robbins et al. 2002). However, this result is at odds with a number of reports that failed to observe an inhibitory cytolytic effect (Hanke et al. 1998; Grundemann et al. 2006); these differing outcomes may be the result of Robbins et al. using an NK clone over-expressing KLRG1. In murine T cells, the cross-linking of TCR and KLRG1 by plate-bound antibodies was shown to lower Ca^{2+} influx (Beyersdorf et al. 2001) and to decrease IL-2 production (Tessmer et al. 2007). The use of KLRG1-transgenic mice showed that antigen-stimulated T cells in the presence of KLRG1's ligand, E-cadherin, inhibited the proliferative capacity of $CD8^+$ T cells (Grundemann et al. 2006).

Data is now emerging suggesting that KLRG1 plays an inhibitory role in human NK cells and T cells. KLRG1-mediated inhibition of NK cell function revealed that KLRG1/ligand interactions inhibit the cytolytic activity of polyclonal human NK cells by interfering with both degranulation and IFNγ release (Schwartzkopff et al. 2007). Consistent with murine data, the authors also show the degree of inhibition to be modest, and to require high expression levels of KLRG1's ligand, E-cadherin (Schwartzkopff et al. 2007).

A recent study has demonstrated a role for KLRG1 as an inhibitory receptor in T cells. The authors used a $CD4^+$ T cell hybridoma transduced with KLRG1 and showed that KLRG1-ligation inhibited the NFAT-signaling pathway and down-regulated CD95 mediated lysis (Rosshart et al. 2008). Furthermore, they also demonstrated that both KLRG1 and CD3/TCR signals have to be provided in a spatially restricted manner in order to inhibit T-cell activation (Rosshart et al. 2008), suggesting that KLRG1 inhibits T cell function only when MHC/antigen and KLRG1 ligands are expressed on the same target cells. Data from our laboratory has also shown KLRG1 to have an inhibitory effect on primary $CD8^+$ T cells; we have shown that blocking KLRG1 signaling during TCR activation using antibodies against its ligand, E-cadherin, enhanced proliferative activity that was linked directly to an Akt-mediated increase in synthesis of cyclin D and E and a decrease in the cyclin inhibitor p27 (Henson et al. 2009). Whist we observed a significant enhancement in proliferative capacity in $CD8^+$ T cells isolated from young individuals the effect was not as great as that of $CD8^+$ T cells isolated from old individuals, suggesting that other, as yet unidentified, age-related defects are contributing to the poor proliferative responses of $CD8^+$ T cells from old donors and these remain to be clarified.

How KLRG1 exerts its inhibitory effects

KLRG1 has been shown to be a cadherin receptor, recognising E-, N- and R-cadherin (Grundemann et al. 2006; Ito et al. 2006; Schwartzkopff et al. 2007). The cadherins comprise a family of transmembrane glycoproteins that mediate Ca^{2+} dependent cell-cell adhesion (Gumbiner 2005). Classically, E-cadherin is expressed on epithelial cells and Langerhans cells, whereas N- and R-cadherin are expressed by the nervous system. We have shown E-cadherin to be expressed on peripheral blood cells, notably on myeloid DCs, with no expression of N-cadherin being found (Henson et al. 2009). Demonstrating that E-cadherin is found not only in the epithelium but on a wide range of antigen-presenting cells suggesting a broader range of scenarios for immune control by KLRG1/cadherin interactions. A recent report using a KLRG1-reporter cell assay with domain-deleted E-

cadherin mutants (Δ1–Δ5) have shown that the first and the second extracellular domains of E-cadherin to be critical for interaction with KLRG1 (Rosshart et al. 2008).

KLRG1 contains one ITIM motif in its cytoplasmic domain, which mediates its effects through the recruitment of SHIP-1 and SHP-2 phosphatases and a tyrosine residue at position 7 in the ITIM (Xu et al. 2001; Tessmer et al. 2007). Murine KLRG1 also contains a PxxP motif in its cytoplasmic domain that could potentially interact with proteins containing SH3 domains (Abramson et al. 2002). KLRG1 forms both monomers and dimers, with a substantial fraction of KLRG1 being found on the cell surface as disulfide-linked trimeric and tetrameric complexes (Rosshart et al. 2008). The cysteine residues in human KLRG1 that are responsible for disulfide-linked multimer formation have not yet been defined; however, murine KLRG1 contains four cysteines proximal to the membrane in the extracellular domain that are probably not involved in intramolecular disulfide-bonding (Voehringer et al. 2001). It has been demonstrated that, in contrast to KLRG1-tetramers (Grundemann et al. 2006; Rosshart et al. 2008), monomeric KLRG1 shows little discernable binding to E-cadherin-expressing cells, suggesting that KLRG1 binds to E-cadherin with relatively low affinity. Multimerisation of

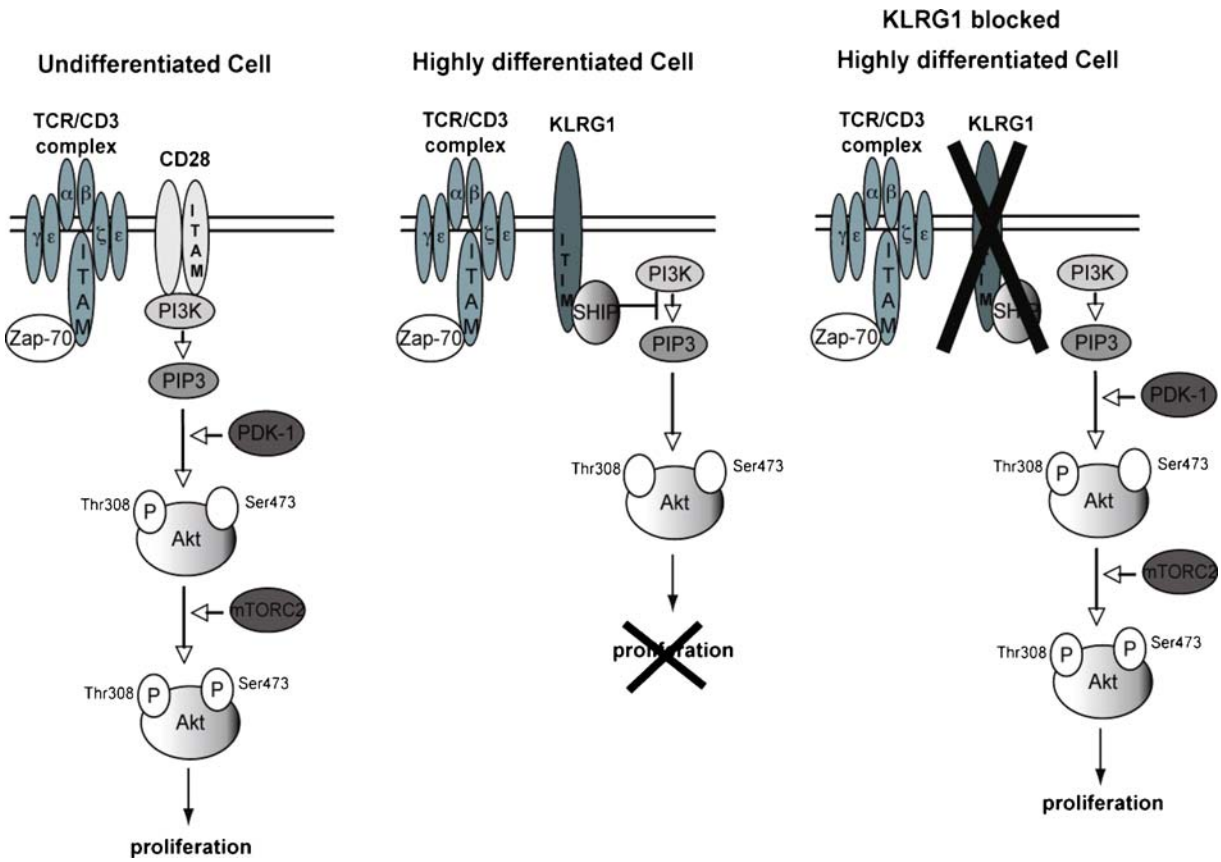

Fig. 1 Changes in Akt signaling with differentiation of $CD8^+$ T cells and co-inhibitory receptor killer-cell lectin like receptor G1 (KLRG1)-blocked highly differentiated $CD8^+$ T cells. An undifferentiated cell signals through CD28, initiating the Akt signalling pathway, which results in a broad range of cellular functions, including the initiation of proliferation. Upon differentiation, $CD8^+$ T cells lose CD28 and gain the inhibitory molecule KLRG1, which acts through SHIP-1 and SHP-2 to degrade PIP3 to PIP2 (Tessmer et al. 2007), preventing phosphorylation of Akt(ser^{473}), thus regulating the function of PI3K. Blocking KLRG1 signals in highly differentiated $CD8^+$ T cells causes the conversion of PIP2 to PIP3 leading to a restoration of pAkt(Ser^{473}) to the levels seen after activation in the less differentiated $CD8^+$ subsets, enhancing proliferation in otherwise dysfunctional cells (Henson et al. 2009)

KLRG1 increases the avidity and may thereby enhance the sensitivity for inhibition (Rosshart et al. 2008).

The effectors SHIP-1 and SHP-2 degrade PIP3 to PIP2, thus regulating the function of PI3K (Tessmer et al. 2007). PI3K plays a crucial role in a broad range of cellular functions in response to extracellular signals. A key downstream effector of PI3K is the serine-threonine kinase Akt, which, in response to PI3K activation, phosphorylates and regulates the activity of a number of targets, including kinases, transcription factors and other regulatory molecules (Donahue and Fruman 2004). The activation of Akt requires the binding of its pleckstrin homology (PH) domain to the phosphoinositide products of PI3K resulting in its recruitment to the plasma membrane. Once there, Akt activation is controlled by phosphorylation at two different sites, Thr^{308} and Ser^{473} (Alessi et al. 1996; Jacinto et al. 2006). Highly differentiated $CD8^+CD28^-CD27^-$ T cells are unable to phosphorylate Akt(ser^{473}), with the Thr^{308} phosphorylation site being unaffected (Plunkett et al. 2007). We assessed whether signalling via KLRG1 contributes to any of the attenuated differentiation-related functional changes in $CD8^+$ T cells. By blocking KLRG1 signalling during TCR activation using antibodies against its major ligand, E-cadherin, we showed a reversal of the defective Akt(ser^{473}) phosphorylation in highly differentiated $CD8^+$ T cells isolated from both young and old donors to the levels that are found after activation in the less differentiated $CD8^+$ subsets (Fig. 1). This indicates that the defect in Akt phosphorylation is not a passive consequence of antigenic-driven differentiation of $CD8^+$ T cells but that it is instead actively maintained by KLRG1 signalling (Henson et al. 2009).

Conclusion

Highly differentiated T cells accumulate with age; these cells have numerous defects including a decreased capacity for proliferation, an inability to produce IL-2, defective Akt(ser^{473}) phosphorylation after activation, short telomeres and low telomerase activity, indicating that they are close to replicative senescence. In addition, these cells express increased levels of the inhibitory receptor KLRG1. Despite the extensive use of KLRG1 as a marker of differentiation, KLRG1 possesses an ITIM in its cytoplasmic domain, suggesting that it may play a functional role in the immune system. KLRG1 signalling has been shown to inhibit the cytolytic activity of polyclonal human NK cells and T cell hybridomas, as well as interfering with proliferation via Akt-mediated changes in cyclins and cyclin inhibitors. Therefore, signalling through KLRG1 may be responsible in part for the defects observed in highly differentiated T cells. It is well recognised that older humans have decreased responses to vaccination (Hayward et al. 1994; Stepanova et al. 2002; Wick et al. 2000) and it is possible that modulating certain inhibitory receptors like KLRG1 that are preferentially expressed in highly differentiated T cells, which expand during ageing, could potentially boost immunotherapeutic regimes such as vaccination for the aged.

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References

Abramson J, Xu R, Pecht I (2002) An unusual inhibitory receptor-the mast cell function-associated antigen (MAFA). Mol Immunol 38:1307–1313. doi:10.1016/S0161-5890(02)00080-9

Ackermann RJ, Monroe PW (1996) Bacteremic urinary tract infection in older people. J Am Geriatr Soc 44:927–933

Akbar AN, Fletcher JM (2005) Memory T cell homeostasis and senescence during aging. Curr Opin Immunol 17:480–485. doi:10.1016/j.coi.2005.07.019

Akbar AN, Terry L, Timms A, Beverley PC, Janossy G (1988) Loss of CD45R and gain of UCHL1 reactivity is a feature of primed T cells. J Immunol 140:2171–2178

Alessi DR, Andjelkovic M, Caudwell B, Cron P, Morrice N, Cohen P, Hemmings BA (1996) Mechanism of activation of protein kinase B by insulin and IGF-1. EMBO J 15:6541–6551

Amyes E, Hatton C, Montamat-Sicotte D, Gudgeon N, Rickinson AB, McMichael AJ, Callan MF (2003) Characterization of the CD4+ T cell response to Epstein-Barr virus during primary and persistent infection. J Exp Med 198:903–911. doi:10.1084/jem.20022058

Appay V, Dunbar PR, Callan M, Klenerman P, Gillespie GM, Papagno L, Ogg GS, King A, Lechner F, Spina CA, Little S, Havlir DV, Richman DD, Gruener N, Pape G, Waters A, Easterbrook P, Salio M, Cerundolo V, McMichael AJ, Rowland-Jones SL (2002) Memory CD8+ T cells vary in differentiation phenotype in different persistent virus infections. Nat Med 8:379–385. doi:10.1038/nm0402-379

Appay V, Almeida JR, Sauce D, Autran B, Papagno L (2007) Accelerated immune senescence and HIV-1 infection. Exp Gerontol 42:432–437. doi:10.1016/j.exger.2006.12.003

Barker WH, Mullooly JP (1980) Impact of epidemic type A influenza in a defined adult population. Am J Epidemiol 112:798–811

Beyersdorf NB, Ding X, Karp K, Hanke T (2001) Expression of inhibitory "killer cell lectin-like receptor G1" identifies unique subpopulations of effector and memory CD8 T cells. Eur J Immunol 31:3443–3452. doi:10.1002/1521-4141(200112)31:12<3443::AID-IMMU3443>3.0.CO;2-J

Blaser C, Kaufmann M, Pircher H (1998) Virus-activated CD8 T cells and lymphokine-activated NK cells express the mast cell function-associated antigen, an inhibitory C-type lectin. J Immunol 161:6451–6454

Bukczynski J, Wen T, Watts TH (2003) Costimulation of human CD28- T cells by 4-1BB ligand. Eur J Immunol 33:446–454. doi:10.1002/immu.200310020

Champagne P, Ogg GS, King AS, Knabenhans C, Ellefsen K, Nobile M, Appay V, Rizzardi GP, Fleury S, Lipp M, Forster R, Rowland-Jones S, Sekaly RP, McMichael AJ, Pantaleo G (2001) Skewed maturation of memory HIV-specific CD8 T lymphocytes. Nature 410:106–111. doi:10.1038/35065118

Chattopadhyay B, Al-Zahawi M (1983) Septicaemia and its unacceptably high mortality in the elderly. J Infect 7:134–138. doi:10.1016/S0163-4453(83)90548-0

Czesnikiewicz-Guzik M, Lee WW, Cui D, Hiruma Y, Lamar DL, Yang ZZ, Ouslander JG, Weyand CM, Goronzy JJ (2008) T cell subset-specific susceptibility to aging. Clin Immunol 127:107–118. doi:10.1016/j.clim.2007.12.002

Donahue AC, Fruman DA (2004) PI3K signaling controls cell fate at many points in B lymphocyte development and activation. Semin Cell Dev Biol 15:183–197. doi:10.1016/j.semcdb.2003.12.024

Douek DC, McFarland RD, Keiser PH, Gage EA, Massey JM, Haynes BF, Polis MA, Haase AT, Feinberg MB, Sullivan JL, Jamieson BD, Zack JA, Picker LJ, Koup RA (1998) Changes in thymic function with age and during the treatment of HIV infection. Nature 396:690–695. doi:10.1038/25374

Eberl M, Engel R, Aberle S, Fisch P, Jomaa H, Pircher H (2005) Human Vgamma9/Vdelta2 effector memory T cells express the killer cell lectin-like receptor G1 (KLRG1). J Leukoc Biol 77:67–70

Effros RB, Boucher N, Porter V, Zhu X, Spaulding C, Walford RL, Kronenberg M, Cohen D, Schachter F (1994) Decline in CD28+ T cells in centenarians and in long-term T cell cultures: a possible cause for both in vivo and in vitro immunosenescence. Exp Gerontol 29:601–609. doi:10.1016/0531-5565(94)90073-6

Effros RB, Dagarag M, Spaulding C, Man J (2005) The role of CD8+ T-cell replicative senescence in human aging. Immunol Rev 205:147–157. doi:10.1111/j.0105-2896.2005.00259.x

Faint JM, Annels NE, Curnow SJ, Shields P, Pilling D, Hislop AD, Wu L, Akbar AN, Buckley CD, Moss PA, Adams DH, Rickinson AB, Salmon M (2001) Memory T cells constitute a subset of the human CD8+CD45RA+pool with distinct phenotypic and migratory characteristics. J Immunol 167:212–220

Fletcher JM, Vukmanovic-Stejic M, Dunne PJ, Birch KE, Cook JE, Jackson SE, Salmon M, Rustin MH, Akbar AN (2005) Cytomegalovirus-specific CD4+ T cells in healthy carriers are continuously driven to replicative exhaustion. J Immunol 175:8218–8225

Goronzy JJ, Fulbright JW, Crowson CS, Poland GA, O'Fallon WM, Weyand CM (2001) Value of immunological markers in predicting responsiveness to influenza vaccination in elderly individuals. J Virol 75:12182–12187. doi:10.1128/JVI.75.24.12182-12187.2001

Goronzy JJ, Lee WW, Weyand CM (2007) Aging and T-cell diversity. Exp Gerontol 42:400–406. doi:10.1016/j.exger.2006.11.016

Gorse GJ, Thrupp LD, Nudleman KL, Wyle FA, Hawkins B, Cesario TC (1984) Bacterial meningitis in the elderly. Arch Intern Med 144:1603–1607. doi:10.1001/archinte.144.8.1603

Grundemann C, Bauer M, Schweier O, von Oppen N, Lassing U, Saudan P, Becker KF, Karp K, Hanke T, Bachmann MF, Pircher H (2006) Cutting edge: identification of E-cadherin as a ligand for the murine killer cell lectin-like receptor G1. J Immunol 176:1311–1315

Gumbiner BM (2005) Regulation of cadherin-mediated adhesion in morphogenesis. Nat Rev Mol Cell Biol 6:622–634. doi:10.1038/nrm1699

Hamann D, Baars PA, Rep MH, Hooibrink B, Kerkhof-Garde SR, Klein MR, van Lier RA (1997) Phenotypic and functional separation of memory and effector human CD8+ T cells. J Exp Med 186:1407–1418. doi:10.1084/jem.186.9.1407

Hanke T, Corral L, Vance RE, Raulet DH (1998) 2F1 antigen, the mouse homolog of the rat "mast cell function-associated antigen", is a lectin-like type II transmembrane receptor expressed by natural killer cells. Eur J Immunol 28:4409–4417. doi:10.1002/(SICI)1521-4141(199812)28:12<4409::AID-IMMU4409>3.0.CO;2-3

Hayward AR, Buda K, Levin MJ (1994) Immune response to secondary immunization with live or inactivated VZV vaccine in elderly adults. Viral Immunol 7:31–36. doi:10.1089/vim.1994.7.31

Henson SM, Franzese O, Macaulay R, Libri V, Azevedo RI, Kiani-Alikhan S, Plunkett FJ, Masters JE, Jackson S, Griffiths S, Pircher HP, Soares MV, Akbar AN (2009) KLRG1 signaling induces defective Akt (Ser473) phosphorylation and proliferative dysfunction of highly differentiated CD8+ T cells. Blood (Apr):30. Epub ahead of print

Ito M, Maruyama T, Saito N, Koganei S, Yamamoto K, Matsumoto N (2006) Killer cell lectin-like receptor G1 binds three members of the classical cadherin family to inhibit NK cell cytotoxicity. J Exp Med 203:289–295. doi:10.1084/jem.20051986

Jacinto E, Facchinetti V, Liu D, Soto N, Wei S, Jung SY, Huang Q, Qin J, Su B (2006) SIN1/MIP1 maintains rictor-mTOR complex integrity and regulates Akt phosphorylation and substrate specificity. Cell 127:125–137. doi:10.1016/j.cell.2006.08.033

Joshi NS, Cui W, Chandele A, Lee HK, Urso DR, Hagman J, Gapin L, Kaech SM (2007) Inflammation directs memory precursor and short-lived effector CD8(+) T cell fates via the graded expression of T-bet transcription factor. Immunity 27:281–295. doi:10.1016/j.immuni.2007.07.010

Koch S, Larbi A, Dehovanessian E, Ozcelik D, Naumova E, Pawelec G (2008) Multiparameter flow cytometric analysis of CD4 and CD8 T cell subsets in young and old people. Immun Ageing 5:6. doi:10.1186/1742-4933-5-6

LaCroix AZ, Lipson S, Miles TP, White L (1989) Prospective study of pneumonia hospitalizations and mortality of U.S. older people: the role of chronic conditions, health behaviors, and nutritional status. Public Health Rep 104:350–360

Linton PJ, Dorshkind K (2004) Age-related changes in lymphocyte development and function. Nat Immunol 5:133–139. doi:10.1038/ni1033

Marcolino I, Przybylski GK, Koschella M, Schmidt CA, Voehringer D, Schlesier M, Pircher H (2004) Frequent expression of the natural killer cell receptor KLRG1 in human cord blood T cells: correlation with replicative history. Eur J Immunol 34:2672–2680. doi:10.1002/eji.200425282

Messaoudi I, Lemaoult J, Guevara-Patino JA, Metzner BM, Nikolich-Zugich J (2004) Age-related CD8 T cell clonal expansions constrict CD8 T cell repertoire and have the potential to impair immune defense. J Exp Med 200:1347–1358. doi:10.1084/jem.20040437

Mousavi SF, Soroosh P, Takahashi T, Yoshikai Y, Shen H, Lefrancois L, Borst J, Sugamura K, Ishii N (2008) OX40 costimulatory signals potentiate the memory commitment of effector CD8+ T cells. J Immunol 181:5990–6001

Ouyang Q, Wagner WM, Voehringer D, Wikby A, Klatt T, Walter S, Muller CA, Pircher H, Pawelec G (2003) Age-associated accumulation of CMV-specific CD8+ T cells expressing the inhibitory killer cell lectin-like receptor G1 (KLRG1). Exp Gerontol 38:911–920. doi:10.1016/S0531-5565(03)00134-7

Pawelec G, Akbar AN, Caruso C, Effros R, Grubeck-Loebenstein B, Wikby A (2004) Is immunosenescence infectious? Trends Immunol 25:406–410. doi:10.1016/j.it.2004.05.006

Plunkett FJ, Franzese O, Belaramani LL, Fletcher JM, Gilmour KC, Sharifi R, Khan N, Hislop AD, Cara A, Salmon M, Gaspar HB, Rustin MH, Webster D, Akbar AN (2005) The impact of telomere erosion on memory CD8+ T cells in patients with X-linked lymphoproliferative syndrome. Mech Ageing Dev 126:855–865. doi:10.1016/j.mad.2005.03.006

Plunkett FJ, Franzese O, Finney HM, Fletcher JM, Belaramani LL, Salmon M, Dokal I, Webster D, Lawson AD, Akbar AN (2007) The loss of telomerase activity in highly differentiated CD8+CD28-CD27- T cells is associated with decreased Akt (Ser473) phosphorylation. J Immunol 178:7710–7719

Robbins SH, Nguyen KB, Takahashi N, Mikayama T, Biron CA, Brossay L (2002) Cutting edge: inhibitory functions of the killer cell lectin-like receptor G1 molecule during the activation of mouse NK cells. J Immunol 168:2585–2589

Rosshart S, Hofmann M, Schweier O, Pfaff AK, Yoshimoto K, Takeuchi T, Molnar E, Schamel WW, Pircher H (2008) Interaction of KLRG1 with E-cadherin: new functional and structural insights. Eur J Immunol 38:3354–3364. doi:10.1002/eji.200838690

Sallusto F, Geginat J, Lanzavecchia A (2004) Central memory and effector memory T cell subsets: function, generation, and maintenance. Annu Rev Immunol 22:745–763. doi:10.1146/annurev.immunol.22.012703.104702

Schwartzkopff S, Grundemann C, Schweier O, Rosshart S, Karjalainen KE, Becker KF, Pircher H (2007) Tumor-associated E-cadherin mutations affect binding to the killer cell lectin-like receptor G1 in humans. J Immunol 179:1022–1029

Serghides L, Bukczynski J, Wen T, Wang C, Routy JP, Boulassel MR, Sekaly RP, Ostrowski M, Bernard NF, Watts TH (2005) Evaluation of OX40 ligand as a costimulator of human antiviral memory CD8 T cell responses: comparison with B7.1 and 4-1BBL. J Immunol 175:6368–6377

Sprenger MJ, Mulder PG, Beyer WE, Van Strik R, Masurel N (1993) Impact of influenza on mortality in relation to age and underlying disease, 1967–1989. Int J Epidemiol 22:334–340. doi:10.1093/ije/22.2.334

Stepanova L, Naykhin A, Kolmskog C, Jonson G, Barantceva I, Bichurina M, Kubar O, Linde A (2002) The humoral response to live and inactivated influenza vaccines administered alone and in combination to young adults and elderly. J Clin Virol 24:193–201. doi:10.1016/S1386-6532(01)00246-3

Tessmer MS, Fugere C, Stevenaert F, Naidenko OV, Chong HJ, Leclercq G, Brossay L (2007) KLRG1 binds cadherins and preferentially associates with SHIP-1. Int Immunol 19:391–400. doi:10.1093/intimm/dxm004

Thimme R, Appay V, Koschella M, Panther E, Roth E, Hislop AD, Rickinson AB, Rowland-Jones SL, Blum HE, Pircher H (2005) Increased expression of the NK cell receptor KLRG1 by virus-specific CD8 T cells during persistent antigen stimulation. J Virol 79:12112–12116. doi:10.1128/JVI.79.18.12112-12116.2005

Voehringer D, Blaser C, Brawand P, Raulet DH, Hanke T, Pircher H (2001) Viral infections induce abundant numbers of senescent CD8 T cells. J Immunol 167:4838–4843

Voehringer D, Koschella M, Pircher H (2002) Lack of proliferative capacity of human effector and memory T cells expressing killer cell lectinlike receptor G1 (KLRG1). Blood 100:3698–3702. doi:10.1182/blood-2002-02-0657

Waller EC, McKinney N, Hicks R, Carmichael AJ, Sissons JG, Wills MR (2007) Differential costimulation through CD137 (4-1BB) restores proliferation of human virus-specific "effector memory" (CD28(-) CD45RA(HI)) CD8 (+) T cells. Blood 110:4360–4366. doi:10.1182/blood-2007-07-104604

Wick G, Jansen-Durr P, Berger P, Blasko I, Grubeck-Loebenstein B (2000) Diseases of aging. Vaccine 18:1567–1583. doi:10.1016/S0264-410X(99)00489-2

Xu R, Abramson J, Fridkin M, Pecht I (2001) SH2 domain-containing inositol polyphosphate 5′-phosphatase is the main mediator of the inhibitory action of the mast cell function-associated antigen. J Immunol 167:6394–6402

Yoshikawa TT (1997) Perspective: aging and infectious diseases: past, present, and future. J Infect Dis 176:1053–1057. doi:10.1086/516547