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The role of IL-29 in immunity and cancer

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ABSTRACT

Interleukin-29 (IL-29) is a new member of the recently discovered interferon λ (IFNλ) family. It is produced predominantly by maturing dendritic cells and macrophages. It has been implicated in numerous immunological responses and has shown antiviral activity similar to the Type I interferons, although its target cell population is more limited than the Type I interferons. In recent years, the role of IL-29 in the pathogenesis of various cancers has also been extensively studied. In this review, we will discuss the recent advances of IL-29 in immunological processes and the pathogenesis of various cancer.

1. Introduction

IL-29 was discovered in 2003. It is a new member of a subfamily of Type II cytokines. The discovery of IL-29, along with IL-28A and IL-28B comprise the Type III interferons, also labeled

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as IFNλ1–IFNλ3, respectively (Donnelly and Kotenko, 2010; Witte et al., 2009; Kotenko et al., 2003). While these three cytokines are usually described in unison under the IFNλ title, there are differences that distinguish IL-29 from IL28A and IL28B. Both IL-28A and IL28B are nearly structurally identical to each other, while IL-29 is more structurally unique (Fujie and Numasaki, 2012). IL-29 is the most potent IFNλ molecule in humans, as well as the most abundant IFNλ molecule in serum, despite only existing as a pseudogene in mice (Donnelly and Kotenko, 2010; Alborzi et al., 2015; Hamming et al., 2010; Lasfar et al., 2006; Maher et al., 2008). Interestingly, IL-29 is also the only human IFNλ molecule to display N-linked glycosylation (Donnelly and Kotenko, 2010).

Previously discovered and well understood interferons consist of the Type I interferons, which include thirteen IFNα subtypes, IFNβ, ω, ε, and κ in humans, and Type II interferons whose sole member is IFNγ. Elucidated roles of interferons include antiviral, anti-proliferative, and immunomodulatory activities, with the induced effect varying depending on the cell type they are acting upon (de Weerd et al., 2007; Platanias, 2005). IFNλs have been shown to exhibit antiviral and anti-proliferative activities produced through the same signaling pathways as those utilized by IFNα and IFNβ (Donnelly and Kotenko, 2010; Kotenko et al., 2003), although these effects are seen to a more limited extent as compared to the vast array of cell types influenced by Type I Interferons (Donnelly and Kotenko, 2010; Witte et al., 2009; Brand et al., 2005). The cellular targets for IFNλ appear to be primarily of epithelial origin, whereas its effects are absent on a broad range of other cells typically affected by Type I interferons, such as leukocytes (Donnelly and Kotenko, 2010; Witte et al., 2009; Kotenko et al., 2003; Meager et al., 2005). Also, despite signaling through pathways used by Type I interferons (Doyle et al., 2006; Dumoutier et al., 2004; Jordan et al., 2007; O'Shea et al., 2002), and recent cDNA microarray analyses indicating that the gene patterns expressed by both Type I and III are essentially the same (Jordan et al., 2007), the two interferon types act through different heterodimeric cell receptors. The Type I receptors (IFNAR) include IFNAR1 and IFNAR2, Type II receptors (IFNGR) include IFNGR1 and IFNGR2, while Type III receptors include IFNLR1 and IL10Rβ (de Weerd et al., 2007; Donnelly et al., 2004; Yoon et al., 2010). In fact, the discovery of the IFNLR receptor, and its ligand's apparent relativeness to the IFNα molecule instigated the discovery of the IFNλs (Pekarek et al., 2007). IL10Rβ is a receptor that is also utilized by other cytokines, including IL-10, IL-22, and IL-26. Its signaling induces pleiotropic effects including protection from hyperactive immune responses and immune response activation in epithelial cells (Yoon et al., 2010; Wolk et al., 2008; Xu et al., 2016).

The discovery of Type III interferons has opened a new chapter in interferon studies. IL-29, due to it being the most potent Type III interferon, is the cytokine of interest in this review. Studies have indicated its ability to serve as a mediator between the innate and adaptive immune responses. Furthermore, its specificity for targeting a limited scope of cell types could allow it to be used in therapeutic treatments while decreasing side toxicities that accompany Type I interferon therapies (Egli et al., 2014). Multiple studies also indicate IL-29′s involvement in the pathogenesis of cancer, as well as its antitumor effects (Meager et al., 2014). In this review, we will discuss the recent advancements in IL-29 immunology and cancer research.

2. The expression, target cells, signaling, and immunological role of IL-29

2.1. The expression of IL-29 and its target cells

The genes that encode IL-29 and its fellow Type III interferons are located on chromosome 19, and are distantly related to the Type I interferon and IL-10 genes (Donnelly and Kotenko, 2010; Kotenko et al., 2003). Members of the IL-10 family are short structured proteins containing six or seven alpha helices arranged in antiparallel configurations, with IL-29 being 181 amino acids in length (Pestka et al., 2004; Mannino et al., 2015).

IL-29 expression involves IRF-3, TBK1, RIG-1, and IPS-1 viral-induced signaling pathways (Onoguchi et al., 2007). Cell types that express high levels of IL-29 include maturing dendritic cells, macrophages, mast cells, and alveolar cells (Wolk et al., 2008; He et al., 2010; Mennechet and Uzé, 2006; Wang et al., 2009). Due to the similar signaling mechanisms that induce Type I and Type III interferons, dendritic cells have been shown to co-express IFNλs with IFNβ, albeit not in every cell type. While IFNβ expression is present in nearly every cell type, IFNλ expression is mostly prominent in tissue epithelia infections. Its expression does not accompany IFNβ expression during infection of tissues such as the brain and spinal cord (Mennechet and Uzé, 2006; Sommereyns et al., 2008).

IL-29 primarily targets epithelial cells. High IL-29 levels are therefore present during infections of the GI, respiratory tracts, and mucosal regions (He et al., 2010; Sommereyns et al., 2008; Iversen et al., 2010; Swider et al., 2014; Lazear et al., 2015). A study by Witte et al. demonstrated that IL-29 targeted skin cells include keratinocytes and melanocytes, while endothelial cells, subcutaneous adipocytes, and fibroblasts are not targeted (Witte et al., 2009). Immune cells have shown less sensitivity to IL-29, despite expressing the appropriate IFNλ receptor. Witte et al. accredit this to the presence of a splice variant of the IFNLR receptor secreted by immune cells. The secreted glycosylated protein moderately binds to IL-29, thus inhibiting its effects. *In vitro* experiments conducted by Doyle et al. (2006) showed that human hepatocytes could also be targeted by IL-29.

Redundancy in the signaling cascade and gene expression of Type I and Type III interferons may be attributed to alternative cell types targeted by Type III interferons. IL-29 therapies may be more beneficial as opposed to Type I interferon therapies due to its specificity for only particular cell types, as opposed to many different cell populations. IL-29 therapies could possibly be specifically targeted towards epithelial tissues and the liver while excluding toxic effects on endothelial cells in the central nervous system, kidney, and spleen seen with Type I interferon effects (Sommereyns et al., 2008).

2.2. IL-29 Signaling

Both IL-29 and Type I interferons activate the JAK-STAT signaling pathway through STAT1 and STAT2. IL-29 induction of STAT3,–STAT5 has also been displayed, albeit to a lesser degree (Kotenko et al., 2003; Doyle et al., 2006; Dumoutier et al., 2004; Jordan et al., 2007; O'Shea et al., 2002; Zhou et al., 2007). The STAT1/STAT2 signaling cascade transpires as follows: once tyrosine residues on STAT1 and STAT2 are phosphorylated, these proteins dimerize and are subsequently transported to the nucleus. Once transported, the dimer combines with interferon regulatory factor 9 to form the interferon-stimulated gene factor 3 (ISGF3) complex (Darnell et al., 1994). In the nucleus the ISGF3 complex binds to interferon-stimulated response elements (ISFE) that further induce interferon-stimulated gene transcription (Maher et al., 2008). The STAT1/STAT2 signaling pathways are the primary signaling pathways for the Type I interferon antiviral response that occurs in the immediate days following viral infection (Steen and Gamero, 2013). The induction of ISFEs by ISGF3 induces the transcription of hundreds of genes involved in the antiviral response. Notable antiviral gene examples include Mx1, OAS, and IFIT (Diamond and Farzan, 2013; Platanias and Fish, 1999).

Gene expression array analyses have demonstrated that similar gene subsets are induced by IL-29 and Type I interferons. To reiterate, the difference is the cell types that the two different interferons exert their effects on. Cellular targets are more limited for IL-29 due to the absence of the IFNLR component of its receptor on many cell types (Sommereyns et al., 2008; Zhou et al., 2007).

It must also be mentioned that auxiliary signaling cascades have been investigated for IFNλs. Brand et al. (2005) showed that IFNλs activated MAP kinase (MAPK) cascades in intestinal epithelial cells, and that MAPK and Akt signaling were induced in colon tissue. These studies, when compared with other studies, have shown discrepancies in the particular MAPKs activated by IFNλs, and future experimentation is needed to elucidate the roles of MAPKs in IFNλ signaling (Zhou et al., 2007).

2.3. The role of IL-29 in immunity

2.3.1. The role of IL-29 on cytokine production

A study by Liu et al. showed scenarios in which IL-29 and IFN-alpha have contrasting effects. IL-29 stimulation causes an increase in toll-like receptor (TLR) stimulated IL-12 secretion by monocyte-derived macrophages, while exhibiting no effect on TLR induced IL-12 secretion in monocytes and monocyte-derived dendritic cells. This can be explained by the presence of IFNLR receptors on monocyte-derived macrophages as opposed to the receptor's lack on monocyte-derived dendritic cells and monocytes. Contrarily, IFNα was shown to downregulate TLR induced IL-12 secretion by monocyte-derived macrophages (Liu et al., 2011).

This study indicates the mediating effects of IL-29 on T-cells. Microorganisms produce ligands that bind to TLRs on antigen-presenting cells, inducing them to secrete IL-12 which mediates the immune response by polarizing T cells into Th1 cells (Liu et al., 2011; Hayes et al., 1998; Trinchieri and Gerosa, 1996). Th1 cells play a critical role in clearance of infections by secreting IFNγ, IL-2, and TNFβ, which activates macrophages to produce cell-mediated and phagocytic immune responses (Romagnani, 1999). Studies by Liu et al. also showed that IL-29 further increases the responsiveness of macrophages to IFNγ, thus enhancing the immune response. Again, this is in contrast to IFNα, which suppressed the responsiveness of macrophages to IFNγ stimulation (Liu et al., 2011; Byrnes et al., 2001; McRae et al., 1998).

Peripheral blood mononuclear cells induced by IL-29 secrete high levels of IL-6 and IL-8 accompanied by moderate levels of IL-10 (Geldhof et al., 1998). IL-6 and IL-8 are both involved in the pro-inflammatory response. While IL-8 is predominantly involved with chemotaxis of neutrophils, IL-6 transitions the innate response to the adaptive response by recruiting monocytes, macrophages, and lymphocytes (Baggiolini and Clark-Lewis, 1992; Kaplanski et al., 2003). IL-10 functions in promoting the proliferation, differentiation, and antibody-secretion of B-cells, while also suppressing T-cell responses and the pro-inflammatory effects of monocytes and macrophages (Mannino et al., 2015; Kaplanski et al., 2003; Itoh and Hirohata, 1995; Levy and Brouet, 1994; Rousset et al., 1992). It must be further noted that IL-29 induced cytokine secretion levels do vary between individuals, but the pattern of secretion remains consistent (Jordan et al., 2007).

The role of IL-29 in allergic asthma has been elucidated in several recent studies. IL-29 has been shown to attenuate the asthma inflammatory response by increasing proliferation of Foxp3 T-regulatory cells, as well as by inhibiting IL-5 and IL-13. The increased presence of T-regulatory cells better controls the hyperactive immune response. IL-5 and IL-13 are pro-inflammatory cytokines produced by Th2 cells in response to infection. IL-13 has shown to play a critical role in airway inflammation during bronchial asthma (Koch and Finotto, 2015; Srinivas et al., 2008; Wills-Karp, 2004). IL-19, another cytokine involved in asthma inflammation is also inhibited by IL-29. IL-19 is thought to induce Th2 cells to secrete pro-inflammatory cytokines (Jordan et al., 2007; Gallagher et al., 2004; Sharma and Matsui, 2006).

Interestingly, contradictory to these studies, He et al. indicated that IL-29 may actually be involved in the pathogenesis of allergic airway reactions due to its induction of pro-inflammatory cytokines, such as IL-6 (He et al., 2010).

The receptor activator of nuclear factor kB (RANKL) has been shown to play a role in differentiation of osteoclasts. Osteoclasts have been identified as the primary player in bone resorption leading to bone and joint disruption in rheumatoid arthritis (Tanaka, 2013). With this knowledge, researchers set out to target the RANKL pathway in an attempt to treat rheumatoid arthritis. Past studies have shown that IL-29 levels are elevated in the blood and synovium of rheumatoid arthritis patients. The cytokine enhances the inflammatory response by inducing secretion of IL-6 and IL-8 (Xu et al., 2013). A more recent study by Xu et al. has confirmed that IL-29 directly induces the RANKL pathway. Targeting and inhibiting IL-29 is now suggested as a new rheumatoid arthritis treatment (Xu et al., 2015).

2.3.2. IL-29 Upregulates MHC class I expression

IL-29 Upregulates the expression of MHC Class I molecules on cells. This observation implicated the antiviral capabilities of IL-29 because MHC Class I upregulation increases the immune system's abilities to recognize viruses (Donnelly and Kotenko, 2010; Kotenko et al., 2003). Huang et al. provided proof that IL-29 upregulates MHC Class I when they placed IL-29 in the presence of Y136, a glycoprotein secreted by Yaba-like disease virus, a yatapoxvirus, which was known to inhibit the antiviral response of Type I interferons. This experiment showed that Y136 also inhibited IL-29 because the upregulation of MHC Class I and subsequent antiviral immune response was inhibited when IL-29 was put in the presence of Y136. The resistance that yatapoxvirus displays against IL-29 indicates the cytokine's antiviral properties (Huang et al., 2007).

2.3.3. The role of IL-29 in skin defenses, NK cells, and antiviral activities

A difference has been observed in the skin's protective capabilities between subjects with psoriasis and atopic dermatitis. Both skin disorders weaken the skin, but the presence of IL-29 in psoriatic lesions makes these lesions less prone to viral infection than atopic dermatitis lesions, which lack the presence of IL-29 (Wolk et al., 2013).

Natural Killer (NK) cells possess special machinery that allows them to target and lyse foreign or altered cells independent of activation from antigen presenting cells (Zamai et al., 2007). IL-12′s role in augmenting the ability of NK cells to recognize target cells led Kramer et al. to discover an indirect link between IL-29-induced IL-12 secretion and NK cell activity (Geldhof et al., 1998; Krämer et al., 2014). Kramer et al. conducted these tests with the knowledge that NK cells did not express the IFNLR receptor. Recent experiments by Souza-Fonseca-Guimaraes et al. (2015) have detected the presence of IFNLR mRNA by RT-PCR in purified mice NK cells. This was the first time that IFNλs had been shown to directly influence NK cells.

Numerous experiments have implicated IL-29′s antiviral activity against a plethora of viruses. For instance, IL-29′s targeting of hepatic cells makes it a potential therapeutic agent towards hepatitis viruses (Doyle et al., 2006; Marcello et al., 2006). Multiple experiments have indicated the significant presence of IL-29 during HCV infection, where it is apparent that IL-29 provides antiviral defense independent of Type I interferons (Diegelmann et al., 2010; Lee et al., 2014; Park et al., 2012). Kanda et al. (2012) demonstrated that IL-29 inhibits internal ribosomal entry site mediated translation by both HCV and HAV. Other studies also show that HBV, which often causes chronic liver inflammation, also induces increased

IL-29 expression. He et al. showed that IL-29 promotes the spontaneous seroconversion of the Hepatitis B e antigen (HBeA). The marked increase in anti-HBeA thus provides subsequent HBV clearance (Liaw, 2009; Yu et al., 2011).

Almeida et al. demonstrated IL-29′s antiviral capabilities against a member of the bunyaviridae family without the assistance of Type I interferons. In fact, addition of Type I interferons was unnecessary to enhance IL-29′s antiviral activities against the bunyavirus (de Freitas Almeida et al., 2008).

Ank et al. showed the potency of IL-29′s antiviral response against a selection of single stranded RNA viruses including encephalomyocarditis virus, vesicular stomatitis virus, and HSV-2. Their studies also further elucidated the mechanisms of IL-29′s antiviral response. They discovered that the IL-29 antiviral response is much stronger *in vivo* as opposed to *in vitro*, and that IL-29 enhanced IFNγ serum levels against HSV-2. These observations led them to suggest that IL-29′s mechanism lies in stimulation of the immune response as opposed to direct induction of the antiviral state (Ank et al., 2006). Studies on viral respiratory infections have indicated that IL-29 is a major interferon produced by type II alveolar cells in response to SARS-coronavirus and influenza A virus (Wang et al., 2009; Qian et al., 2013; Wang et al., 2011).

3. The role of IL-29 in cancer

In recent years, the role of IL-29 in the pathogenesis of a variety of cancers has been investigated. IL-29 can either induce tumor promoting effects or tumor inhibiting effects depending on the cancer cell type being affected. For instance, while IL-29 has typically shown anti-tumor effects in most cancers, it has been shown that the cytokine produces tumor promoting effects in multiple myeloma B, as summarized in Table 1.

3.1. Protumor effect of IL-29

Anti-apoptotic factors have been suggested as a root cause of unchecked plasma cell proliferation in lymphomas. IL-6, IL-10 and TNFα have been linked to the proliferation of plasma cells in multiple myeloma B, although the effects of TNFα on multiple myeloma varies among multiple myeloma cell lines (Alexandrakis et al., 2015; Gadó et al., 2000; Jourdan et al., 1999). The multiple myeloma promoting effects of these cytokines resulted in further investigation of the effects of other cytokines on multiple myeloma biology.

A study by Novak et al. tested the role of IL-29 in multiple myeloma (Novak et al., 2008). Despite usually displaying antiviral and anti-tumor effects, IL-29 was considered as a possible myeloma promotor because it shares receptor similarities with IL-10, and utilizes signaling pathways similar to TNFα. It was shown that multiple myeloma cells do indeed express the IL-10Rβ and IFNL1 receptors and bind to soluble IL-29. While it was not clear what cells in bone marrow produced the IL-29, there was indeed significantly increased levels of IL-29 in multiple myeloma bone marrow as compared to regular bone marrow.

The same study by Novak et al. also attempted to further elucidate the exact signaling pathways activated in the myeloma cells by IL-29. It was found that IL-29 activates the STAT1, STAT3, and MAPK/Erk pathways in myeloma. These are the same pathways that IFNα utilizes in order to induce pro-myeloma effects. While IL-10 effects on myeloma do not occur as a result of STAT1 activation, IL-10 does induce effects through the MAPK/Erk pathway similarly to IL-29 and IFNα.

While the precise role of IL-29 in the myeloma microenvironment remain unclear, it is suggested that the dynamics of receptor expression and heterodimerization, and the activation of cell-specific signaling cascades play a role in the IL-29 effects on multiple myeloma. It is also suggested that IL-29 does not promote myeloma growth independently, but participates in signaling cross-talk with IL-6, which is known to promote multiple myeloma cell growth. Nevertheless, IL-29 shows protumor effect on multiple myeloma B.

3.2. Anti-tumor effects of IL-29

IFNλs were considered as potential antitumor medications upon their discovery due to the Type I interferon-like effects they display (Fujie et al., 2011). Type I, II, and III interferons have been tested in immunotherapy trials, and all have displayed pro-apoptotic effects in tumors (Jiang and Zhou, 2015). While the displayed antitumor effects are redundant amongst the interferons, the limited scope of target cells for Type III interferons may allow them to more specifically target tumors while displaying less side-effects compared to Type I interferons (Fujie et al., 2011; Steen and Gamero, 2010).

3.2.1. IL-29 In skin cancers

IL-29′s specificity for epithelial skin cells may also bolster its effects in combatting skin tumors. Amongst skin cells, it has been discussed how keratinocytes and melanocytes are the specific skin cells that express IL-29 receptors. Wolf et al. stated that growth of keratinocytes is inhibited by IL-29 (Wolk et al., 2010), while Guenterberg et al. showed that melanoma cancer cell lines express the IFNλ receptor. IL-29 may therefore home specifically to keratinocyte carcinoma cells and melanoma cells, exerting anti-proliferative and pro-apoptotic effects through the JAK-STAT signaling pathways (Guenterberg et al., 2010; Nicholas and Lesinski, 2011).

The antitumor effects of IL-29 have been investigated by various studies using B16 melanoma cells in murine models. The B16 melanoma line is the cell line of choice due to its aggressive nature (Lasfar et al., 2011). Sato et al. demonstrated IL-29′s antitumor effects on B16 cells in murine mice trials. The upregulation of MHC class I and NK cell augmentation were included in their list of discovered IL-29-induced antitumor mechanisms (Merritt et al., 2004; Romee et al., 2014). Cell cycle checkpoint mediators, including the p21 molecule and retinoblastoma (Rb) protein were also affected. The previously discussed p21 molecule has increased levels and an increase in dephosphorylated Rb levels is also noted. Dephosphorylated Rb exists in differentiated and G0 arrested cells (Sato et al., 2006; Yen and Varvayanis, 1994).

3.2.2. IL-29 In lung cancer

Today, lung cancer persists as the deadliest cancer. We have discussed how IL-29 specifically targets epithelial cells and is expressed in the respiratory system. Specific studies have shown non-small cell lung carcinoma (NSCLC) patients have displayed elevated levels of IL-29 in serum. Therefore, IL-29 serum levels were initially considered as a diagnostic measure for NSCLC. It has since been discovered that IL-29 provides anti-proliferative effects by upregulating the p21 molecule in cells through its STAT signaling pathways (Fujie et al., 2011; Barrera et al., 2015). The p21 molecule serves as a cyclin-dependent kinase inhibitor, and its upregulation leads to cell arrest and apoptosis (Abbas and Dutta, 2009).

3.2.3. IL-29 In oesophageal carcinomas

Similar to the mechanisms it utilizes against skin cancer proliferation, IL-29 also upregulates MHC Class I, p21, and Rb in oesophageal carcinoma cell lines, as shown by Li et al. (Li et al., 2010). The upregulation of p21 and Rb proteins evidenced that the cell lines were G1 phase arrested. Furthermore, apoptosis was also evidenced by cleavage activity on caspase 3 and poly (ADP-ribose) polymerase, both of which are involved in apoptotic pathways.

Table 1
The Effect of IL-29 in Human Cancers.

Cancer type	Effect	Cell lines	Mechanism	Reference
Multiple myeloma	Promotion	KAS-6/1 and KP-6 MM	↑Activation of STAT1 and STAT3	Novak et al. (2008)
Gastric	Inhibition	SGC-7901 and HGC-27	↓Bcl-2 and ↑caspase cascades	Gao et al. (2014)
Colorectal	Inhibition	C26	↑NK and NKT cell activity	Aulino et al. (2010)
Glioblastoma	Inhibition	LN319	Unknown	Meager et al. (2005)
Liver	Inhibition	BEL-7402	Unknown	Lu et al. (2015)
Lung	Inhibition	Sq-1, Sq-19, LK-1, LK-2, OBA-LK1, 11–18, LK-79, 86-2, Lu99, EBC-1 and A549	↑p21 by STAT pathway	Fujie et al. (2011), Barrera et al. (2015)
Esophagus	Inhibition	TE-1, TE-2, TE-10, TE-11, YES-2, YES-4, YES-5, YES-6 and T.Tn	↑MHC Class I, ↑p21, ↑Rb protein	Li et al. (2010)
Skin	Inhibition	A375, B16, Hs294T, and SK-MEL-5	↑MHC Class I, ↑p21, ↑Rb protein	Merritt et al. (2004), Romee et al. (2014), Sato et al. (2006), Yen and Varvayanis (1994)

↑: Upregulate/increase ↓: Downregulate/decrease.

Li et al. targeted nine human oesophageal carcinoma cell lines that specifically expressed the IFNLR. Data showed that IL-29, accompanied by chemotherapy, exhibited antitumor effects towards oesophageal carcinoma cells, but did not affect normal cells. This is in contrast to IFNα, which also affected normal cells. Major findings such as this indicate that IL-29 may be used to target specific epithelial cell types, while limiting the side effects caused by Type I interferons.

3.2.4. IL-29 In gastric cancer

Recent studies have demonstrated anti-proliferative and pro-apoptotic effects of IL-29 towards gastric adenocarcinoma cell line, SGC-7901. Xuefeng et al. infected the gastric cells with a recombinant plasmid adenovirus that was shown to induce elevated levels of human IL-29 expression. The plasmid adenovirus-IL-29 transfected cells also demonstrated a higher rate of apoptosis due to anti-proliferative effects (Bu et al., 2016). Related studies using murine models infected with SGC-7901 cells also showed that IL-29 adenovirus plasmids inhibit gastric cancer cells. Furthermore, this same study indicated that IL-29 induces a possible NK cell-mediated immune response against the gastric tumors (Bu et al., 2014).

A separate *in vitro* study by Gao et al. showed that IL-29 causes cell cycle arrest and apoptosis in SGC-7901 and HGC-27 gastric carcinomas by upregulating p21, 927, and Bax while downregulating Bcl-2. This study also highlighted how IL-29 depolarizes the mitochondria membrane, resulting in cytochrome c and apoptosis-inducing factor release and subsequent activation of pro-apoptotic caspase cascades (Gao et al., 2014).

Lu et al. have recently discovered that IL-29 anti-proliferative effects on cancer can be enhanced by creating mutant IL-29 through site-directed mutagenesis techniques. Human IL-29 mutants have been shown to display enhanced anti-tumor activities against the HCT-8 ileocecal adenocarcinoma line, and the previously discussed SGC-7901 gastric adenocarcinoma line (Lu et al., 2015). These findings indicate that mutant IL-29s may be even stronger immunotherapy treatment prospects when compared to native IL-29.

3.2.5. IL-29 In colorectal cancers

Sato et al. (2006) also tested the effects of IL-29 in mice with colorectal cancer. The mice were ectopically implanted with C26 tumor cells, which display characteristics of undifferentiated transformed cells and cause severe muscle wasting and weight loss (Aulino et al., 2010). In this study, Il-29 augmented NK and NKT cell activity and the innate immune response. C26 cells that had metastasized to the liver were targeted and mice mortality subsequently decreased.

3.2.6. IL-29 In pancreatic cancer

Toll-like receptor 7 (TLR7) has been associated with immune response initiation against cancer cells. Until recently the precise responses initiated by TLR7 activation have been unclear. New studies have demonstrated that IL-29 and matrix metalloproteinase 9 were the most significantly elevated immune response factors induced by TLR7 signaling against pancreatic cancer cells (Wang et al., 2016).

3.2.7. IL-29 In hepatocellular carcinomas

We have discussed how Type III interferons are an attractive idea for antiviral and antitumor therapies due to their Type I-like effects in addition to their potentially decreased side-effects. This was precisely the case when the IL-29 effects were compared to Type I interferon effects on hepatocellular carcinomas (HCC), a cancer linked to chronic Hepatitis B infection. Tian et al. used a pegylated IL-29 (PEG IL-29) and found that it inhibited HCC antitumor activities while significantly decreasing toxic side effects. It must be noted that while PEG IL-29 accomplished this, standard IL-29 did not (Tian et al., 2014).

Pegylated interferons have been used in IFNα therapies for hepatitis and multiple sclerosis. The larger-sized pegylated interferons increase the length of time that the interferon is able to exert its biological effects (Baker, 2001). Pegylated interferons are larger due to the addition of polyethylene glycol (PEG).

The previously discussed study by Lu et al., in which IL-29 mutants demonstrated anti-proliferative effects in gastric cell lines, also demonstrated that mutant IL-29 displays enhanced anti-tumor activities against the BEL-7402 hepatoma line (Lu et al., 2015).

3.2.8. IL-29 In neuroendocrine tumor cells

The IFNλs have been incorporated into neuroendocrine tumor studies as potential antitumor medications due to their signaling similarities to IFNα. IFNα has been used in neuroendocrine carcinoma therapies as it has proven to induce anti-proliferative effects in neuroendocrine tumors through induction of the STAT1–STAT3 pathways. Zitzmann et al. showed that IFNλs induce the same signaling pathways and anti-proliferative effects in BON1 cells, a commonly used cell line in pancreatic neuroendocrine tumor research (Vandamme et al., 2015; Zitzmann et al., 2006).

In the same study, Zitmann et al. also elucidated negative regulation mechanisms on cytokines by demonstrating that suppressors of cytokine signaling (SOCS) proteins, SOCS1 and SOCS3, completely suppress these anti-proliferative effects caused by IFNλs. SOCS have played a significant role in elucidating the negative regulation mechanisms of cytokines, an area of study that was once sparse compared to knowledge on positive cytokine regulation (Larsen and Röpke, 2002).

3.2.9. IL-29 In glioblastomas

IL-29 has also shown antitumor effects against the human glioblastoma line, LN319 (Meager et al., 2014). While the IFNLR/IL-10Rβ heterodimer receptor was present on multiple human glioblastoma cell lines, it was expressed at a much greater magnitude on LN319 cells. It is significant that cell lines expressing significant levels of the IFNLR/IL-10Rβ were unresponsive and the responsiveness of the LN319 was IL-29 dose-specific, as this highlights the weakness and tissue specificity of IFNλ compared to Type I interferons.

4. Conclusion

The recent discovery of IL-29 has ushered in a new era of cytokine research. This cytokine and its IFNλ relatives have been the focus of intense study in the fields of antiviral and immunotherapy research. Structural similarities to IL-10 family members and the signaling similarities shared with Type I interferons (Vandamme et al., 2015) instantly suggested the potential antiviral, antiproliferative, and immunomodulatory capabilities of IL-29. A vast array of studies over the past thirteen years have solidified these hypotheses. The ability to mediate the innate and adaptive immune responses against viruses and tumors, coupled with decreased side effects due to its limited cellular targets, will make IL-29 an important cytokine of consideration for antiviral and immunotherapy research moving into the future.

Conflict of interest

The authors have no conflict of interest.

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