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Novel type III interferons produce anti-tumor effects through multiple functions

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TABLE OF CONTENTS

1. ABSTRACT

Type III interferons (IFNs), a new type IFN family consisting of 3 IFN-lambdas, have been identified through a homology search. They include IFN-lambda1, IFN-lambda2 and IFN-lambda3, which are also named as interleukin (IL)-29, IL-28A and IL-28B, respectively. The receptor complex of IFN-lambdas is composed of the IL-10 receptor beta (IL-10Rbeta) and a novel IL-28 receptor alpha (IL-28Ralpha). The signal transductions of type III IFNs seem to be similar to those of type I IFNs. Both type I and III IFNs activate Janus activated kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway and transcribe a number of IFN-associated genes. Various types of viruses induce expressions of type III IFNs as well as type I IFNs; however, the biological functions of type III IFNs could be distinct from those of type I IFNs partly because of the tissue-restricted expression of the type III receptor complexes. In this review, we encapsulate recent understandings about type III IFNs in particular the anti-tumor effects, and discuss possible mechanisms and a potential use for cancer therapy.

2. INTRODUCTION

IFN-mediated interference of virus replications was found about 50 years ago (1). Initially a single molecule was regarded to be responsible for the anti-viral action but subsequent studies demonstrated a large family of IFNs with complex gene diversifications (2). At this moment the type I IFN family primarily consists of IFN-alpha and IFN-beta, which include 12 and 1 subtype in human, respectively (3). The genes that encode type I IFNs are clustered on chromosome 9 in human and on chromosome 4 in mice. All of the type I IFNs bind a common receptor complex on cell surface, which are composed of 2 chains, IFNAR1 and IFNAR2. The interaction of type I IFNs with its receptor complex induces activation of STAT family members, resulting in formation of many kinds of hetero- and homodimer pairs, as well as complexes with other transcription factors (3-5). The type I IFNs are multi-functional cytokines with potent anti-viral, growth-suppressive and immune-regulatory functions. Clinical studies demonstrated that type I IFNs had improved outcomes of many diseases such as viral

infections, autoimmune disorders and various malignancies (6-9).

Type III IFNs, belonging to a novel IFN family, have been identified as IFN-lambdas with 3 subtypes, IFN-lambda1, -lambda2 and -lambda3, which are also known as IL-29, IL-28A and IL-28B, respectively. The new cytokines have been demonstrated to have an anti-viral activity but they could have different functions from the type I IFNs since respective IFN-lambdas bind a specific receptor complex as we discuss later (10,11). We summarize current knowledge of molecular and biological properties of type III IFNs and discuss the anti-tumor responses with a possible mechanism in this review.

3. INDUCTION OF TYPE III IFNS

Type I IFNs use 2 kinds of signaling pathways, the Toll-like receptors (TLRs)-mediated pathway that is essential in sensing of pathogens, and a cytosolic receptor pathway (12). Among the TLRs family, TLR3, TLR4, TLR7, TLR8 and TLR9 mediate type I IFNs production at variable levels, depending on cell types, and the same TLRs also presumably activate type III IFNs expressions (13,14). TLRs act as prototypical signaling receptors that activate innate immunity since TLRs recognize different types of nucleic acids to detect most types of viruses. TLR3 recognizes double-stranded RNAs, a principal form of both DNA and RNA viruses. TLR4 detects lipopolysaccharides derived from gram-negative bacteria and augments IFNs expression in antigen presenting cells such as dendritic cells and macrophages. TLR7 and TLR8 recognize single-stranded RNAs (ssRNAs) and viruses that contain these genomes. TLR9 detects unmethylated CpG motifs in DNA, which are commonly found in DNA viruses and bacteria (12).

Several types of cytosolic receptor pathways are another signal system mediating induction of type I IFNs (12). The melanoma differentiation antigen 5 (MDA5), retinoic acid inducible gene-I (RIG-I) and caspase recruitment domain (CARD)-containing RNA helicases are all involved in viruses-detection systems (15). CARD-containing adaptor protein, mitochondrial anti-viral signaling protein (MAVS), is also important for IFN-beta induction (16). Mice deficient of the *MDA5* or *RIG-I* gene showed defective responses of type I IFNs to many types of viruses including influenza and vesicular stomatitis virus (VSV) (17,18). In all likelihood, mechanisms of virally stimulated type III IFNs induction seem to be similar to those of type I IFNs (19). Onoguchi *et al.* demonstrated that the IFN regulatory factor-3 (IRF-3), MAVS, Traf family member-associated NF-kappaB activator-binging kinase 1 and RIG-I played an important role in the induction of both type I and type III IFNs (19). Similarly, cis-regulatory elements of the human *IFN-lambda1* gene have a cluster of IRF binding and NF-kappaB binding sites, and moreover, recent studies showed that type III IFNs were also induced by bacterial infections as demonstrated in type I IFNs (20,21). Previous functional analyses revealed that all of these above-mentioned genes and binding sites were involved in viruses-induced cellular responses, and thus these findings collectively suggest that expressions of both *types I* and *type III IFN* genes are regulated by a common mechanism in viral infections.

A recent study however demonstrated that both RNA and DNA viruses are less potent to produce type III IFNs compared with type I IFNs (22). Moreover, the expression level of IFN-lambdas was influenced by IFN-alpha and tumor necrosis factor-alpha both of which increased IFN-lambdas through up-regulating TLRs and RIG-I signaling pathways (14,23,24). Interestingly, hepatitis C virus (HCV) infection induced *IFN-lambdas* but not *IFN-alpha* or *IFN-beta* mRNA (25). In addition, IFN-lambda expression was dependent on the NF-kappaB pathway more significantly than the case with IFN-alpha and IFN-beta (26). These data suggest an unidentified mechanism underling type III IFNs induction and imply that type III IFNs have a protective function from a specific virus when type I IFNs are unavailable.

4. TYPE III IFNS AND ITS RECEPTOR COMPLEX

The structures of type III IFN are related to type I IFNs and to IL-10 family (10,11). All the genes of the type III family are clustered on chromosome 19 (q13.13 region) in human and consist of several exons (5 exons for *IFN-lambda1*, 6 for *IFN-lambda2* and *IFN-lambda3*), whereas the genes for type I IFNs members are clustered on chromosome 9 and are composed of a single exon. The *type III IFN* genes encode about 20 kDa molecules secreted as a monomeric structure and IFN-lambda1, but not IFN-lambda2 or IFN-lambda3, has a potential N-linked glycosylation site. IFN-lambda2 shows 96% identity with IFN-lambda3 at an amino acid level and IFN-lambda1 is also highly homologous to IFN-lambda3 (81%). The exon-intron structure of the *IFN-lambdas* genes resembles that of IL-10 and IL-10-related cytokines (10,11), and thus type III IFN family can represent a possible evolutionary linkage between the type I IFNs and the IL-10 family.

Murine *type III IFN* genes have also been indentified to encode 3 kinds of protein, mIFN-lambda1, mIFN-lambda2 and mIFN-lambda3, which are homologous to but distinct from the human counterparts. An analysis of the mouse genome revealed that the *mIFN-lambda2* and *mIFN-lambda3* genes encoded the human respective orthologues but the *mIFN-lambda1* gene had a stop codon in the first exon which resulted in truncated protein perhaps to be subjected to degradation (27). The IFN genes themselves have been well conserved in bird and fish. Bird genome contains the type I IFN genes without an intron structure and the type III IFN genes bearing 5 exons, whereas fish possess the IFN genes holding 5 exons (28,29). Precisely, IFN of zebra fish is an orthologue of mammalian type III IFN but that of some kinds of fish corresponds to mammalian type I rather than type III based on the structure analyses of the IFN receptors (29). These phylogenical studies collectively suggest that type III IFNs represent an ancestral IFN prototype that gave rise to intron-less type I IFNs presumably by retroposition events and gene duplications (30-32)

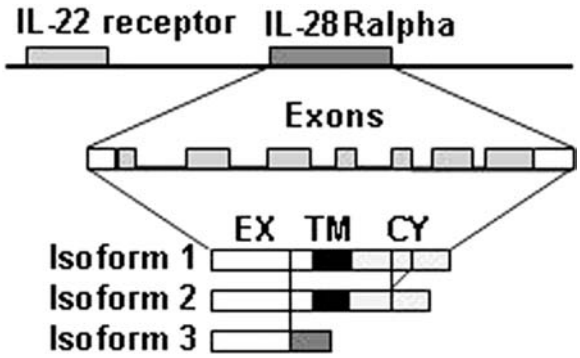

Figure 1. Genomic location and 3 isoforms of IL-28Ralpha. The *IL-28Ralpha* gene is located on human chromosome 1. Isoform 1 (NP_734464) has an extracellular (EX) region of 226 amino acids, a single transmembrane (TM) region and a cytoplasmic (CY) region of 271 amino acids. Isoform 2 (NP_775087) has a 29 amino acids deletion within the CY region and is likely defective of the signaling transduction ability. Isoform 3 (NP_775088) lacks both TM and CY regions and could be a soluble molecule.

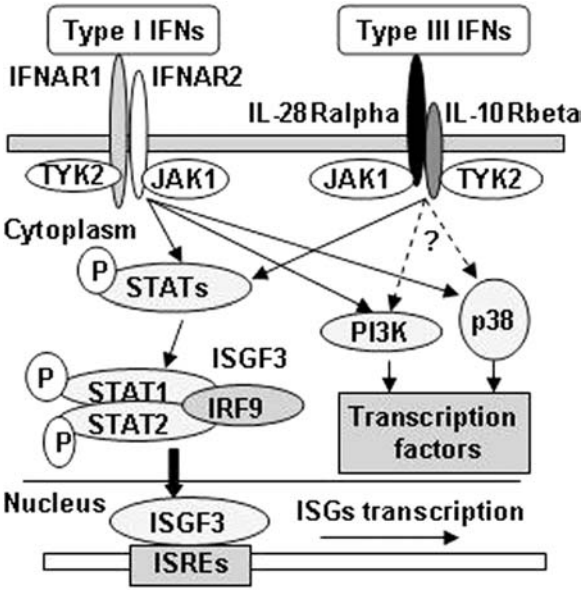

Figure 2. Compared signaling transductions between type I and type III IFNs. Type I IFNs binding to its receptor complex induces JAK1/tyrosine kinase 2 (TYK2) activation and subsequent phosphorylation of STAT1 and STAT2. The phosphorylated complexes with IRF-9 forms ISGF3, which migrates into nucleus to bind ISREs and then initiate transcription of ISGs. Type I IFNs also activate PI3K and the p38 pathways, and stimulate transcription of the relevant genes. Similarly, type III IFNs induce the JAK-STAT pathway; however, it is currently unknown whether type III IFNs activate the PI3K and the p38 pathways.

All of the type III IFNs bind the same heterodimeric receptor, which contains a newly identified subunit, IL-28Ralpha (also known as IFN-lambdaR1, CRF2-12 or LICR), and the IL-10Rbeta subunit (IL-10R2 and CRF2-4). IL-10Rbeta also serves as a subunit of the IL-10 receptor complexes and IL-10-related inflammatory cytokines such as IL-10, IL-22 and IL-26 (10,11,33,34). The *IL-28Ralpha* gene is located on chromosome 1 in human, mapped closely to the gene encoding the IL-22 receptor (Figure 1). IL-28Ralpha is divided into 3 portions, an extracellular domain, a single transmembrane domain and a cytoplasmic portion. The 7 exon-intron structures, a predicted 3 dimensional structure of its ectodomain and positions of the conserved cysteine sites, all together show that IL-28Ralpha is classified as the class II cytokine receptor family, which includes the receptors for IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, type I IFNs and IFN-gamma (11,34). Similar to other class II cytokines receptors, IL-28Ralpha probably determines specificity of the ligand binding and facilitates recruitments of intracellular signaling molecules. In addition to the full-length IL-28Ralpha, 2 alternatively spliced variants receptors have been identified in human (isoform 2 and 3) (Figure 1) (11). The isoform 2 encodes a receptor with a 29-amino acids deletion in its intracytoplasmic part, which is likely devoid of a signal transduction ability, and the isoform 3 encodes only the ectodomain, which is probably secreted as soluble molecules. The biological significances of the 2 isofoms however remain uncharacterized but could be antagonistic to authentic isoform 1.

All the type I IFNs bind a common receptor complexes consisting of 2 subunits, IFNAR1 and IFNAR2. The type I IFN receptors are expressed in virtually all the somatic cells and malignant cells as well. In contrast, IL-28Ralpha expression seems to be restricted with a tissues-specific manner although IL-10Rbeta is ubiquitously expressed. The *IL-28Ralpha* transcripts are in fact undetectable in several cell types such as fibroblastic and endothelial cells, which are thereby unresponsive to IFN-lambdas (30). Lymphoblastoid cells such as Daudi cells express the IL-28Ralpha but at a very low level, making them also insensitive to IFN-lambda1 (35). Peripheral blood mononuclear cells (PBMC), when freshly isolated, do not express the IL-28Ralpha but become positive for the expression when differentiate into dendritic cells upon IL-4 and granulocyte-macrophage colony-stimulating factor treatments (36). Subsequent studies also supported the restricted expression of IL-28Ralpha in a certain type of cells, which is consistent to the previous studies (30,37,38). The limited expression of the type III IFN receptors influences the responsiveness, which may generate biological functions distinct from those of type I IFNs.

5. INTRACELLULAR SIGNALING PATHWAYS

There are 2 kinds of intracellular signaling pathways induced following the interaction of type I IFNs with their receptors, a conventional and an unconventional signaling pathway (Figure 2). The signal transduction of type III IFNs seems to be similar to that of type I IFNs although detailed signaling pathways by type III IFNs remain relatively uncharacterized. The conventional pathway is linked with the JAK-STAT pathway. Ligation of IFN-alpha or -beta with the receptors results in rapid

phosphorylation and activation of the receptors associated tyrosine kinase 2 and JAK1, which in turn induces phosphorylation and activation of STAT1, STAT2, STAT3 and STAT5. The activation of these STATs seems to be shared among different kinds of type I IFNs because all of these IFNs bind to the same receptor complexes (37,39,40). Nevertheless, type I IFNs-mediated activation of STAT4 and STAT6 is restricted to a certain cell type such as endothelial and lymphoid lineages, suggesting a possible tissue-specific and diversified response of type I IFNs (39-43). Phosphorylated STATs form homodimers or heterodimers, which are subsequently translocated into nucleus and bind to IFN-stimulated response elements (ISREs) in regulatory regions of the IFN-stimulated genes (ISGs) (36-38). ISG factor 3 (ISGF3) is a crucial transcriptional complex, which is composed of phosphorylated STAT1 and STAT2, and IRF9, and initiates transcriptions of ISGs (34,40). Similarly, the interaction of the IFN-lambdas and their receptor complex induces signaling events by activating these transducer components. Ligation of type III IFNs and the receptors initiates activation of the JAK-STAT signaling pathway and generate tyrosine phosphorylation of STAT1, STAT2, STAT3, STAT4 and STAT5. ISGF3 is formed thereafter and transferred into nucleus to bind ISREs (11,30,32,37). Type I and III IFNs thus share the same downstream signal pathways and the repertoires of IFN target genes are similar each other. The similarity of the transcriptional regulation between the 2 types was confirmed by a microarray analysis with several cell lines (35,44). On the other hand, differential activation kinetics of IFN-alpha- and IFN-lambda1-induced genes was demonstrated in hepatocellular carcinoma during HCV replications (45). Recent publications further demonstrated that an IFN-lambda treatment resulted in strong and sustained phosphorylation of STATs, whereas IFN-alpha-induced STAT activations were transient (46,47). The above differences can be generated by a distinctive STATs stimulation at least in a certain type of cells.

All the biological effects of type I IFNs are not solely attributable to downstream events of the JAK-STAT-mediated system. The phosphatidyl-inositol-3-kinase (PI3K) and the p38 kinase pathways have a certain role in the IFN-induced signal transduction as an unconventional pathway, and precise functional significances between the conventional and the unconventional pathways are summarized in previous reviews (37,40). Activation of the PI3K pathway in response to type I IFNs is different in its mechanism from the JAK-STAT pathway, and is dependent on cell types. IFN-alpha phosphorylated STAT3 to provide a docking site for PI3K bindings in Daudi cells (48), whereas it also activated the p38 kinase and induced STAT1 phosphorylation in HeLa cells, both of which are mandatory for anti-viral responses and ISRE-dependent gene expressions (49,50). Increasing evidences also suggest that the p38 kinase pathway plays a role in modulating type I IFN-dependent responses (40). It is however currently unknown whether type III IFNs activate the PI3K and the p38 kinase pathways. Recent studies nevertheless showed that IFN-lambda1 induced activation of ribosomal protein S6 kinase in HT-29 cells (51) and the PI3K-AKT pathways in HepG2 cells (52), and that both the p38 and Jun N-terminal kinase-mitogen-activated protein kinases were involved in IFN-lambda1-induced gene expression in Raji cells (53). At present biological significances of the unconventional pathway remain less characterized but it functions alternatively to activate type III IFN-mediated cascades in a specific cell lineage. Type I IFNs activate a variety of signaling molecules through the unconventional pathways together with or without STATs systems (54).Type III IFNs use the JAK-STAT pathway similar to type I IFNs but a possible contribution of the unconventional pathways to type III IFNs-mediated responses needs further investigations.

6. PROTECTION AGAINST VIRAL INFECTION AND MODULATION OF IMMUNITY

Type III IFNs protect host cells from viral infections by inhibiting the replication. Type III IFNs activate 2 representative cellular genes that favor anti-viral host responses; 2'5'-oligoadenylate synthetase which mediates a cleavage of ssRNAs and myxovirus resistance A which impairs an intracellular trafficking of viruses (10,22). The anti-viral activity of type III IFNs is however relatively limited compared with that of type I IFNs. IFN-lambdas inhibits the replication of different virus species such as encephalomyocarditis virus, VSV, cytomegalovirus, herpes simplex virus, and influenza A virus (10,11,13,55) but did not prevent that of Lassa virus in dendritic cells and macrophages (56). Meager *et al.* reported that anti-viral actions generated by type III IFNs were restricted in the repertoires and were less strong in the potency than type I IFNs (38). The reason why type III IFNs have less and even no anti-viral activity in some cases is partly due to low or limited expression of the receptor complexes. Type III IFNs-mediated anti-viral activities could be alternative or supplementary to type I IFNs. The possible subsidiary function of type III IFNs has not been in fact experimentally shown and *IFN-lambda* or *IL-28Ralpha* gene-knockout mice are required for further investigations to characterize functional difference between type I and type III IFNs. Recently IFN-lambda has been shown to produce inhibitory effects on common viruses such as human immunodeficiency virus (57), rhinovirus (58) and rotavirus (59) and interestingly, genotypes of IFN-lambda3 determined sensitivity of an anti-viral agent to HCV infections (60). The type III IFNs therefore can be a possible therapeutic agent for a certain type of viruses or for patients suffering from type I IFNs-resistant infection, and a combinatory use of both IFN types is an option for severe infection cases.

Type I IFNs have a wide range of immune stimulatory activities including augmentation of T helper type 1 (Th1) cell responses, up-regulation of the major histocompatibility complex (MHC) class I molecules and consequent generation of natural killer (NK) cell- and T cell-mediated cytotoxicity (12,54,61). Type I IFNs thus function to elevate both innate and adaptive immune responses. Type III IFNs could support cell-mediated immunity and there have been several studies that IFN-lambda3 activated $CD8^+$ T cells (62), and IFN-lambda1 and

IFN-lambda2 induced production of Th1-cytokines such as IL-12 and IFN-gamma (63-64). Jordan *et al.* recently reported that IFN-lambda1 markedly diminished IL-13 levels and moderately elevated IFN-gamma production (65). The subsequent study demonstrated that IFN-lambda-primed $CD3^+$ cells inhibited Th2 cell-mediated inflammation in the intestine and suggested an inhibitory role in Th2 differentiation (66). On the other hand, type III IFNs have not been demonstrated to increase antibody formation. In addition, IFN-lambda1 also elevated transcription of the *monokine induced by IFN-gamma* (Mig), *IFN-gamma inducible protein-10* (IP-10) and *IFN-gamma inducible T-cell alpha chemoattractant* genes in PBMC with a IFN-gamma-independent manner (67,68). These chemokines are involved in anti-angiogenesis and consequently suppress tumor growth. These studies indicate that type III IFNs modulate Th1/Th2 cells equilibrium and influence the balance through a different mechanism from type I IFNs.

7. APOPTOSIS AND CELL CYCLE ARREST

The anti-proliferative activity of IFNs is presumably similar to anti-viral actions from the standpoint of host defense mechanisms and may be ubiquitously detected in all the somatic cells. IFN-mediated apoptosis induction is one of the mechanisms for depleting virally-infected cells but the precise intracellular pathways are not fully characterized. Type I IFNs have anti-proliferative property through inducing apoptosis and cell cycle arrest, both which are also favorable to anti-tumor activities as well. Similarly, type III IFNs have anti-proliferative actions on tumor cells, which is evidenced in experimental models *in vitro* (27,35,38,69,70). Several lines of studies recently demonstrated that IFN-lambdas inhibited growth of glioblastoma and neuroendocrine tumor cells (38,69), and also intestinal epithelial cells (22). Tyrosine phosphorylation of IL-28Ralpha at residues of 343 and 517, which is required for optimal activation of STAT2, is crucial for growth suppression of IFN-lambda-treated cells (35). We recently demonstrated that IFN-lambda1 induced G1-phase arrest with p21 induction and Rb dephosphorylation (71,72). We also revealed that IFN-lambda1 achieved anti-proliferative activity through the 2 different mechanisms, cell cycle arrest and apoptosis induction, depending on esophageal carcinoma cell lines used (71). In addition, other studies also demonstrated that IFN-lambda induced cleavage of caspase-3, -8 and -9 and confirmed apoptosis of tumor cells (73-75). One of the interesting points is that the induction of cell cycle arrest and apoptosis with type III IFNs does not occur in all the receptor-positive cells but is subject to cell types. Up-regulation of class I molecules of MHC and induction of anti-viral molecules were in contrast ubiquitously observed in all the receptor-positive cells. Signal pathways mediating the growth suppression could be different from those of MHC up-regulation and induction of anti-viral molecules.

8. *IN VIVO* ANTI-TUMOR EFFECTS AND ITS MECHANISMS

Type I IFNs produce anti-tumor effects and IFN-alpha is in fact clinically in use to treat several types of malignancies. Anti-tumor effects of type III IFNs were also investigated in several experimental animal models and the mechanism acting in *in vivo* settings was not solely attributable to the anti-proliferative activity. Growth of murine B16 melanoma expressing mIFN-lambda2 was retarded and even lost the tumorigenicity (27). Interestingly, mice that rejected the B16 tumors secreting mIFN-lambda2 failed to induce immunological memory responses, suggesting that mIFN-lambda2 is not involved in adaptive immune responses. One of possible mechanisms other than immunity is inhibited angiogenesis *in vivo* since type I and type III IFNs up-regulate Mig and IP-10, both of which suppress neo-angiogenesis within tumors. A different study however showed that both genes were not always induced *in vivo* despite IFN-lambda2-mediated anti-tumor responses (76). In contrast, Numasaki et al. showed that local secretion of mIFN-lambda2 from murine fibrosarcoma produced anti-tumor responses which were mediated by neutrophils, NK and $CD8^+$ T cells (70). The study also showed that IFN-gamma but not IL-12, IL-17 or IL-23 was essential for the anti-tumor responses. Type III IFNs thereby seem to possess multiple functions in immune-modulating ability. IFN-lambda1 augmented the expression of MHC class I molecules which subsequently increase the expression levels of putative tumor antigens (71). Type III IFNs thereby enhance antigenicity of tumors and increase sensitivity of the tumors to cytotoxic T cells. On the other hand, several experimental models showed that activated NK cells were primarily responsible for IFN-lambda-mediated anti-tumor effects (77-79) although enhanced expressions of MHC class I molecules rather suppressed NK cells-mediated cytotoxicity. IFN-lambdas can thereafter function to activate adaptive immune responses probably through NK cell-mediated tumor cell death and antigen presentation thereafter (70). These studies suggest that mechanisms of type III IFNs-mediated anti-tumor effects are dependent on tumor models and that many factors influence the type III IFNs-induced activities.

9. CONCLUSIONS AND PROSPECTS

Type III IFNs are similar to type I IFNs in the biological properties but detailed comparison between the types showed distinctive expression patterns of the respective receptors. The restricted expression of type III receptor complex in contrast with ubiquitous expression of type I IFNs receptors suggest differential functions of the type III IFNs in *in vivo* settings. Type III IFNs have the multiple functions including anti-viral, immunomodulatory and anti-proliferative actions and the majority of these functions overlap with those of type I IFNs. Several studies nevertheless demonstrated that differential activities between the 2 type IFNs in a certain experimental model. As for anti-tumor activities, mechanisms of type III IFN-mediated effects seem to be the same as that of type I IFNs and are attributable to direct and indirect actions (Figure 3). Type III IFNs directly inhibit growth of tumors by inducing apoptosis and/or cell cycle arrest and augment host immunity by up-regulating innate and adaptive immune responses. We also speculate that type III IFNs can be favorable to anti-angiogenesis.

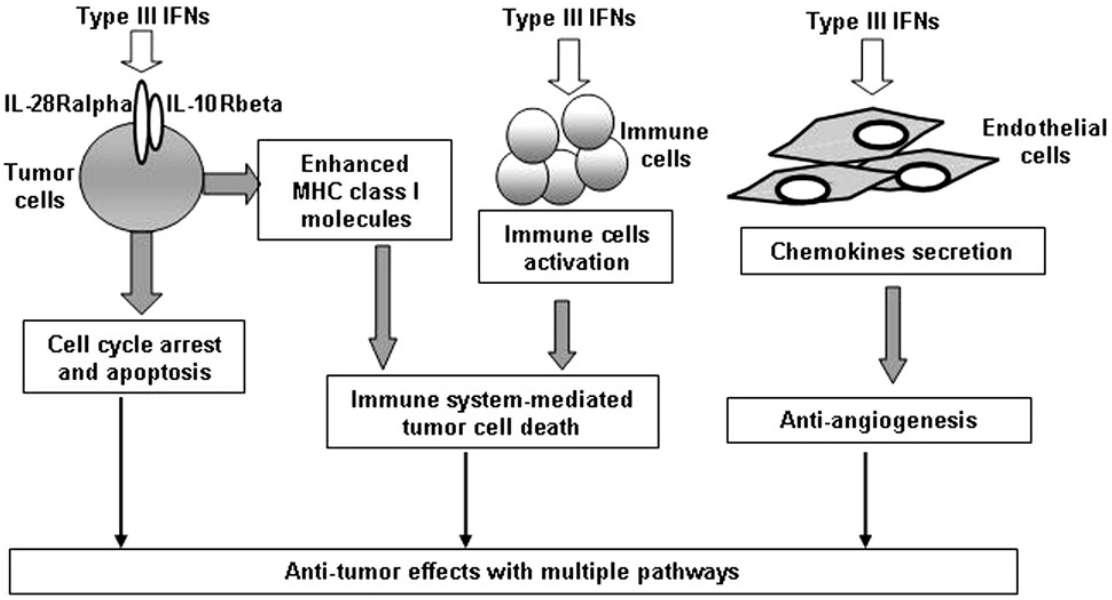

Figure 3. Mechanisms of type III IFNs-mediated anti-tumor responses. Type III IFNs directly act on tumor cells and indirectly on immune cells and endothelial cells. These actions are probably coordinated to induce cytotoxicity.

Feasible clinical applications of type III IFNs are determined by the biological activities and the potency. At this moment, abilities to up-regulate MHC class I expression and to suppress cell growth were weaker in type III IFNs than in type I IFNs. In addition, the anti-tumor effects *in vivo* of type III IFNs in comparison with type I IFN are not well characterized. The restricted expression of type III IFN receptors can be a clue for cell-mediated delivery of IFN-lambdas specific to target tumors. Fibroblasts, negative for IL-28Ralpha, are resistant to IFN-lambdas-mediated apoptosis but can deliver IFN-lambdas to the target cells in the vicinity. Transduction of fibroblasts with the *IFN-lambda* gene and injection of the cells into target tumors can generate anti-tumor effects against the tumors by inducing apoptosis of tumors and activating host immune responses. Cell-mediated delivery of a soluble factor can be more beneficial than direct injection of the vector bearing the factor gene since local concentrations of the factor is relatively maintained in the cell-mediated delivery system. Cells, in particular with tumor-migratory propensity such as tumors-associated fibroblasts or mesenchymal stem cells, can be localized at the target site better than an expression vector itself. Continuous secretion of the factor from the producing cells can thus be achieved, whereas the expression vector is washed out with easy. Type III IFNs have different response repertoires to viruses from type I IFNs and combinatory use of type I and type III IFNs might cover wider range of viral infections than an individual IFN. Anti-cancer agents, when combined with IFNs, may augment the cytotoxic effects but IFN-lambda1 together with chemotherapeutic agents did not produce significant synergistic effects in clinical settings (80). Adenoviruses bearing *IFN-lambda* gene could produce large amounts of IFN-lambda in the infected tumors, which makes the local concentrations high in the microenvironment and subsequently can produce better anti-tumor effects in combination with anti-cancer agents. Further preclinical studies regarding the therapeutic effects are required and high transduction efficacy by adenoviruses or other vector systems is one of the crucial factors to make the clinical application feasible as suggested in other cases of cancer gene therapy.

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11. REFERENCES

1. Isaacs A & Lindenmann J: Virus interference. I. The interferon. *Proc R Soc Lond B Biol Sci* 147, 258-267 (1957)

2. De Maryer E & De Mayer-Guiginard J: Interferons and other regulatory cytokines. *John Wiley & Sons Inc*, NY (1988)

3. Pestka S, Langer JA, Zoon KC & Samuel CE: Interferons and their actions. *Annu Rev Biochem* 56, 727-777 (1987)

4. Pestka S, Krause CD & Walter MR: Interferons, interferon-like cytokines, and their receptors. *Immunol Rev* 202, 8-32 (2004)

5. Pestka S: The interferon receptors. *Semin Oncol* 24(3 Suppl 9), 18-40 (1997)

6. Parmar S & Platanias LC: Interferons: mechanisms of action and clinical applications. *Curr Opin Oncol* 15, 431-439 (2003)

7. Malik AH & Lee WM: Chronic hepatitis B virus infection: treatment strategies for the next millennium. *Ann Intern Med* 132, 723-731 (2000)

8. Liang TJ, Rehermann B, Seeff LB & Hoofnagle JH: Pathogenesis, natural history, treatment, and prevention of hepatitis C. *Ann Intern Med* 132, 296-305 (2000)

9. Loutfy MR, Blatt LM, Siminovitch KA, Ward S, Wolff B, Lho H, Pham DH, Deif H, LaMere EA, Chang M, Kain KC, Farcas GA, Ferguson P, Latchford M, Levy G, Dennis JW, Lai EK & Fish EN: Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. *JAMA* 290, 3222-3228 (2003)

10. Sheppard P, Kindsvogel W, Xu W, Henderson K, Schlutsmeyer S, Whitmore TE, Kuestner R, Garrigues U, Birks C, Roraback J, Ostrander C, Dong D, Shin J, Presnell S, Fox B, Haldeman B, Cooper E, Taft D, Gilbert T, Grant FJ, Tackett M, Krivan W, McKnight G, Clegg C, Foster D & Klucher KM: IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nat Immunol* 4, 63-68 (2003)

11. Kotenko SV, Gallagher G, Baurin VV, Lewis-Antes A, Shen M, Shah NK, Langer JA, Sheikh F, Dickensheets H & Donnelly RP: IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. *Nat Immunol* 4, 69-77 (2003)

12. Stetson DB & Medzhitov R: Type I interferons in host defense. *Immunity* 25, 373-381 (2006)

13. Coccia EM, Severa M, Giacomini E, Monneron D, Remoli ME, Julkunen I, Cella M, Lande R & Uze G: Viral infection and Toll-like receptor agonists induce a differential expression of type I and lambda interferons in human plasmacytoid and monocyte-derived dendritic cells. *Eur J Immunol* 34, 796-805 (2004)

14. Siren J, Pirhonen J, Julkunen I & Matikainen S: IFN-alpha regulates TLR-dependent gene expression of IFN-alpha, IFN-beta, IL-28, and IL-29. *J Immunol* 174, 1932-1937 (2005)

15. Yoneyama M, Kikuchi M, Natsukawa T, Shinobu N, Imaizumi T, Miyagishi M, Taira K, Akira S & Fujita T: The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. *Nat Immunol* 5, 730-737 (2004)

16. Kawai T, Takahashi K, Sato S, Coban C, Kumar H, Kato H, Ishii KJ, Takeuchi O & Akira S: IPS-1, an adaptor triggering RIG-I- and Mda5-mediated type I interferon induction. *Nat Immunol* 6, 981-988 (2005)

17. Kato H, Sato S, Yoneyama M, Yamamoto M, Uematsu S, Matsui K, Tsujimura T, Takeda K, Fujita T, Takeuchi O & Akira S: Cell type-specific involvement of RIG-I in antiviral response. *Immunity* 23, 19-28 (2005)

18. Kato H, Takeuchi O, Sato S, Yoneyama M, Yamamoto M, Matsui K, Uematsu S, Jung A, Kawai T, Ishii KJ, Yamaguchi O, Otsu K, Tsujimura T, Koh CS, Reis e Sousa C, Matsuura Y, Fujita T & Akira S: Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. *Nature* 441, 101-105 (2006)

19. Onoguchi K, Yoneyama M, Takemura A, Akira S, Taniguchi T, Namiki H & Fujita T: Viral infections activate types I and III interferon genes through a common mechanism. *J Biol Chem* 282, 7576-7581 (2007)

20. Lebreton A, Lakisic G, Job V, Fritsch L, Tham TN, Camejo A, Mattei PJ, Regnault B, Nahori MA, Cabanes D, Gautreau A, Ait-Si-Ali S, Dessen A, Cossart P & Bierne H: A bacterial protein targets the BAHD1 chromatin complex to stimulate type III interferon response. *Science* 331, 1319-1321 (2011)

21. Bierne H, Travier L, Mahlakoiv T, Tailleux L, Subtil A, Lebreton A, Paliwal A, Gicquel B, Staeheli P, Lecuit M & Cossart P: Activation of Type III Interferon Genes by Pathogenic Bacteria in Infected Epithelial Cells and Mouse Placenta. *PLoS One* 7, e39080 (2012)

22. Brand S, Beigel F, Olszak T, Zitzmann K, Eichhorst ST, Otte JM, Diebold J, Diepolder H, Adler B, Auernhammer CJ, Goke B & Dambacher J: IL-28A and IL-29 mediate antiproliferative and antiviral signals in intestinal epithelial cells and murine CMV infection increases colonic IL-28A expression. *Am J Physiol Gastrointest Liver Physiol* 289, G960-G968 (2005)

23. Tissari J, Siren J, Meri S, Julkunen I & Matikainen S: IFN-alpha enhances TLR3-mediated antiviral cytokine expression in human endothelial and epithelial cells by up-regulating TLR3 expression. *J Immunol* 174, 4289-4294 (2005)

24. Matikainen S, Siren J, Tissari J, Veckman V, Pirhonen J, Severa M, Sun Q, Lin R, Meri S, Uze G, Hiscott J & Julkunen I: Tumor necrosis factor alpha enhances influenza A virus-induced expression of antiviral cytokines by activating RIG-I gene expression. *J Virol* 80, 3515-3522 (2006)

25. Mihm S, Frese M, Meier V, Wietzke-Braun P, Scharf JG, Bartenschlager R & Ramadori G: Interferon type I gene expression in chronic hepatitis C. *Lab Invest* 84, 1148-1159 (2004)

26. Iversen MB, Ank N, Melchjorsen J & Paludan SR: Expression of type III interferon (IFN) in the vaginal mucosa is mediated primarily by dendritic cells and displays stronger dependence on NF-kappaB than type I IFNs. *J Virol* 84, 4579-4586 (2010)

27. Lasfar A, Lewis-Antes A, Smirnov SV, Anantha S, Abushahba W, Tian B, Reuhl K, Dickensheets H, Sheikh F, Donnelly RP, Raveche E & Kotenko SV: Characterization of the mouse IFN-lambda ligand-receptor system: IFN-

lambdas exhibit antitumor activity against B16 melanoma. *Cancer Res* 66, 4468-4477 (2006)

28. Krause CD & Pestka S: Evolution of the Class 2 cytokines and receptors, and discovery of new friends and relatives. *Pharmacol Ther* 106, 299-346 (2005)

29. Robertsen B: The interferon system of teleost fish. *Fish Shellfish Immunol* 20, 172-191 (2006)

30. Kotenko SV & Donnelly RP: Type III interferons: The interferon lambda family. In: The interferons: characterization and application. Eds: Meager A, *Wiley-VCH*, Weinheim, Germany (2006)

31. Lutfalla G, Roest Crollius H, Stange-Thomann N, Jaillon O, Mogensen K & Monneron D: Comparative genomic analysis reveals independent expansion of a lineage-specific gene family in vertebrates: the class II cytokine receptors and their ligands in mammals and fish. *BMC Genomics* 4, 29 (2003)

32. Levraud JP, Boudinot P, Colin I, Benmansour A, Peyrieras N, Herbomel P & Lutfalla G: Identification of the zebrafish IFN receptor: implications for the origin of the vertebrate IFN system. *J Immunol* 178, 4385-4394 (2007)

33. Dumoutier L, Lejeune D, Hor S, Fickenscher H & Renauld JC: Cloning of a new type II cytokine receptor activating signal transducer and activator of transcription (STAT)1, STAT2 and STAT3. *Biochem J* 370(Pt 2), 391-396 (2003)

34. Langer JA, Cutrone EC & Kotenko S: The Class II cytokine receptor (CRF2) family: overview and patterns of receptor-ligand interactions. *Cytokine Growth Factor Rev* 15, 33-48 (2004)

35. Dumoutier L, Tounsi A, Michiels T, Sommereyns C, Kotenko SV & Renauld JC: Role of the interleukin (IL)-28 receptor tyrosine residues for antiviral and antiproliferative activity of IL-29/interferon-lambda 1: similarities with type I interferon signaling. *J Biol Chem* 279, 32269-32274 (2004)

36. Mennechet FJ & Uze G: Interferon-lambda-treated dendritic cells specifically induce proliferation of FOXP3-expressing suppressor T cells. *Blood* 107, 4417-4423 (2006)

37. de Weerd NA & Nguyen T: The interferons and their receptors-distribution and regulation. *Immunol Cell Biol* 90, 483-491 (2012)

38. Meager A, Visvalingam K, Dilger P, Bryan D & Wadhwa M: Biological activity of interleukins-28 and -29: comparison with type I interferons. *Cytokine* 31, 109-118 (2005)

39. Farrar JD, Smith JD, Murphy TL & Murphy KM: Recruitment of Stat4 to the human interferon-alpha/beta receptor requires activated Stat2. *J Biol Chem* 275, 2693-2697 (2000)

40. Platanias LC: Mechanisms of type-I- and type-II-interferon-mediated signalling. *Nat Rev Immunol* 5, 375-386 (2005)

41. Torpey N, Maher SE, Bothwell AL & Pober JS: Interferon alpha but not interleukin 12 activates STAT4 signaling in human vascular endothelial cells. *J Biol Chem* 279, 26789-26796 (2004)

42. Matikainen S, Sareneva T, Ronni T, Lehtonen A, Koskinen PJ & Julkunen I: Interferon-alpha activates multiple STAT proteins and upregulates proliferation-associated IL-2Ralpha, c-myc, and pim-1 genes in human T cells. *Blood* 93, 1980-1991 (1999)

43. Fasler-Kan E, Pansky A, Wiederkehr M, Battegay M & Heim MH: Interferon-alpha activates signal transducers and activators of transcription 5 and 6 in Daudi cells. *Eur J Biochem* 254, 514-519 (1998)

44. Doyle SE, Schreckhise H, Khuu-Duong K, Henderson K, Rosler R, Storey H, Yao L, Liu H, Barahmand-pour F, Sivakumar P, Chan C, Birks C, Foster D, Clegg CH, Wietzke-Braun P, Mihm S & Klucher KM: Interleukin-29 uses a type 1 interferon-like program to promote antiviral responses in human hepatocytes. *Hepatology* 44, 896-906 (2006)

45. Marcello T, Grakoui A, Barba-Spaeth G, Machlin ES, Kotenko SV, MacDonald MR & Rice CM: Interferons alpha and lambda inhibit hepatitis C virus replication with distinct signal transduction and gene regulation kinetics. *Gastroenterology* 131, 1887-1898 (2006)

46. Maher SG, Sheikh F, Scarzello AJ, Romero-Weaver AL, Baker DP, Donnelly RP & Gamero AM: IFNalpha and IFNlambda differ in their antiproliferative effects and duration of JAK/STAT signaling activity. *Cancer Biol Ther* 7, 1109-1115 (2008)

47. Makowska Z, Duong FH, Trincucci G, Tough DF & Heim MH: Interferon-beta and interferon-lambda signaling is not affected by interferon-induced refractoriness to interferon-alpha in vivo. *Hepatology* 53, 1154-1163 (2011)

48. Pfeffer LM, Mullersman JE, Pfeffer SR, Murti A, Shi W & Yang CH: STAT3 as an adapter to couple phosphatidylinositol 3-kinase to the IFNAR1 chain of the type I interferon receptor. *Science* 276, 1418-1420 (1997)

49. Uddin S, Majchrzak B, Woodson J, Arunkumar P, Alsayed Y, Pine R, Young PR, Fish EN & Platanias LC: Activation of the p38 mitogen-activated protein kinase by type I interferons. *J Biol Chem* 274, 30127-30131 (1999)

50. Goh KC, Haque SJ & Williams BR: p38 MAP kinase is required for STAT1 serine phosphorylation

and transcriptional activation induced by interferons. *EMBO J* 18, 5601-5608 (1999)

51. Kroczynska B, Joshi S, Eklund EA, Verma A, Kotenko SV, Fish EN & Platanias LC: Regulatory effects of ribosomal S6 kinase 1 (RSK1) in IFN-lambda signaling. *J Biol Chem* 286, 1147-1156 (2011)

52. Chai Y, Huang HL, Hu DJ, Luo X, Tao QS, Zhang XL & Zhang SQ: IL-29 and IFN-alpha regulate the expression of MxA, 2',5'-OAS and PKR genes in association with the activation of Raf-MEK-ERK and PI3K-AKT signal pathways in HepG2.2.15 cells. *Mol Biol Rep* 38, 139-143 (2011)

53. Zhou Z, Hamming OJ, Ank N, Paludan SR, Nielsen AL & Hartmann R: Type III interferon (IFN) induces a type I IFN-like response in a restricted subset of cells through signaling pathways involving both the Jak-STAT pathway and the mitogen-activated protein kinases. *J Virol* 81, 7749-7758 (2007)

54. van Boxel-Dezaire AH, Rani MR & Stark GR: Complex modulation of cell type-specific signaling in response to type I interferons. *Immunity* 25, 361-372 (2006)

55. Ank N, West H & Paludan SR: IFN-lambda: novel antiviral cytokines. *J Interferon Cytokine Res* 26, 373-379 (2006)

56. Baize S, Pannetier D, Faure C, Marianneau P, Marendat I, Georges-Courbot MC & Deubel V: Role of interferons in the control of Lassa virus replication in human dendritic cells and macrophages. *Microbes Infect* 8, 1194-1202 (2006)

57. Tian RR, Guo HX, Wei JF, Yang CK, He SH & Wang JH: IFN-lambda inhibits HIV-1 integration and post-transcriptional events in vitro, but there is only limited in vivo repression of viral production. *Antiviral Res* 95, 57-65 (2012)

58. Vareille M, Kieninger E, Alves MP, Kopf BS, Moller A, Geiser T, Johnston SL, Edwards MR & Regamey N: Impaired type I and type III interferon induction and rhinovirus control in human cystic fibrosis airway epithelial cells. *Thorax* 67, 517-525 (2012)

59. Pott J, Mahlakoiv T, Mordstein M, Duerr CU, Michiels T, Stockinger S, Staeheli P & Hornef MW: IFN-lambda determines the intestinal epithelial antiviral host defense. *Proc Natl Acad Sci U S A* 108, 7944-7949 (2011)

60. Hayes CN, Imamura M, Aikata H & Chayama K: Genetics of IL28B and HCV-response to infection and treatment. *Nat Rev Gastroenterol Hepatol* 9, 406-417 (2012)

61. Pfeffer LM, Dinarello CA, Herberman RB, Williams BR, Borden EC, Bordens R, Walter MR, Nagabhushan TL, Trotta PP & Pestka S: Biological properties of recombinant alpha-interferons: 40th anniversary of the discovery of interferons. *Cancer Res* 58, 2489-2499 (1998)

62. Morrow MP, Yan J, Pankhong P, Shedlock DJ, Lewis MG, Talbott K, Toporovski R, Khan AS, Sardesai NY & Weiner DB: IL-28B/IFN-lambda3 drives granzyme B loading and significantly increases CTL killing activity in macaques. *Mol Ther* 18, 1714-1723 (2010)

63. Liu BS, Janssen HL & Boonstra A: IL-29 and IFNalpha differ in their ability to modulate IL-12 production by TLR-activated human macrophages and exhibit differential regulation of the IFNgamma receptor expression. *Blood* 117, 2385-2395 (2011)

64. Koltsida O, Hausding M, Stavropoulos A, Koch S, Tzelepis G, Ubel C, Kotenko SV, Sideras P, Lehr HA, Tepe M, Klucher KM, Doyle SE, Neurath MF, Finotto S & Andreakos E: IL-28A (IFN-lambda2) modulates lung DC function to promote Th1 immune skewing and suppress allergic airway disease. *EMBO Mol Med* 3, 348-361 (2011)

65. Jordan WJ, Eskdale J, Srinivas S, Pekarek V, Kelner D, Rodia M & Gallagher G: Human interferon lambda-1 (IFN-lambda1/IL-29) modulates the Th1/Th2 response. *Genes Immun* 8, 254-261 (2007)

66. He SH, Chen X, Song CH, Liu ZQ, Zhou LF, Ma WJ, Zhao LD, Li TL, Tang SG, Xing Z & Yang PC: Interferon-lambda mediates oral tolerance and inhibits antigen-specific, T-helper 2 cell-mediated inflammation in mouse intestine. *Gastroenterology* 141, 249-258 (2011)

67. Pekarek V, Srinivas S, Eskdale J & Gallagher G: Interferon lambda-1 (IFN-lambda1/IL-29) induces ELR(-) CXC chemokine mRNA in human peripheral blood mononuclear cells, in an IFN-gamma-independent manner. *Genes Immun* 8, 177-180 (2007)

68. Jordan WJ, Eskdale J, Boniotto M, Rodia M, Kellner D & Gallagher G: Modulation of the human cytokine response by interferon lambda-1 (IFN-lambda1/IL-29). *Genes Immun* 8, 13-20 (2007)

69. Zitzmann K, Brand S, Baehs S, Goke B, Meinecke J, Spottl G, Meyer H & Auernhammer CJ: Novel interferon-lambdas induce antiproliferative effects in neuroendocrine tumor cells. *Biochem Biophys Res Commun* 344, 1334-1341 (2006)

70. Numasaki M, Tagawa M, Iwata F, Suzuki T, Nakamura A, Okada M, Iwakura Y, Aiba S & Yamaya M: IL-28 elicits antitumor responses against murine fibrosarcoma. *J Immunol* 178, 5086-5098 (2007)

71. Li Q, Kawamura K, Ma G, Iwata F, Numasaki M, Suzuki N, Shimada H & Tagawa M: Interferon-lambda induces G1 phase arrest or apoptosis in oesophageal carcinoma cells and produces anti-tumour effects in combination with anti-cancer agents. *Eur J Cancer* 46, 180-190 (2010)

72. Fujie H, Tanaka T, Tagawa M, Kaijun N, Watanabe M, Suzuki T, Nakayama K & Numasaki M: Antitumor activity of type III interferon alone or in combination with type I interferon against human non-small cell lung cancer. *Cancer Sci* 102, 1977-1990 (2011)

73. Li W, Lewis-Antes A, Huang J, Balan M & Kotenko SV: Regulation of apoptosis by type III interferons. *Cell Prolif* 41, 960-979 (2008)

74. Guenterberg KD, Grignol VP, Raig ET, Zimmerer JM, Chan AN, Blaskovits FM, Young GS, Nuovo GJ, Mundy BL, Lesinski GB & Carson WE: Interleukin-29 binds to melanoma cells inducing Jak-STAT signal transduction and apoptosis. *Mol Cancer Ther* 9, 510-520 (2010)

75. Hui X, Chen H, Zhang S, Ma X, Wang X & Huang B: Antitumor activities of recombinant human interferon (IFN)-lambda1 in vitro and in xenograft models in vivo for colon cancer. *Cancer Lett* 311, 141-151 (2011)

76. Li Q, Kawamura K, Okamoto S, Fujie H, Numasaki M, Namba M, Nagata M, Shimada H, Kobayashi H & Tagawa M: Adenoviruses-mediated transduction of human oesophageal carcinoma cells with the interferon-lambda genes produced anti-tumour effects. *Br J Cancer* 105, 1302-1312 (2011)

77. Sato A, Ohtsuki M, Hata M, Kobayashi E & Murakami T: Antitumor activity of IFN-lambda in murine tumor models. *J Immunol* 176, 7686-7694 (2006)

78. Abushahba W, Balan M, Castaneda I, Yuan Y, Reuhl K, Raveche E, de la Torre A, Lasfar A & Kotenko SV: Antitumor activity of type I and type III interferons in BNL hepatoma model. *Cancer Immunol Immunother* 59, 1059-1071 (2010)

79. Wongthida P, Diaz RM, Galivo F, Kottke T, Thompson J, Pulido J, Pavelko K, Pease L, Melcher A & Vile R: Type III IFN interleukin-28 mediates the antitumor efficacy of oncolytic virus VSV in immune-competent mouse models of cancer. *Cancer Res* 70, 4539-4549 (2010)

80. Parra HS, Tixi L, Latteri F, Bretti S, Alloisio M, Gravina A, Lionetto R, Bruzzi P, Dani C, Rosso R, Cosso M, Balzarini L, Santoro A & Ardizzoni A: Combined regimen of cisplatin, doxorubicin, and alpha-2b interferon in the treatment of advanced malignant pleural mesothelioma: a Phase II multicenter trial of the Italian Group on Rare Tumors (GITR) and the Italian Lung Cancer Task Force (FONICAP). *Cancer* 92, 650-656 (2001)

Abbreviations: IFN: interferon; IL: interleukin; IL-10Rbeta: IL-10 receptor beta; IL-28Ralpha: IL-28 receptor alpha; JAK: Janus activated kinase; STAT: signal transducer and activator of transcription; TLRs: Toll-like receptors; ssRNAs: single-stranded RNAs; MDA5: melanoma differentiation antigen 5; RIG-I: retinoic acid inducible gene-I; CARD: caspase recruitment domain; MAVS: mitochondrial anti-viral signaling protein; VSV: vesicular stomatitis virus; IRF: IFN regulatory factor; HCV: hepatitis C virus; PBMC: peripheral blood mononuclear cells; ISREs: IFN-stimulated response elements; ISGs: IFN-stimulated genes; ISGF3: IFN-stimulated genes factor 3; PI3K: phosphatidyl-inositol-3-kinase; Th1: T helper type 1; MHC: major histocompatibility complex; NK: natural killer; Mig: monokine induced by IFN-gamma; IP-10: IFN-gamma inducible protein-10.

Key Words: IFN-lambda, Type III IFN, Type I IFN, Anti-tumor effects, Apoptosis, Review

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