Cell Biology International ISSN 1065-6995
doi: 10.1002/cbin.10778

REVIEW

The Schlafen family: complex roles in different cell types and virus replication

Furao Liu, Pingting Zhou, Qian Wang, Meichao Zhang and Dong Li*

Department of Oncology, Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Abstract

The Schlafen (slfn) gene family members express broadly, but the research has mainly focused on human slfn (h-slfn) and mouse slfn (m-slfn). The slfn members can be divided into three groups, and each group has its own characteristics and functions. Although the effects of slfns are still poorly understood, it has been confirmed that slfns are involved in the defense of immune system and regulate immune cells' proliferation and differentiation. In some malignant tumors, the slfn proteins can inhibit the growth and invasion of cancer cells, promote cancer cells sensibility to chemotherapeutics, and can be a promising new therapeutic target. In addition, the slfn proteins also disturb replication and virulence of viruses. In this review, we summarize the characteristics of the Schlafen family's structures and functions with the aim to achieve a more comprehensive understanding of slfns.

Keywords: cancer biology; cell proliferation; immunology; Schlafen; structural model; virus replication

Introduction

Schlafen genes are conservative in evolution, especially in genome of mice and humans. Mouse slfn genes cluster on chromosome 11, while human slfn genes cluster on chromosome 17 (Katsoulidis et al., 2009; Recher et al., 2014). Although the slfn family has been identified for almost 20 years, the descriptions of its members are inconsistent. It is generally believed that mouse slfns consist of 10 members, m-slfn1, m-slfn1L, m-slfn2, m-slfn3, m-slfn4, m-slfn5, m-slfn8, m-slfn9, m-slfn10, and m-slfn14, respectively (Mavrommatis et al., 2013b). However, the constitution of human slfns is controversial. Bustos et al. (2009) described five human gene members (h-slfn5, h-slfn11, h-slfn12, h-slfn13, h-slfn14), while van Zuylen et al. (2011) proposed six human slfn members, including h-slfn5, h-slfn11, h-slfn12, h-slfn12L, h-slfn13, h-slfn14.

Slfn family was first identified as a regulator for thymocyte maturation and activation in mice and was subsequently shown to function in other cells (Schwarz et al., 1998). The functions of most slfns have been studied over the years and can be summarized into five aspects: (1) Regulating cell proliferation. For instance, Slfns can inhibit cyclin D1 function, resulting in cell cycle arrest in NIH 3T3 cells (Brady et al., 2005). Overexpression of slfn1 or slfn8 perturbs T cell growth (Neumann et al., 2008). In malignant tumors, the expression of slfns is lower than that in normal tissues. And slfn genes are generally inhibited in anchorage-independent cells, indicating their roles in anchorage-independent cell growth (Sassano et al., 2015). (2) Modulating the differentiation of T cells and macrophages. Slfn members are differentially regulated during T cell maturation: slfn1 and slfn2 are upregulated, while slfn4 is downregulated. In contrast, the level of slfn4 is high in primitive bone marrow cells, but low in macrophages (van Zuylen et al., 2011). (4) Slfn members inhibit migration and invasion of cancer cells and sensitize cancers to chemotherapy (Kovalenko and Basson, 2014; Tian et al., 2014). In addition, recent studies have shown that slfn protein can serve as markers of gastric metaplasia (Ding et al., 2016). (4) Slfns also involve in virus replication, acting on the open reading frame to restrain viral replication (Gubser et al., 2007; Li et al., 2012). (5) Slfn expression can be induced by type I interferon (IFN), whose responses rely on the mitogen-activated protein kinase (MAPK)-integrating kinase (Mnk) and MAPK pathway. Stimulated with IFNα or IFNβ, the expression of slfn is enhanced, indicating that it may participate in inflammatory response mediated by IFN signal pathway (Mavrommatis et al., 2013b).

*Corresponding author: e-mail: lidong@shsmu.edu.cn
The copyright line for this article was changed on 03 March 2018 after original online publication.

Furthermore, the localization of each slfn protein possesses functional specificity. Based on different subcellular localization, mouse slfns can be divided into two groups. M-slfn1, m-slfn2, m-slfn3, and m-slfn4 mainly localize in the cytosol, which are reported to modulate growth arrest. In contrast, m-slfn5, m-slfn8, m-slfn9, m-slfn10, and m-slfn14 are found to localize in the nucleus, which might localize along with active form of RNA polymerase II (Neumann et al., 2008). The transfer of slfns from cytosol to nucleus is of great significance in regulating cell functions. However, the specific location and relative functions of human slfns are not well understood. H-slfn5 was identified to localize in the nucleus (Katsoulidis et al., 2010), while h-slfn12 and h-slfn11 were indicated to localize in the cytosol (Li et al., 2012; Kovalenko and Basson, 2014).

The structural characteristics of Schlafen family

In previous studies, slfns' structures have been well described. Based on the size and domain composition, slfn proteins can be divided into three groups (Figure 1). Group I includes m-slfn1 and m-slfn2, with the size between 37 kDa and 42 kDa. Group II comprises of m-slfn3, m-slfn4, and h-slfn12, sizing between 58 kDa and 68–kDa. Group III contains the largest slfns, including m-slfn5, m-slfn8, m-slfn9, m-slfn10, m-slfn14, h-slfn5, h-slfn11, h-slfn13, and h-slfn14, whose molecular mass is between 100–kDa and 104–kDa (Mavrommatis et al., 2013b). All of the slfn proteins share a common N-terminal AAA domain, which is involving in GTP/ATP binding. AAA domain performs various functions, such as protein degradation, transcription, etc (Oh et al., 2011).

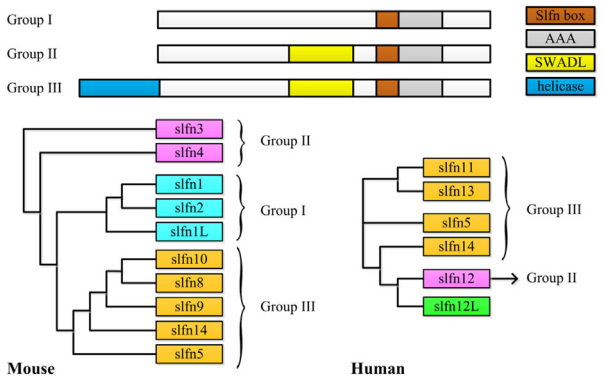

Figure 1 Linear structural model of Schlafen family proteins. The members of schlafen family can be divided into three groups: group I ( ) includes m-slfn1, m-slfn1L, and m-slfn2; group II ( ) includes m-slfn3, m-slfn4, and h-slfn12; group III ( ) includes m-slfn5, m-slfn8, m-slfn9, m-slfn10, m-slfn14, h-slfn5, h-slfn11, h-slfn13, and h-slfn14. AAA structure and slfn box are common to all slfn genes. SWADL belongs to groups II and III. Only group III contains helicase structure of C-terminal. Others ( ): h-slfn12 did not belong to the three groups.

Adjacent to the AAA N-terminal part is a domain referred to as "Slfn box," whose function is not clear. However, groups II and III preserve a unique motif, consisting of a five-amino-acid sequence. Among the whole slfn family, only the members of group III are distinct, preserving additional C-terminal domains homologous to the DNA/RNA helicases of superfamily I (Patel et al., 2009). In addition, there is evidence indicating that C-terminal extension of group III genes harbors a nuclear localization signal and may exert a function in the nucleus.

Slfns involve in immune cell development

The expression of most slfn genes is abundant in immune cells and alters during the development of immune cells. Slfn genes participate in the modulation of immune system. M-slfn1, m-slfn2, m-slfn8, h-slfn12, and h-slfn12L are the members that have been reported to modulate T cell activation, macrophage differentiation, and monocyte maturation.

Human slfns may promote differentiation of dendritic cells

The members of human slfns are regulated differently during the process of differentiation from monocytes to dendritic cells (DCs). H-slfn11 is expressed highly in the unstimulated monocytes and DCs, suggesting that it may play an important role in regulating the function of monocytes and DC cells. When monocytes are induced into DCs, the expressions of h-slfn12L and h-slfn13 increase substantially, which suggest that they might be an influencing factor in cell differentiation. In contrast, the level of h-slfn12 is downregulated, which suggests that it may play a negative role in the process of DC differentiation (Puck et al., 2015). To the contrary, h-slfn12 is upregulated during the activation of T cells (Puck et al., 2017).

Mouse slfns regulate the development of T cells and macrophages

M-slfn1 and m-slfn8 can inhibit the proliferation of T cells. When m-slfn1 or m-slfn8 was overexpressed, T cell proliferation was reduced drastically (Geserick et al., 2004; Neumann et al., 2008). In addition, slfn proteins also maintain the quiescence of T cells, characterized by low metabolism and resistance to apoptosis. Quiescent T cells are regarded as the T cell repertoire and can be selectively induced to the state of proliferation or differentiation with proper activation (Horton and Powell, 2010). M-Slfn1 and m-slfn2 are the major slfn proteins involved in the modulation of T cell quiescence (Zhao et al., 2008). M-slfn1 is an inflammation-related gene, mainly locating

in cytoplasm and nucleus of quiescent T cells (Lund et al., 2006; Kuang et al., 2014). It blocks T cell cycle progression to maintain T cell quiescence by translocating from the cytoplasm to the nucleus. During this process, DnaJB6, a member of Hsp40, assists in the transfer of m-slfn1 (Zhang et al., 2008). M-slfn2 is another recognized gene that regulates T cell quiescence, avoiding the excessive activation of immune system. The mutation of m-slfn2 gene results in disorders of T cell function. T cells are subject to apoptosis when m-slfn2 gene is expressed abnormally. M-slfn2$^{-/-}$ T cells are activated excessively, making the animals sensitive to bacterial infection (Berger et al., 2010; Recher et al., 2014). In contrast to m-slfn1 and m-slfn2, m-slfn3 might promote T cell development, because it is upregulated during T cell activation (Condamine et al., 2010).

In addition to regulating T cell development, some members of the slfns such as m-slfn4 are involved in differentiation and activation of macrophages and disrupt normal myelopoiesis. The mRNA levels of m-slfn4 are downregulated during macrophages differentiation, but increase during macrophages activation. The macrophage numbers are elevated in the livers and spleens of transgenic mice with constitutive m-slfn4 overexpression (van Zuylen et al., 2011).

Slfns regulate the biological function and drug-sensitivity of tumor

There is accumulating evidence that slfn family plays important roles in T cell proliferation and also can modulate the biological function of tumor cells. These genes, which include m-slfn2, m-slfn3, m-slfn12, h-slfn5, and h-slfn11, are widely expressed in normal melanocytes, renal cells, lung cells, ovary cells, as well as their cancer counterparts. Although their basal expression is low in normal cells, the RNA and protein levels of these slfns change dramatically when malignant transformation occurs.

Slfns regulate cancer cell functions

Human slfns regulate the biological function of cancer cells

IFNα is an important biological regulator and negatively regulates the growth of malignant tumors, such as melanoma or renal cell carcinoma. Katsoulidis' group demonstrated that several slfns members are induced to express by IFNα in melanoma. When melanoma cells are stimulated with IFNα, h-slfn5 is upregulated significantly, leading to cancer cell growth reduction. When the expression of h-slfn5 is decreased, the colony formation ability of IFN-treated melanoma is increased. These findings suggest that h-slfn5 may be a negative regulator of melanoma cell proliferation (Katsoulidis et al., 2010).

In addition to the effect on colony formation of the IFN-treated melanoma, h-slfn5 also acts as a suppressor of melanoma invasion. The malignant carcinoma cells invade other organs by migrating in three-dimensional collagen. When h-slfn5 is downregulated, production of three-dimensional collagen is elevated, causing invasion and anchorage-independent growth of melanoma cells to enhance (Katsoulidis et al., 2010).

In renal cell carcinoma, h-slfn5 is a better survival marker for renal cell carcinoma (RCC) patients. Knockdown of h-slfn5 in RCC results in significant increase of cancer cells (Mavrommatis et al., 2013a). H-Slfn5 regulates the motility and invasion of RCC through the IFN signal pathway. Treatment of cells with IFN causes the expression of h-slfn5 to increase and results in subsequent suppression of tumor invasion. It has been reported that h-slfn5 can regulate the expression of matrix metalloproteinase (MMP) genes, such as MMP-1 and MMP-13, which involve in the migration of RCC. Knockdown of h-slfn5 increases the expression of MMP genes, and promotes cell motility. In contrast, when h-slfn5 is overexpressed, mice with RCC survive longer than those in the control group. However, downregulation of other h-slfn genes such as h-slfn11, h-slfn12 or h-slfn13 fails to have effects on survival (Mavrommatis et al., 2013a; Sassano, et al., 2015).

Although h-slfn12 does not act as a regulator in melanoma, it influences the prostate cancer cell differentiation. Dipeptidyl-peptidase 4 (DPP4) and E-cadherin are the markers induced during prostate epithelia differentiation. PSA is a marker of prostate cancer progression. When h-slfn12 is overexpressed, the relative levels of DPP4 and E-cadherin are elevated. In contrast, the relative level of PSA is reduced. It has been reported that mixed lineage kinase (MLK) or extracellular signal-related kinase (ERK) activation regulates the differentiation of prostate cancer cells. Nevertheless, blocking the MLK or the ERK pathway cannot neutralize the effect of h-slfn12 on DPP4 or PSA, suggesting that h-slfn12 regulates prostate cancer differentiation independent of the MLK or the ERK pathway (Kovalenko and Basson, 2014).

Mouse slfns regulate the biological function of cancer cells

Besides human slfns, m-slfn2 and m-slfn3 can also inhibit metastasis and colony formation of malignant cells. Downregulation of either m-slfn2 or m-slfn3 enhances the proliferation of melanoma cells (Katsoulidis et al., 2009; Mavrommatis et al., 2013a). M-slfn3 is also a regulator of internal differentiation (Chaturvedi et al., 2014; Mary et al., 2015). When compared with that of the control cells, the differentiation ratio of colon cancer cells increases by 40% with m-slfn3 overexpression (Patel et al., 2009).

Slfns sensitize cancer cells to chemotherapy

Human slfns enhance the drug-sensitivity of cancer cells
Topoisomerase (TOP) inhibitor is a type of DNA-damaging agents (DDA), playing an important role in oncotherapy. Earlier studies show that the expression level of h-slfns correlates with the responses of cancer cells to TOPs. Among the slfn family members, h-slfn11 is an important gene that sensitizes tumors to chemotherapeutics. Compared with cells with low h-slfn11 levels, cells with high h-slfn11 expression exhibits inhibited proliferation after irinotecan treatment (Zoppoli et al., 2012). Colorectal carcinoma cells with h-slfn11 downregulated are resistant to SN-38 (an active CPT-11 metabolite), because h-slfn11 promotes SN-38-induced apoptosis and cell cycle inhibition to enhance the anti-proliferation function of chemotherapeutics (Tian et al., 2014). The cancer cell line with hypermethylated CpG promoter of h-slfn11 expresses low-level h-slfn11. In non-small cell lung cancer cells, CpG island hypermethylation of h-slfn11 promoter results in the silence of h-slfn11 gene and enhances cancer cell resistance to platinum. When pre-treated with the inhibitor of DNA methylation 5-azacytidine, cancer cells show enhanced sensitivities to platinum compounds (Nogales et al., 2016). In addition to h-slfn11, h-slfn12 also promotes the drug-sensitivity of malignant tumors. H-slfn12 can enhance the tumor sensitivity to DNMDP when combined with phosphodiesterase 3A (PDE3A) in lung adenocarcinoma cell lines (de Waal et al., 2016).

Mouse slfns enhance the drug-sensitivity of cancer cells
HCT-116 and HT-29 are human colon cancer cell lines resistant to FOLFOX therapy (i.e., the combination of 5- fluorouracil and oxaliplatin). Those cells highly express cancer stem cell (CSC) markers such as CD44, CD133, and CD166. Transfection of HCT-116 and HT-29 cells with m-slfn3 causes the expression of CSC markers to reduce, while m-slfn3 functions through the transforming growth factor α/epidermal growth factor receptor (TGFα/EGFR) pathway. Meanwhile, HCT-116 and HT-29 cells transfected with m-slfn3 exhibits higher apoptosis rate than that of the control cells after treated with FOLFOX. Because m-slfn3 can restrain the expression of the drug transporter gene, ATP binding cassette subfamily G member 2 (ABCG2), thereby promoting the susceptibility to chemotherapy in FOLFOX-resistant colon cancer cells (Oh et al., 2011).

Slfns regulate virus production and virulence

Interferon-stimulated genes (ISGs) are a class of IFN-inducible genes that play key roles in viral replication. Slfns were reported to be induced by type I IFN and are thus classified as ISGs that possess anti-viral ability. Human immunodeficiency virus (HIV) and camelpox virus are the typical targets of slfn proteins (Abdel-Mohsen et al., 2013; Jakobsen et al., 2013).

H-slfn11 negatively regulate the HIV replication

HIV is a non-typical virus that cannot stimulate the production of IFN, but instead can induce the expression of h-slfn11, a subset of ISGs (Jakobsen et al., 2013). In 293 cells, the level of HIV proteins increases substantially after h-slfn11 level is reduced. In contrast, in cells with h-slfn11 upregulation, the level of HIV proteins decreases dramatically. Therefore, it was concluded that h-slfn11 can restrain the synthesis of HIV (Li et al., 2012; Abdel-Mohsen et al., 2015). The inhibitory effect of h-slfn11 on HIV differs from other inhibitory factors that act on either the DNA replication or the early phase of mRNA transcription. H-slfn11 can prevent the function of HIV t-RNA and therefore inhibits the synthesis of HIV proteins in infected cells, leading to the block of HIV replication (Li et al., 2012; Razzak, 2012). In addition to the inhibitory role of slfn11 in human cells, Lin et al. (2016) also showed that slfn11 reduces the Gag polyprotein of EIAV, a retrovirus similar to HIV-1.

V-slfn is a significant virulence factor of camelpox virus

Camelpox virus is a type of orthopoxvirus (OPVs) that spread in arid zones of Africa, the middle-east, and central Asia (Afonso et al., 2002). The camelpox virus gene can encode a protein called v-slfn that is homologous to mouse slfns. The expression of v-slfn in viruses is restricted. Although all of the OPVs possess the v-slfn sequence, only the virus conserving an open reading frame can encode v-slfn proteins. V-slfns mainly locate in cytoplasm, without obvious expression in nuclei or other organelles. The structure of v-slfn is close to short mouse slfns, lacking c-terminal extension. However, unlike short m-slfns, v-slfns cannot obstruct the proliferation of fibroblast cells. Besides, during the early state of virus invasion, it can be observed that v-slfn expression increases prominently in host cells, suggesting its anti-infection function in immune system (Bustos et al., 2009; Nagarajan et al., 2013). In contrast to the inhibitory function of slfns in HIV and other cells, v-slfn cannot restrain the production of virus or influence the growth of cells. It is a type of virulence factor, in relation to the virulence of orthopovirus. V-slfn expression in NIH-3T3 cells fails to alter cell proliferation. In intranasal mouse model, the virulence of vaccinia virus (VACV) that expresses v-slfn decreases clearly (Gubser et al., 2007).

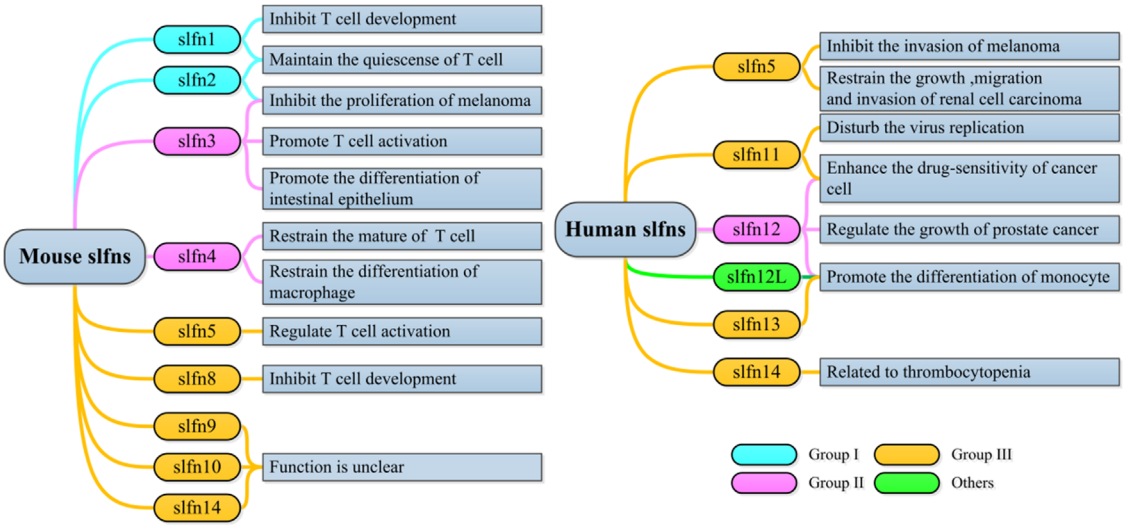

Figure 2 **Linear functional model of Schlafen family protein.** In the group I ( ), both m-slfn1and m-slfn2 involve the development of T cells and maintain the quiescence of T cells. Slfn2 can also inhibit the proliferation of melanoma. In group II ( ), m-slfn3, m-slfn4, and h-slfn12 regulate the functions of immune cells, including T cells, macrophages, and monocytes. Slfn3 and slfn12 are regulators for malignant tumor. In group III ( ), the functions of m-slfn9, m-slfn10, and m-slfn14 need to be explored. M-slfn5, m-slfn8, and h-slfn13 are identified to regulate the functions of T cells and monocytes. H-slfn5 is an inhibitor of biological functions of melanoma, while h-slfn11 acts as a modulator on virus production and drug-sensitivity of cancer. H-slfn14 is an especial gene which is related to thrombocytopenia. Others ( ): h-slfn12 is a promoter of monocyte differentiation.

Conclusion

It is evident from the above contents that studies in the past few years have significantly enriched our knowledge about expression of the slfns in humans and mice, offering evidence to support the roles for these genes in mediating T cell function, cancer cells proliferation, and virus replication through the activation of the MAPK, the stress-activated protein kinases (SAPK)/Jun N-terminal kinases (JNK) or the myd88 pathway (Sohn et al., 2007).

The members of the slfn family show distinct expression patterns, despite the high homology of their N-termial AAA domain, and display different functions both related to physiology and pathology. This suggests that the structure of the N-termial AAA domain is important and that, on the other hand, the non-conserved C-terminal domains provide affecting factors for the specific role of large slfn proteins.

The slfn family is highly integrated into cellular function and development (Figure 2), functioning throughout IFNα and many other cellular mechanisms. Its presence is notable for the maturation of T cell, blood cell differentiation, and inhibition of cell proliferation during development and in specific adult tissues. However, due to the lack of appropriate and specific tools such as antibodies, much of the studies only showed slfns expression at the RNA level, without results from proteins. Because of the limitations of previous studies, the role of the slfns in functional regulation and the detailed molecular mechanisms, particularly for those relating to post-translational modifications of slfns and their major interacting partners, still require further investigation.

It will be of great interest to explore the interactions between slfns and other factors during development in vivo. A key and vital step in understanding mammalian slfns function in the future will be to illustrate its RNA substrates, transcriptome level. Understanding slfns may promote the development of novel medicine to treat cancer, immune diseases, and viral infections.

Acknowledgments and funding

This work was supported by National Natural Science Foundation of China (grants 81370600); the Program for Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning (TP2015022); Shanghai Pujiang Program (15PJ1404800).

Conflict of interest

The authors declare no conflict of interest.

References

Abdel-Mohsen M, Raposo RA, Deng X, Li M, Liegler T, Sinclair E, Salama MS, Ghanem Hel-D, Hoh R, Wong JK, David M, Nixon DF, Deeks SG, Pillai SK (2013) Expression profile of host restriction factors in HIV-1 elite controllers. Retrovirology 10: 106.

Abdel-Mohsen M, Wang C, Strain MC, Lada SM, Deng X, Cockerham LR, Pilcher CD, Hecht FM, Liegler T, Richman DD, Deeks SG, Pillai SK (2015) Select host restriction factors are associated with HIV persistence during antiretroviral therapy. Aids 29: 411–20.

Afonso CL, Tulman ER, Lu Z, Zsak L, Sandybaev NT, Kerembekova UZ, Zaitsev VL, Kutish GF, Rock DL (2002) The genome of camelpox virus. Virology 295: 1–9.

Berger M, Krebs P, Crozat K, Li X, Croker BA, Siggs OM, Popkin D, Du X, Lawson BR, Theofilopoulos AN, Xia Y, Khovananth K, Moresco EM, Satoh T, Takeuchi O, Akira S, Beutler B (2010) An Slfn2 mutation causes lymphoid and myeloid immunodeficiency due to loss of immune cell quiescence. Nat Immunol 11: 335–43.

Brady G, Boggan L, Bowie A, O'Neill LA (2005) Schlafen-1 causes a cell cycle arrest by inhibiting induction of cyclin D1. J Biol Chem 280: 30723–34.

Bustos O, Naik S, Ayers G, Casola C, Perez-Lamigueiro MA, Chippindale PT, Pritham EJ, De la Casa-Esperon E (2009) Evolution of the Schlafen genes, a gene family associated with embryonic lethality, meiotic drive, immune processes and orthopoxvirus virulence. Gene 447: 1–1.

Chaturvedi L, Sun K, Walsh MF, Kuhn LA, Basson MD (2014) The P-loop region of Schlafen 3 acts within the cytosol to induce differentiation of human Caco-2 intestinal epithelial cells. Biochim Biophys Acta 1843: 3029–37.

Condamine T, Le Luduec JB, Chiffoleau E, Beriou G, Louvet C, Heslan M, Tilly G, Cuturi MC (2010) Characterization of Schlafen-3 expression in effector and regulatory T cells. J Leukocyte Biol 87: 451–6.

de Waal L, Lewis TA, Rees MG, Tsherniak A, Wu X, Choi PS, Gechijian L, Hartigan C, Faloon PW, Hickey MJ, Tolliday N, Carr SA, Clemons PA, Munoz B, Wagner BK, Shamji AF, Koehler AN, Schenone M, Burgin AB, Schreiber SL, Greulich H, Meyerson M (2016) Identification of cancer-cytotoxic modulators of PDE3A by predictive chemogenomics. Nat Chem Biol 12: 102–8.

Ding L, Hayes MM, Photenhauer A, Eaton KA, Li Q, Ocadiz-Ruiz R, Merchant JL (2016) Schlafen 4-expressing myeloid-derived suppressor cells are induced during murine gastric metaplasia. J Clin Invest 126: 2867–80.

Geserick P, Kaiser F, Klemm U, Kaufmann SH, Zerrahn J (2004) Modulation of T cell development and activation by novel members of the Schlafen (slfn) gene family harbouring an RNA helicase-like motif. Int Immunol 16: 1535–48.

Gubser C, Goodbody R, Ecker A, Brady G, O'Neill LA, Jacobs N, Smith GL (2007) Camelpox virus encodes a schlafen-like protein that affects orthopoxvirus virulence. J Gen Virol 88: 1667–76.

Horton MR, Powell JD (2010) Quieting T cells with Slfn2. Nat Immunol 11: 281–2.

Jakobsen MR, Mogensen TH, Paludan SR (2013) Caught in translation: innate restriction of HIV mRNA translation by a schlafen family protein. Cell Res 23: 320–2.

Katsoulidis E, Carayol N, Woodard J, Konieczna I, Majchrzak-Kita B, Jordan A, Sassano A, Eklund EA, Fish EN, Platanias LC (2009) Role of Schlafen 2 (SLFN2) in the generation of interferon alpha-induced growth inhibitory responses. J Biol Chem 284: 25051–64.

Katsoulidis, Mavrommatis E, Woodard J, Shields MA, Sassano A, Carayol N, Sawicki KT, Munshi HG, Platanias LC (2010) Role of interferon α (IFNα)-inducible Schlafen-5 in regulation of anchorage-independent growth and invasion of malignant melanoma cells. J Biol Chem 285: 40333–41.

Kovalenko PL, Basson MD (2014) Schlafen 12 expression modulates prostate cancer cell differentiation. J Surg Res 190: 177–84.

Kuang CY, Yang TH, Zhang Y, Zhang L, Wu Q (2014) Schlafen 1 inhibits the proliferation and tube formation of endothelial progenitor cells. PLoS ONE 9: e109711.

Li M, Kao E, Gao X, Sandig H, Limmer K, Pavon-Eternod M, Jones TE, Landry S, Pan T, Weitzman MD, David M (2012) Codon-usage-based inhibition of HIV protein synthesis by human schlafen 11. Nature 491: 125–8.

Lin YZ, Sun LK, Zhu DT, Hu Z, Wang XF, Du C, Wang YH, Wang XJ, Zhou JH (2016) Equine schlafen 11 restricts the production of equine infectious anemia virus via a codon usage-dependent mechanism. Virology 495: 112–21.

Lund S, Christensen KV, Hedtjarn M, Mortensen AL, Hagberg H, Falsig J, Hasseldam H, Schrattenholz A, Porzgen P, Leist M (2006) The dynamics of the LPS triggered inflammatory response of murine microglia under different culture and in vivo conditions. J Neuroimmunol 180: 71–87.

Mary FW, Hermann R, Lee JH, Chaturvedi L, Basson MD (2015) Schlafen 3 mediates the differentiating effects of Cdx2 in rat IEC-Cdx2L1 enterocytes. J Invest Surg 28: 202–7.

Mavrommatis E, Arslan AD, Sassano A, Hua Y, Kroczynska B, Platanias LC (2013a) Expression and regulatory effects of murine Schlafen (Slfn) genes in malignant melanoma and renal cell carcinoma. J Biol Chem 288: 33006–15.

Mavrommatis E, Fish EN, Platanias LC (2013b) The Schlafen family of proteins and their regulation by interferons. J Interferon Cytokine Res 33: 206–10.

Nagarajan G, Swami SK, Dahiya SS, Sivakumar G, Yadav VK, Tuteja FC, Narnaware SD, Patil NV (2013) Phylogenetic analysis of immunomodulatory protein genes of camelpoxvirus obtained from India. Comp Immunol Microbiol Infect Dis 36: 415–24.

Neumann B, Zhao L, Murphy K, Gonda TJ (2008) Subcellular localization of the Schlafen protein family. Biochem Biophys Res Commun 370: 62–6.

Nogales V, Reinhold WC, Varma S, Martinez-Cardus A, Moutinho C, Moran S, Heyn H, Sebio A, Barnadas A, Pommier Y, Esteller M (2016) Epigenetic inactivation of the putative DNA/RNA helicase SLFN11 in human cancer confers resistance to platinum drugs. Ooncotarget 7: 3084–97.

Oh PS, Patel VB, Sanders MA, Kanwar SS, Yu Y, Nautiyal J, Patel BB, Majumdar AP (2011) Schlafen-3 decreases cancer stem cell marker expression and autocrine/juxtacrine signaling in

FOLFOX-resistant colon cancer cells. Am J Physiol Gastrointest Liver Physiol 301: G347–55.

Patel VB, Yu Y, Das JK, Patel BB, Majumdar AP (2009) Schlafen-3: a novel regulator of intestinal differentiation. Biochem Biophys Res Commun 388: 752–6.

Puck A, Aigner R, Modak M, Cejka P, Blaas D, Stöckl J (2015) Expression and regulation of Schlafen (SLFN) family members in primary human monocytes, monocyte-derived dendritic cells and T cells. Results Immunol 5: 23–32.

Puck A, Hopf S, Modak M, Majdic O, Cejka P, Bluml S, Schmetterer K, Arnold-Schrauf C, Gerwien JG, Frederiksen KS, Thell E, Leitner J, Steinberger P, Aigner R, Seyerl-Jiresch M, Zlabinger GJ, Stockl J (2017) The soluble cytoplasmic tail of CD45 (ct-CD45) in human plasma contributes to keep T cells in a quiescent state. Eur J Immunol 47: 193–205.

Razzak M (2012) Genetics: Schlafen 11 naturally blocks HIV. Nat Rev Urol 9: 605.

Recher M, Karjalainen-Lindsberg ML, Lindlof M, Soderlund-Venermo M, Lanzi G, Vaisanen E, Kumar A, Sadeghi M, Berger CT, Alitalo T, Anttila P, Kolehmainen M, Franssila R, Chen T, Siitonen S, Delmonte OM, Walter JE, Pessach I, Hess C, Simpson MA, Navarini AA, Giliani S, Hedman K, Seppanen M, Notarangelo LD (2014) Genetic variation in schlafen genes in a patient with a recapitulation of the murine Elektra phenotype. J Allergy Clin Immunol 133: 1462–5.e1-5.

Sassano A, Mavrommatis E, Arslan AD, Kroczynska B, Beauchamp EM, Khuon S, Chew TL, Green KJ, Munshi HG, Verma AK, Platanias LC (2015) Human schlafen 5 (SLFN5) is a regulator of motility and invasiveness of renal cell carcinoma cells. Mol Cell Biol 35: 2684–98.

Schwarz DA, Katayama CD, Hedrick SM (1998) Schlafen, a new family of growth regulatory genes that affect thymocyte development. Immunity 9: 657–68.

Sohn WJ, Kim D, Lee KW, Kim MS, Kwon S, Lee Y, Kim DS, Kwon HJ (2007) Novel transcriptional regulation of the schlafen-2 gene in macrophages in response to TLR-triggered stimulation. Mol Immunol 44: 3273–82.

Tian L, Song S, Liu X, Wang Y, Xu X, Hu Y, Xu J (2014) Schlafen-11 sensitizes colorectal carcinoma cells to irinotecan. Anticancer Drugs 25: 1175–81.

van Zuylen WJ, Garceau V, Idris A, Schroder K, Irvine KM, Lattin JE, Ovchinnikov DA, Perkins AC, Cook AD, Hamilton JA, Hertzog PJ, Stacey KJ, Kellie S, Hume DA, Sweet MJ (2011) Macrophage activation and differentiation signals regulate schlafen-4 gene expression: evidence for Schlafen-4 as a modulator of myelopoiesis. PLoS ONE 6: e15723.

Zhang YF, Yang ZM, Cao YH, Zhang SJ, Li H, Huang Y, Ding YQ, Liu XL (2008) The Hsp40 family chaperone protein DnaJB6 enhances Schlafen1 nuclear localization which is critical for promotion of cell-cycle arrest in T-cells. Biochem J 413: 239–50.

Zhao L, Neumann LB, Murphy K, Silke J, Gonda TJ (2008) Lack of reproducible growth inhibition by Schlafen1 and Schlafen2 in vitro. Blood Cells Mol Dis 41: 188–93.

Zoppoli G, Regairaz M, Leo E, Reinhold WC, Varma S, Ballestrero A, Doroshow JH, Pommier Y (2012) Putative DNA/RNA helicase Schlafen-11 (SLFN11) sensitizes cancer cells to DNA-damaging agents. Proc Natl Acad Sci USA 109: 15030–5.

Received 20 January 2017; accepted 23 April 2017.
Final version published online 13 June 2017.