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Gene Section
Review

BCL2L14 (BCL2-like 14 (apoptosis facilitator))

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Abstract

Review on BCL2L14, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: BCLG

HGNC (Hugo): BCL2L14

Location: 12p13.2

Local order: Flanked by ETV6 and LOC100506248 (prothymosin alpha-like).

Note

BCL2L14 encodes members of the Bcl-2 family. Proteins in the family contain at least one Bcl-2 homology (BH) domain (of which there are four in total; termed BH1-4) and regulate cell life/death decisions at the level of the mitochondrion (intrinsic apoptotic pathway). Family members can be broadly divided into anti-apoptotic and pro-apoptotic regulators; the former class includes Bcl-2, Mcl-1 and Bcl-xL, which contain all four BH domains, whereas the latter class can be subdivided into: i. effector molecules, such as the multidomain (BH1-3) Bax and Bak molecules, and ii. upstream sentinel BH3-only proteins (e.g. Bim, Bid, Puma and Noxa). Bcl-2 family members undergo complex protein-protein interactions with each other. Crucially, it is the balance between pro- and anti-apoptotic Bcl-2 family members which determines if activation of the mitochondrial (intrinsic) apoptotic pathway occurs and, ultimately, whether the cell lives or dies.

Human BCL2L14 was first characterized in 2001 (Guo et al., 2001). Two full-length transcripts, encoding long and short protein isoforms (termed Bcl-G_L and Bcl-G_S), were isolated. Bcl-G_S is a BH3-only protein, whereas Bcl-G_L unusually contains only BH2 and BH3 domains (Guo et al., 2001); a similar Bcl-2 family member, termed Bfk, has subsequently been identified (Coultas et al., 2003). The two Bcl-G isoforms exhibit pro-apoptotic activity, but Bcl-G_L is less potent than Bcl-G_S, attributed to negative regulation by the BH2 domain (Guo et al., 2001). Differences are also apparent between Bcl-G_S and Bcl-G_L in their patterns of tissue expression (restricted to testes versus ubiquitous), subcellular distribution (cytosolic organelles versus diffuse) and interaction with other Bcl-2 family members (Bcl-G_S only shows interaction) (Guo et al., 2001). Pig and mouse BCL2L14 encode only one BclG protein isoform (termed pBcl-G and mBcl-G, respectively), which contains BH2 and BH3 domains, similar to Bcl-G_L (Giam et al., 2012a; Jiang et al., 2012). Phylogenetic analysis of Bcl-G protein sequences from 14 different species has revealed the presence of three different clades comprising human/apes, rodents and pigs/cattle, raising the possibility of species differences in Bcl-G action (Jiang et al., 2012).

The BCL2L14 promoter contains a cAMP responsive element, an interferon-γ-activated site (GAS) and an interferon regulatory factor element (IRF-E); interferon-α and γ co-operatively hyperactivate BCL2L14 expression in hepatoma cells (Zhang et al., 2006). A consensus site for certain proline- and acid rich basic region leucine zipper proteins is also present; binding of thyrotroph embryonic factor (TEF) or albumin D-site-binding protein (DBP) enhances promoter activity, whereas binding of nuclear factor, interleukin-3 regulated (NFIL3) is repressive (Benito et al., 2006).

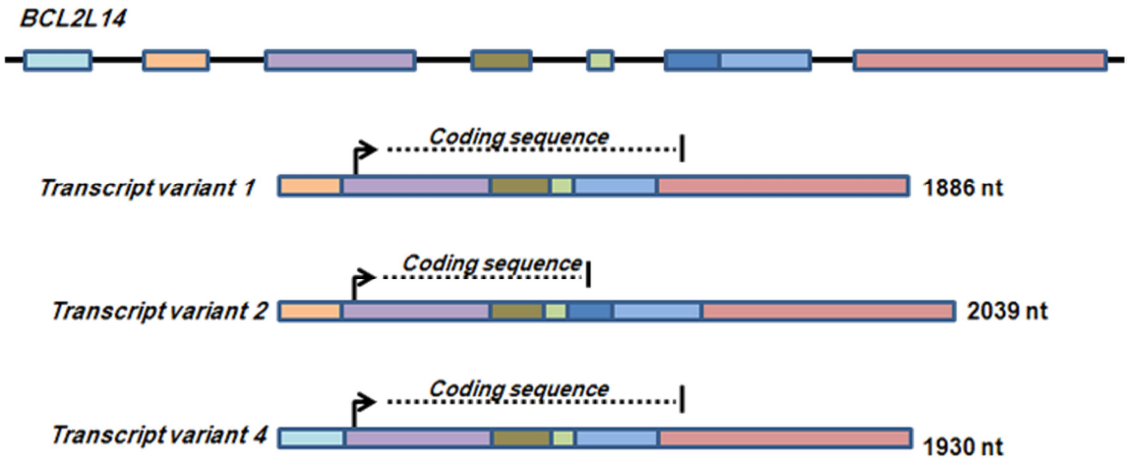

Figure 1. Alternative splicing of BCL2L14 yields at least three transcript variants. Note that exons only are drawn to scale and that only those transcript variants for which reference sequences exist are shown. Transcript variants 1 and 4 differ only in their 5'-UTR sequence and produce an identical protein isoform (Bcl-G_L), whereas the coding sequence of transcript variant 2 is shorter and gives rise to a protein isoform (Bcl-G_S) with a distinct C-terminus.

BCL2L14 has also been identified as a p53 target gene; the putative binding site is located within the first intron (Miled et al., 2005). BCL2L14 expression is regulated in a reciprocal manner by protein kinase C (PKC) isozyme signalling; its expression is repressed by PKCε but enhanced by PKCδ (Caino et al., 2011). Along with other apoptotic regulatory genes and the putative tumour suppressor gene, WISP3, BCL2L14 has been identified as a target for oncogenic miR-221 (Vandenboom et al., 2008).

Several different post-translational modifications, which impact upon protein function, have been reported for Bcl-G isoforms. Bcl-G_L is a target for phosphorylation, catalysed by the candidate oncoprotein maternal embryonic leucine zipper kinase (MELK), which is overexpressed in breast cancer and a range of other solid tumors (Lin et al., 2007). The N-terminal region (amino acids 12 - 71) of Bcl-G_L (conserved in Bcl-G_S) is required for this interaction, and its phosphorylation inhibits apoptotic activity (Lin et al., 2007). Furthermore, in mouse cells, mBclG is a target for modification by a ubiquitin-like protein, termed FUBI, which in humans is encoded by the putative tumour suppressor gene FAU (Nakamura and Tanigawa, 2003; Nakamura and Yamaguchi, 2006). The N-terminal region of mBclG appears to be cleaved from the adduct. In mouse macrophages the FUBI/mBclG complex associates with ERKs and inhibits their activation by MEK1; recent work has further demonstrated that the adduct enhances lipopolysaccharide/interferon γ - induced apoptosis (Watanabe et al., 2013). Indeed, in human cells, ectopic expression of FAU promotes apoptosis, and both Fau and $BclG_L$ are thought to act in the same pathway, with the pro-apoptotic activity of Fau being mediated via $BclG_L$ (Pickard et al., 2009; Pickard et al., 2010; Pickard et al., 2011). Finally, interactions between Bcl-G_S and JAB1 (c-Jun activation domain binding protein-1; aka the fifth subunit of the COP9 signalosome or CSN5) have also been reported (Liu et al., 2008). The N-terminal region (amino acids 1 - 67) of Bcl-G_S is required for this interaction, and these two genes co-operatively induce apoptosis in HeLa cells; JAB1 inhibits Bcl-2/Bcl-X_L binding by the BH3 domain of Bcl-G_S and knock-down studies indicate that JAB1 is essential for Bcl-G_S to induce apoptosis (Liu et al., 2008).

BCL2L14 lies within 12p12, which is frequently deleted in lymphoid/myeloid malignancies and solid tumours, suggestive of the presence of tumour suppressor gene(s) in this locus (Montpetit et al., 2002).

In the case of pre-B acute lymphoblastic leukemia, ETV6 (rather than BCL2L14) is the target of deletions (Montpetit et al., 2004). In advanced prostate cancer however, the minimal deleted region is more distal to the telomere and extends into 12p13 (Kibel et al., 2004); expression mapping has demonstrated reduced BCL2L14 expression (Kibel et al., 2004).

BCL2L14 expression is also dysregulated in breast cancer (Pickard et al., 2009), ovarian cancer (Heinzelmann-Schwarz et al., 2006) and in tongue squamous cell carcinoma (Zhang et al., 2013). Mutations in the BH3 domain are not however common occurences in cancer (Soung et al., 2006; Yoo et al., 2007).

BCL2L14 expression is markedly up-regulated in $CD4^+$ T-cells from patients with the autoimmune disorder, systemic lupus erythematosus (SLE) and several lines of evidence implicate this dysregulation in pathogenesis (Luo et al., 2009). Dysregulated expression of BCL2L14 in mammalian cells has also been noted in response to infection with a variety of pathogens (Flori et al.,

2008; Mehra et al., 2010; Balas et al., 2011; Singh et al., 2011; Taubert et al., 2010; Almeida et al., 2012; Wang et al., 2012), indicative of a role in innate immunity.

DNA/RNA

Description

The gene is located on chromosome 12 on the plus strand at 12202778 bp from pter to 12364018 from pter (size is 161241 bases). It was originally thought to comprise 6 exons (Guo et al., 2001) but 7 possible additional exons have subsequently been identified (Montpetit et al., 2002).

Transcription

The gene encodes multiple transcripts; reference sequences exist for 3 transcript variants. These give rise to two different protein isoforms (Fig. 1). Transcript variants 1 and 4 differ only in their 5'-UTR and both encode the same protein, termed isoform 1 or Bcl-G_L. Usage of a different splice acceptor site results in the production of transcript variant 2. This contains extra nucleotides within the coding sequence, resulting in a frameshift and consequently a truncated protein product with distinct C-terminal amino acids, termed isoform 2 or Bcl-G_S. Transcript variant 2 may be a candidate for nonsense-mediated mRNA decay (NMD), but the RefSeq record (NM_030766.1) has been retained, since there is evidence for the expression of protein product. However, the RefSeq (NM_138724.1) for a further variant, originally termed variant 3, which encodes Bcl-G-Median (Bcl-G_M) (Montpetit et al., 2002), has been permanently suppressed, as this transcript is also a candidate for NMD and evidence for protein expression is lacking.

Pseudogene

There are no known pseudogenes.

Protein

Description

The two protein isoforms are members of the Bcl-2 family. Bcl-G_L comprises 327 amino acids and contains BH2 and BH3 domains, whereas Bcl-G_S comprises 252 amino acids and contains the BH3 domain only (Fig. 2). The two proteins are identical in sequence for the first 226 amino acids.

Expression

Highest levels of gene expression in the adult human are found in testis, hence the name Bcl-G, for Bcl-Gonad. Indeed Bcl-G_S is uniquely expressed in this tissue (as also noted for Bcl-G_M) (Guo et al., 2001; Montpetit et al., 2002). Bcl-G_L is predominantly expressed in testis, with transcripts also present in lung, pancreas, prostate, bone marrow and colon (Guo et al., 2001; Montpetit et al., 2002). The expression of Bcl-G_L has also been reported in freshly isolated human T-lymphocytes ($CD4^+$ and $CD8^+$ cells) and B-lymphocytes (Luo et al., 2009). Both Bcl-G_L and Bcl-G_S transcripts are expressed in a wide range of breast cancer cell lines and cultured mammary epithelial cells, but protein expression has been demonstrated for the former isoform only (Benito et al., 2006; Lin et al., 2007). Bcl-G transcript expression is more variable across prostate cell lines (Pickard et al., 2010). High levels of Bcl-G_S transcripts are found in testicular embryonal cancer cell lines, with lower levels present in urinary bladder and mantle cell lymphoma cell lines, followed by myeloid and breast cancer cell lines, but protein was detected for the testicular embryonal cancer cell lines only (Benito et al., 2006).

Localisation

Expression of GFP-tagged proteins in COS-7 cells has revealed a diffuse localization throughout the cell for Bcl-G_L (similar to GFP alone), but a more punctate cytosolic localization, with partial co-localization to mitochondria, for Bcl-G_S (Guo et al., 2001). The latter has been confirmed using Myc-tagged Bcl-G_S (Liu et al., 2008). Deletion of the BH3 domain from Bcl-G_S has no effect on its subcellular distribution, despite preventing interaction with Bcl-X_L (Guo et al., 2001). However interaction with JAB1 results in a more diffuse cytoplasmic localisation for Bcl-G_S (Liu et al., 2008).

Function

The original paper on BCL2L14 reported that GFP- or FLAG-tagged Bcl-G_L and Bcl-G_S have pro-apoptotic activity in a range of cell lines (COS-7, HEK293T and PC3), and that the latter is the more potent isoform (Guo et al., 2001). Deletion of the BH2 domain from Bcl-G_L allowed its interaction with Bcl-X_L and enhanced apoptotic activity, whereas the BH3 domain of Bcl-G_S was required for interaction with Bcl-X_L and apoptotic activity (Guo et al., 2001).

The pro-apoptotic activity of Bcl-G_L in COS-7 cells has been independently confirmed, and it has been further demonstrated that this activity is negatively regulated by phosphorylation, catalyzed by MELK (Lin et al., 2007). Similarly, Bcl-G_S has been reported to induce basal apoptosis in HeLa cells; an effect that is potentiated by JAB1 (Liu et al., 2008).

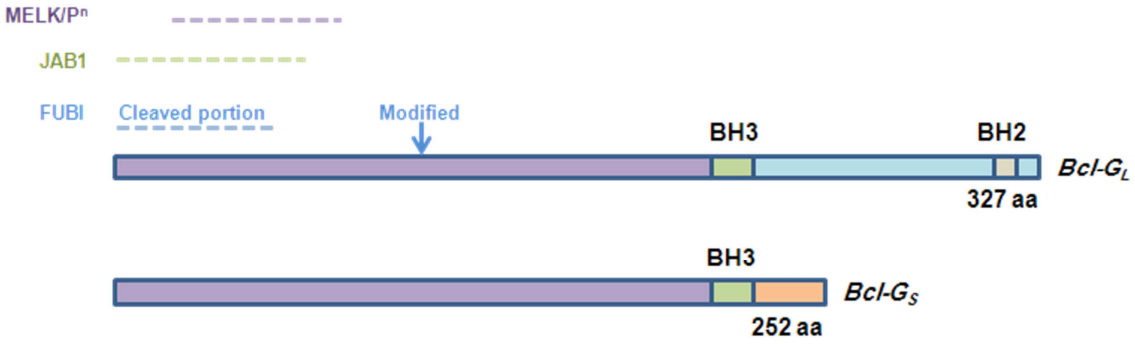

Figure 2. Protein isoforms encoded by BCL2L14. Homologous sequence between the two isoforms is depicted by the same colour pattern. Note that $BclG_L$ contains BH2 and BH3 domains whereas $BclG_S$ is a BH3-only protein. Potential sites of post-translational modification/interaction with non-Bcl-2 family members are also indicated.

The latter is thought to out-compete Bcl-2/Bcl-X_L for binding of Bcl-G_S (Liu et al., 2008). On the other hand, transfection of Huh-7 cells with Bcl-G_L has no effect on basal apoptosis (Zhang et al., 2006), while the survival of HCT116 and NTERA2 cells is unaffected by elevated levels of Bcl-G_S consequent upon ectopic TEF expression (Benito et al., 2006), suggesting that cell context is important for the apoptotic activity of Bcl-G protein isoforms. Crucially lentiviral transfection of Bcl-G_L results in enhanced apoptosis of $CD4^+$ T-cells from healthy subjects, demonstrating that pro-apoptotic activity is not restricted to transformed cells (Luo et al., 2009).

Furthermore, siRNA-mediated silencing of BCL2L14 gene expression attenuates apoptosis induction in several cell lines in response to diverse stimuli, including: ultraviolet-C irradiation (22Rv1 and HEK293T cells) (Pickard et al., 2010; Pickard et al., 2011), etoposide (HCT116 cells) (Benito et al., 2006), neratinib (SKBR-3 cells) (Seyhan et al., 2012), p53-induction (Saos-2 cells) (Miled et al., 2005), and ectopic expression of the putative tumour suppressor gene FAU (HEK293T cells) (Pickard et al., 2011). BCL2L14 is itself a target gene for the apoptosis master regulator p53 (Miled et al., 2005), and it is one of a subset of pro-apoptotic genes whose expression is hyperactivated in response to interferon-α and -γ co-treatment of hepatoma cells (Zhang et al., 2006). Its expression is also increased in mammalian cells following exposure to a diverse range of apoptotic stimuli (including chemotherapeutic agents) such as: gamma- radiation therapy (Finnberg et al., 2008), UV-C irradiation (Pickard et al., 2011), arsenic trioxide (Galimberti et al., 2012), nanoparticulate tetraiodothyroacetic acid (Glinskii et al., 2009), etoposide and cisplatin (Benito et al., 2006).

Mutations in pancreatic/duodenum homeobox protein 1 (PDX1) can result in human type 2 diabetes. Haploinsufficiency of this gene in mice also causes diabetes and is associated with enhanced apoptosis/necrosis of β-cells. In this regard, BCL2L14 has been identified as one of several genes encoding pro-apoptotic Bcl-2 family members whose expression is markedly up-regulated following shRNA-mediated depletion of Pdx1 in mouse insulinoma MIN6 cells (Fujimoto et al., 2010). Additionally BCL2L14 is one of several pro-apoptotic genes that is up-regulated upon exposure of human fibroblasts to pressure-induced oxidative stress (Oh et al., 2008).

The recent production of a mouse in which BCL2L14 is inactivated has demonstrated no apparent deleterious effects on cell types that normally express this gene (Giam et al., 2012b), perhaps suggesting some degree of functional redundancy. These authors further demonstrated that mBclG had negligible pro-apoptotic activity in human 293T cells and that the BH3 domain was incapable of binding Bcl-2 family members. Rather mBclG was capable of binding several novel partners, including transport particle protein (TRAPP) complex proteins, suggesting a potential role for mBclG in vesicle trafficking (Giam et al., 2012b). As regards pig Bcl-G, its ectopic expression in a porcine kidney cell line stimulates apoptosis induced by polyinosinic: polycytidylic acid (synthetic analogue of dsRNA and mimic of viral infection) (Jiang et al., 2012).

Homology

Homologues of BCL2L14 have been identified in a wide range of species (e.g. see Jiang et al., 2012). However, the Bcl-G_S protein isoform is specific to humans (Giam et al., 2012a). Mouse and pig Bcl-G share 68% and 71% amino acid identity, respectively, with human Bcl-G_L.

Implicated in

Prostate cancer

Note

In advanced prostate cancer, deletion of 12p12 is frequently seen. Expression mapping of genes within/adjacent to the minimal deleted region in

clinical tumours has demonstrated reduced expression of BCL2L14 and two other genes (DUSP16 and FLJ10298) (Kibel et al., 2004); reduced expression of BCL2L14 has been independently confirmed (Pickard et al., 2010). In the latter study, transcript levels were highly correlated with those of FAU, which also regulates apoptosis and which may act via the post-translational modification of Bcl-G (Pickard et al., 2010). Notably, down-regulation of BCL2L14 gene expression in the prostate cancer 22Rv1 cell line protects cells from apoptosis induction by ultraviolet-C irradiation (Pickard et al., 2010). BCL2L14 has been identified as a member of a four gene signature that accurately predicts prostate cancer recurrence, but high expression of BCL2L14 is associated with tumour recurrence (Latil et al., 2003).

Breast cancer

Note

Single nucleotide polymorphisms of high frequency loss of heterozygosity that affect BCL2L14 are found more commonly in infiltrating ductal carcinoma than in infiltrating lobular carcinoma of the breast (Loo et al., 2008). In breast ductal carcinoma, BCL2L14 expression is reduced, and silencing of BCL2L14 expression in the T-47D breast cancer cell line attenuates apoptosis induction by exogenous stimuli (Pickard et al., 2009). A genome-wide RNAi screen has recently shown that BCL2L14 silencing in SKBR-3 results in resistance to the novel pan-ErbB inhibitor, neratinib (Seyhan et al., 2012). BCL2L14 has also been implicated in the anti-survival effects of nanoparticulate tetraiodothyroacetic acid on MDA-MB-231 cells (Glinskii et al., 2009).

As regards genes involved in the post-translational modification of Bcl-G, FAU expression is down-regulated and MELK expression is up-regulated in breast tumour tissue (Pickard et al., 2009). These latter changes were associated with poor patient prognosis, but no relationship was apparent between BCL2L14 gene expression and patient survival (Pickard et al., 2009), suggesting that the regulation of Bcl-G activity by post-translational modification is more important than the level of BCL2L14 expression per se in determining patient survival.

Ovarian cancer

Note

Elevated levels of BCL2L14 gene expression have been reported for mucinous ovarian cancer relative to other histological subtypes of ovarian cancer (Heinzelmann-Schwarz et al., 2006). The functional significance of these changes are unknown. Subdivision of patients with high grade ovarian serous carcinoma into TP53 mutation-positive and p53 protein-null groups has revealed a number of differences in the genomic landscape, including gains of 12p13.2-12p13.1 (affecting DUSP16, BCL2L14 and ETV6) in the former group (Wojnarowicz et al., 2012). TP53 mutation-positive patients were also characterized by increased overall and disease-free survival (Wojnarowicz et al., 2012).

Cervical cancer

Note

An integration site for HPV16 in cervical carcinoma has been mapped to BCL2L14 (Xu et al., 2013).

Lung cancer

Note

Analysis of variants in inflammation pathway genes has identified single nucleotide polymorphisms of BCL2L14 in former smokers that are associated with increased risk of developing lung cancer (Spitz et al., 2012).

Precursor B acute lymphoblastic leukemia (ALL)

Note

A novel TEL-AML1 fusion transcript, comprising an in-frame insertion of 33 nucleotides derived from BCL2L14 between exon 5 of TEL and exon 2 of AML1 has been described in a case of pediatric precursor B ALL (Abdelhaleem et al., 2006). This fusion transcript appears to be rare, and its biological effects are unknown.

Tongue squamous cell carcinoma

Note

BCL2L14 expression has been reported to be markedly up-regulated in tongue squamous cell carcinoma tissue (Zhang et al., 2013).

Systemic lupus erythematosus (SLE)

Note

BCL2L14 expression is up-regulated (ca. 8-fold) in $CD4^+$ T-cells (but not $CD8^+$ or B-cells) from patients with systemic lupus erythematosus (SLE) (Luo et al., 2009). In SLE, apoptosis is increased in $CD4^+$ T-cells, and the degree of apoptosis in freshly isolated cells from SLE patients was directly correlated with Bcl-G_L levels, as were other measures of disease activity status (Luo et al., 2009). Healthy control $CD4^+$ T-cells in vitro demonstrated enhanced apoptosis both after transfection with a lentiviral vector expressing $BclG_L$ and after treatment with serum from SLE patients; the latter effect was associated with increased $BclG_L$ cellular levels and could be partially inhibited by prior knockdown of $BclG_L$ (Luo et al., 2009). The serum factor(s) that mediate this response remain unknown; whilst interferon-α

was increased in SLE sera it alone could not account for enhanced Bcl-G_L cellular levels (Luo et al., 2009).

Innate immune response

Note

There are several reports of dysregulated expression of BCL2L14 in response to infection with a wide range of pathogens/parasites. For example, in Rhesus Macaque monkeys infected with Mycobacterium tuberculosis, BCL2L14 expression is initially enhanced in granulomas relative to normal lung tissue during the acute phase of disease but silenced several weeks post-infection (Mehra et al., 2010).

While multiple markers of the pro-inflammatory response show a similar pattern, the silencing of BCL2L14 in chronic disease may contribute to pathogen survival. Studies with murine cells have further shown that exosomes derived from macrophages infected with Mycobacterium tuberculosis can block the activation of a subset of interferon-γ inducible genes, including BCL2L14, which may serve to suppress the host innate immune response beyond the site of infection (Singh et al., 2011).

BCL2L14 is one of several Bcl-2 family members that is dysregulated in bovine endothelial cells following infection with the parasite Eimeria bovis (Taubert et al., 2010). It is markedly upregulated in human alveolar macrophages within a few hours of infection with H1N1 influenza A virus PR/8 (Wang et al., 2012) and it is also induced following the infection of human monocyte-derived dendritic cells with wild type Dengue 3 virus (a Flavivirus) or the chimeric CYD3 vaccine virus (Balas et al., 2011). On the other hand, BCL2L14 expression is down-regulated in porcine epithelial cells following infection with Pseudorabies virus (a herpes virus) (Flori et al., 2008).

BCL2L14 may also be implicated in the host response to viral evasion mechanisms per se. For example, selective expression of the African Swine Fever Virus evasion gene, A238L, in mouse T-lymphocytes results in the production of an aggressive lymphoma (Almeida et al., 2012). Transgenic animals exhibit massively enlarged thymuses characterized, inter alia, by enhanced BCL2L14 expression and apoptosis (Almeida et al., 2012).

While attendant changes in host cell interferon signalling may account for many of the above changes in BCL2L14 expression, it should be noted that Bcl-G can directly interact with a component of the Flavivirus replication complex (Le Breton et al., 2011).

However, the biological significance of this interaction for both host and virus remains to be determined. The 3'-UTR of BCL2L14 transcripts also contains potential binding sites for Epstein-Barr virus-derived miRNAs (Marquitz et al., 2011).

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