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Pleiotropic functions of the CXC-type chemokine CXCL14 in mammals

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CXCL14 is a member of the CXC chemokine family. CXCL14 possesses chemoattractive activity for activated macrophages, immature dendritic cells and natural killer cells. CXCL14-deficient mice do not exhibit clear immune system abnormalities, suggesting that the function of CXCL14 can be compensated for by other chemokines. However, CXCL14 does appear to have unique biological roles. It suppresses the *in vivo* growth of lung and head-and-neck carcinoma cells, whereas the invasiveness of breast and prostate cancer cells appears to be promoted by CXCL14. Moreover, recent evidence revealed that CXCL14 participates in glucose metabolism, feeding behaviour-associated neuronal circuits, and anti-microbial defense. Based on the expression patterns of CXCL14 and CXCL12 during embryonic development and in the perinatal brain in mice, the functions of these two chemokines may be opposite or interactive. Although CXCL14 receptors have not yet been identified, the intracellular activity of CXCL14 in breast cancer cells suggests that the CXCL14 receptor(s) and signal transduction pathway(s) may be different from those of conventional CXC-type chemokines.

Keywords: chemokine/CXCL14/feeding behaviour/glucose metabolism/tumuorigenesis.

Abbreviations: GPCRs, G-protein-coupled receptors; iDCs, immature dendritic cells; ROS, reactive oxygen species; WAT, white adipose tissue; HFD, high-fat diet; PGE2, prostaglandin E2; NK cells, natural killer cells; RBP4, retinol binding protein-4; IL-6, interleukin-6; KO mice, knockout mice; CNS, central nervous system; PTX, pertussis toxin.

CXCL14 as a Member of a Large Chemokine Family

Chemokines are critical regulators of cell migration during organogenesis and immune surveillance (*1*). In humans, there are at least 46 ligands that bind to 18 G-protein-coupled receptors (GPCRs) and two decoy receptors (*2*). Two major chemokine classes, CC and CXC, are defined by the spacing of two N-terminal cysteine residues, which are either adjacent to each other or separated by one amino acid residue, respectively.

CXCL14 (originally identified as *BRAK*, *BMAC* or *Mip-2γ*) was isolated as a gene whose expression is lost or down-regulated in various human cancer cell lines and tumour specimens (*3–6*). The 99 amino acid residue precursor of CXCL14 has a 22 amino acid signal peptide that is cleaved to produce a 77 amino acid mature protein. The calculated molecular weight of the human CXCL14 protein is 9.4 kDa with an isoelectric point of 10.3. Human and murine CXCL14 differ by only two amino acid residues. The amino acid composition of CXCL14 is well conserved between humans, birds, frogs and fish (*7*). CXCL12 (also known as SDF-1) and CXCL14 are considered to be primordial or ancient chemokines based on sequence conservation among species and their homeostatic roles (*7*). Recent report implicated that expression patterns of *Cxcl14* mRNA in chick are closely associated with developmental processes where CXCL12-CXCR4 system plays crucial roles (*8*). This result suggested that these two chemokines might cooperatively regulate organogenesis.

Expression of *CXCL14* mRNA and its Transcriptional Regulation

The human *CXCL14* gene, located on chromosome 5q31.1, produces mRNA 1.6 kilobases in length. *CXCL14* mRNA is abundant in the kidneys, brain, skin, lungs, small intestine and taste buds (*3–5*, *9*), with some variation between expression levels in human and mouse. In comparison, expression of *Cxcl14* mRNA is detectable in eye, fin, heart, integument, liver and muscle in adult zebrafish according to The Zebrafish Model Organism Database (http://zfin.org/).

The *CXCL14* transcript is present at high levels in basal epidermal keratinocytes and squamous epithelial cells (*4*, *10*). It is known that chemokines play a pivotal role in the initiation and amplification of atopic skin inflammation. However, CXCL14 expression in keratinocytes is rather suppressed at the sites of skin inflammation caused by atopic dermatitis and psoriasis (*11*), suggesting a homeostatic function of CXCL14 in healthy keratinocytes. *CXCL14* mRNA is also produced by lipopolysaccharide-stimulated monocytes and B cells, but not by T cells (*4*). In human immature dendritic cells (iDCs), stimulation with activin-A increases the expression of *CXCL14* and *CXCL12*, thereby promoting their migration (*12*).

Recent investigations have demonstrated that the expression of *CXCL14* is transcriptionally altered in association with the progression of various diseases.

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CXCL14 mRNA is induced by treatment with the pharmacological EGF receptor inhibitor gefitinib in the human head-and-neck carcinoma cell line HSC-3 in a MEK–ERK pathway-dependent manner (*13*). In this system, the MEK–ERK pathway is inhibitory for the synthesis of *CXCL14* mRNA. In the human breast cancer cell line MCF7, *CXCL14* expression is up-regulated by reactive oxygen species (ROS) through the binding of the AP1 transcription factor to an enhancer/promoter region of the *CXCL14* gene (*14*). In addition, expression levels of *CXCL14* in white adipose tissue (WAT) and skeletal muscle are elevated in high-fat diet (HFD)-induced obese mice, leptin-deficient *ob*/*ob* mice and leptin receptor-defective *db*/*db* mice (*15*, *16*). In obese individuals, *CXCL14* expression may be increased by elevated levels of free fatty acids, endoplasmic reticulum stress and/or ROS, which can activate c-Jun N-terminal kinase-1. Phosphorylation of c-Jun derepresses the transcription of inflammation-associated genes, including *CXCL14*, by removing the nuclear receptor–corepressor complex (*17*).

Roles of CXCL14 in Immune Cell Trafficking

Previously, CXCL14 was demonstrated to be a highly selective chemoattractant for human monocytes pre-treated with prostaglandin E2 (PGE2) or forskolin (*11*). However, later studies revealed that human monocyte-derived iDCs, but not mature dendritic cells, are responsive to CXCL14 in the absence of PGE2 treatment. In humans, CXCL14 is a chemoattractant for iDCs isolated from peripheral blood or induced *in vitro* from $CD14^+$ monocytes or $CD34^+$ hematopoietic progenitor cells (*10*, *18*, *19*). CXCL14 up-regulates the expression of dendritic cell maturation markers and enhances the proliferation of allogenic T cells in mixed lymphocyte reactions (*19*). Therefore, chemoattraction of iDCs and functional maturation of dendritic cells by CXCL14 would substantially contribute to anti-tumour immune surveillance. In addition, natural killer (NK) cells have also been reported to be chemoattracted by CXCL14 (*20*, *21*).

All of the studies described above were carried out in human cells. There has been little evidence to show that CXCL14 acts as a chemoattractant for iDCs or NK cells of mouse origin. Studies conducted in our laboratory have confirmed that $Mac1^+$ myeloid progenitor cells in mouse bone marrow and *in vitro* differentiated mouse iDC-like cells respond to CXCL14 in the presence of the anti-CXCL14 monoclonal antibody MAB730 (T. Hara, K. Tanegashima, unpublished data). However, the total numbers of macrophages and dendritic cells in the epidermis are not significantly different between CXCL14 knockout (KO) mice and wild-type mice (*22*). This is probably due to the overlapping activities of other chemokines. Very recently, it was reported that CXCL14-transgenic mice exhibit a higher incidence of collagen-induced arthritis due to an enhanced Th1 response and elevated levels of auto-antibodies (*23*). The total numbers of lymphocytes, dendritic cells and macrophages were not significantly changed in these CXCL14-transgenic mice, again suggesting that CXCL14 is dispensable for steady-state immunity.

Tumour-Suppressive or Tumour-Supportive Functions of CXCL14

CXCL14 is expressed in normal tissues, such as skin and lung, in the absence of inflammatory stimulation. Pioneering studies revealed that *CXCL14* mRNA expression is repressed in various malignant cancer samples and several tumour cell lines (*3–5*). The *in vivo* tumour-forming activity of head-and-neck carcinoma HSC-3 cells was abrogated when *CXCL14* was introduced, indicating that CXCL14 has a tumour-suppressing function (*24*). In addition, recent studies demonstrated that *CXCL14* is epigenetically silenced in several lung adenocarcinoma and prostate cancer cells of human origin (*25*, *26*). Forced expression of *CXCL14* cDNA in one such lung cancer cell line (H23) resulted in a dramatic decrease in tumourigenicity in xenotransplantation experiments (*25*). In these cells, the expression of cell cycle regulators, including *cyclin-A* and *CDC2*, was down-regulated, while genes encoding growth inhibitors and apoptosis inducers were up-regulated. Interestingly, *CXCL14* is a downstream gene of the atypical Rho GTPase, RhoBTB2, which is often mutated, deleted or silenced in breast and lung cancers (*27*).

Since CXCL14 potentially recruits iDCs and activated NK cells (Fig. 1), the down-regulation of *CXCL14* in malignant cancer cells may allow them to escape immune surveillance. *CXCL14* is strongly expressed in inflammatory and stromal cells adjacent to tongue carcinomas and prostate tumours (*4*, *28*) and is a potent inhibitor of angiogenesis stimulated by CXCL8, basic fibroblast growth factor, or vascular endothelial growth factor (*18*). Thus, in addition to the attenuation of the proliferative capacity of tumour cells and enhanced recruitment of surrounding immune cells, it is possible that CXCL14 also inhibits neovascularization within solid tumours by blocking chemotaxis of endothelial cells. Supporting this hypothesis, *in vivo* growth of immunocompatible melanoma cells or lung carcinoma cells in CXCL14-transgenic mice was significantly suppressed (*29*).

It is of note that CXCL14 is rapidly degraded via the ubiquitin-26S proteasome machinery in several cancer cell lines (*30*). Five amino acid residues (Val^{41}–Ser–Arg–Tyr–Arg^{45}), which are unique to CXCL14 among the CXC chemokines, are responsible for this degradation. Therefore, the expression of CXCL14 is negatively regulated either by a transcriptional or post-translational mechanism in cancer cells.

Although a number of studies have demonstrated a tumour-suppressive role for CXCL14, this is not always the case. In some prostate and pancreatic cancers, the expression levels of *CXCL14* are higher than that in the respective normal tissues (*31*, *32*). Moreover, endogenously expressed *CXCL14* promoted the growth and invasiveness of breast and pancreatic cancer cells (*14*, *32*, *33*). Breast cancer cells acquire invasive characteristics through ROS-mediated

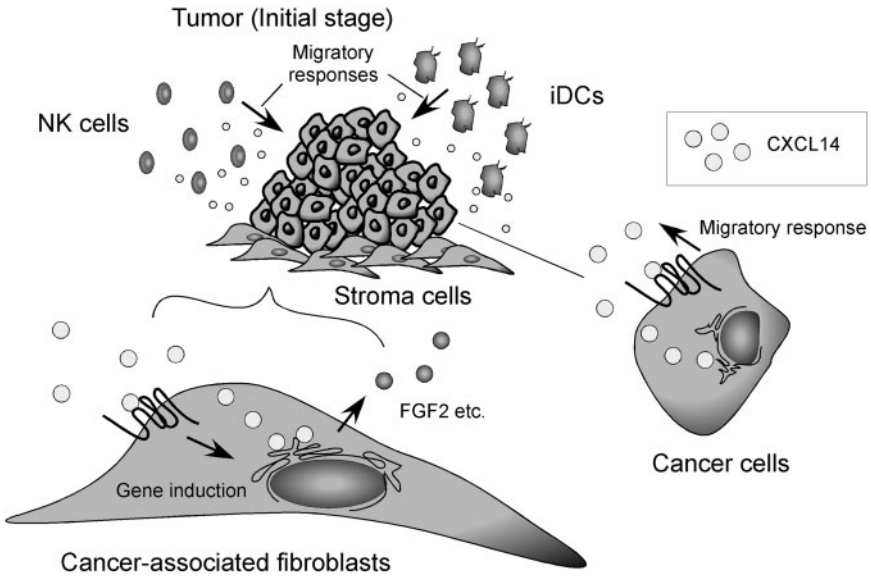

Fig. 1 Proposed roles of CXCL14 during tumourigenesis. Current knowledge of the tumour-suppressive and tumour-promoting roles of CXCL14 is schematically represented. In an earlier stage of tumourigeneis, CXCL14 produced from stroma cells chemoattracts iDCs and NK cells to activate the host immunity against neoplasm. However, CXCL14 gene is epigenetically silenced in many cases of lung cancer and head-and-neck carcinoma, thereby allowing tumour cells to escape this immune surveillance. On the other hand, breast cancer and prostate cancer cells utilize CXCL14 for enhancing their migratory capacity and invasiveness. An intracellular action of CXCL14 has also been suggested in breast cancer cells. In addition, CXCL14 in cancer-associated fibroblasts supports the migration of cancer cells by inducing secondary chemoattractants.

up-regulation of CXCL14 (*14*). In addition, the expression of CXCL14 is very high in prostate cancer-associated fibroblasts (*28*). NIH3T3 cells expressing *CXCL14* effectively supported the growth and migration of the prostate cancer cell line LNCap by secreting secondary cytokines and chemoattractants such as FGF-2 (*28*). Therefore, in certain malignant cancers, CXCL14 in the tumour microenvironment enhances the invasiveness and metastatic capacity of tumour cells (Fig. 1).

CXCL14 is a Causative Factor of Insulin Resistance in Obese Mice

We reported previously that HFD-fed CXCL14-KO female mice exhibit lower body weight (79% of control), a reduction in WAT macrophages (28% of control), and significantly ($P<0.01$) improved insulin sensitivity compared to HFD-fed obese control mice (*15*). However, HFD-fed CXCL14-KO mice have nearly the same amount of visceral and subcutaneous fat as HFD-fed control mice. Obesity-associated hypertrophy of adipocytes in WAT occurs in HFD-fed CXCL14-KO mice, indicating that they are not defective in adipogenesis or fat storage. However, fewer numbers of $Mac1^+$ macrophages infiltrated the WAT of HFD-fed CXCL14-KO mice compared to HFD-fed control mice (*15*). Macrophage infiltration of visceral WAT triggers local inflammation, thereby causing obesity-induced insulin resistance (*34*, *35*). Consistently, HFD-fed CXCL14-KO mice exhibited a better insulin responsiveness to decreasing blood glucose levels when compared to HFD-fed control mice (*15*). Enhanced production of CXCL14 in HFD-fed mice also affected the expression of adipokines, including adiponectin, retinol binding protein-4 (RBP4), interleukin-6 (IL-6) and CCL2 (*15*), which directly or indirectly inhibit glucose uptake in skeletal muscle and WAT, and enhance gluconeogenesis in the liver (Fig. 2).

In the skeletal muscle of HFD-fed CXCL14-KO mice, Ser^{473}-phosphorylation of Akt following insulin injection occurred more robustly than in HFD-fed control mice. Pretreatment of C2C12-derived myocytes with CXCL14 resulted in a reduction in insulin-stimulated phosphorylation of Akt and 2-deoxy-glucose uptake (*15*). Therefore, the direct effect of CXCL14 on skeletal muscle is likely to contribute to insulin resistance in obese mice (Fig. 2).

The livers of HFD-fed wild-type mice are enlarged, with a large amount of fat deposition. Interestingly, CXCL14-KO mice are protected from this HFD-induced hepatic hypertrophy and steatosis (*15*). The concentration of triglycerides in the liver is decreased in HFD-fed CXCL14-KO mice, suggesting that CXCL14-deficiency affects lipid turnover. It remains to be determined whether this phenotype is directly related to the effect of CXCL14 on hepatocytes or is an indirect effect of the insulin-sensitive phenotype of CXCL14-KO mice. With regard to these observations, carbon tetrachloride-induced hepatic regeneration and steatosis in mice were ameliorated when an anti-CXCL14 neutralizing antibody was administered (*36*).

Lastly, serum insulin concentrations in HFD-fed CXCL14-KO female mice were significantly lower than those of HFD-fed control female mice (*15*), suggesting that the CXCL14-KO mice were protected from HFD-induced hyperinsulinemia. However, HFD-fed CXCL14-KO mice were clearly defective in

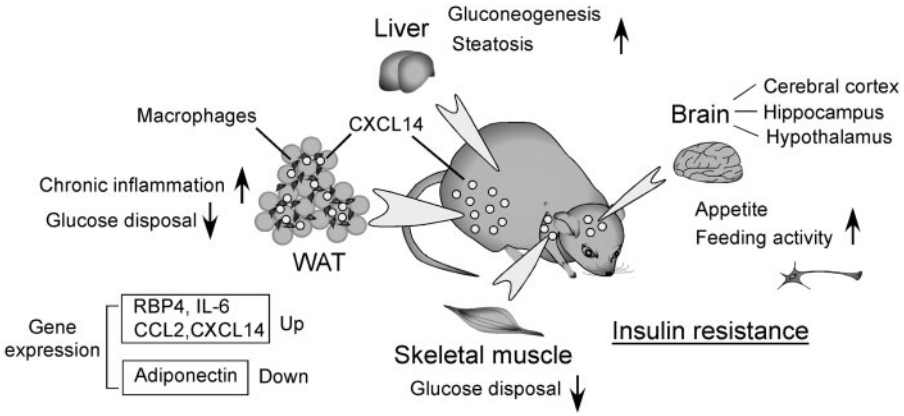

Fig. 2 Multiple functions of CXCL14 for inducing obesity-induced insulin resistance. Based on the phenotypic abnormalities of HFD-fed CXCL14-KO female mice, metabolic functions of CXCL14 in various organs are summarized. These actions are closely related to the onset of hyperphagia and obesity-induced insulin resistance.

glucose disposal when large amounts of glucose were administered. Thus, CXCL14 deficiency is associated with improved insulin sensitivity in obese mice, whereas it also impairs insulin production by an unknown mechanism.

Functions of CXCL14 in the Nervous System

In the mouse brain, *CXCL14* mRNA is most abundantly expressed in the cortex, hippocampus and cerebellum (http://www.brain-map.org), and investigation of the physiological roles of CXCL14 in the central nervous system (CNS) is underway. CXCL14-KO mice present an unexpected phenotype in which the mice have both a lower body weight and a reduced birth rate (*37*). A major cause of the lower body weight observed in these mice is a reduction of food intake without increased energy expenditure. Since weaned CXCL14-KO mice were already lighter than their control littermates, reduced food intake in CXCL14-KO mice was established within postnatal weeks, and the mice gained body weight in proportion to maintain the lighter phenotype over their lifespan. The lower body weight phenotype caused by CXCL14-deficiency was more prominent in *ob*/*ob* and A^y mice, which are representative of hyperphagic mutant mouse strains.

In fasted CXCL14-KO mice, expression of *Npy* and *Agrp* mRNA is decreased when compared to fasted control mice (*37*). AgRP and NPY are appetite stimulating factors produced in the hypothalamus. Hence, fasting-induced up-regulation of *Npy* and *Agrp* is functionally impaired in CXCL14-KO mice. Consistent with this observation, *CXCL14* mRNA is expressed in several appetite-related regions, including the paraventricular hypothalamus, suprachiasmatic nucleus and piriform cortex in the mouse brain (http://www.brain-map.org). In addition, it was recently reported that CXCL14 immunoreactive signals are also present in the arcuate nucleus, paraventricular hypothalamic nucleus and ventromedial hypothalamic nucleus in the rat brain (*38*).

More intriguingly, the food intake of CXCL14-KO mice is significantly repressed when mice are transferred to a novel environment (*37*). This abnormal feeding behaviour is observed on the first night after being moved to a different type of cage. Food intake gradually returns to a level similar to control mice by the third night. In contrast, locomotor activity in CXCL14-KO mice is not significantly different from control mice on the first night. Thus, the feeding-suppression phenotype of CXCL14-KO mice is not caused by a lowered exploratory capacity. As CXCL14 is present not only in the hypothalamus but also in the cortex and hippocampus, we speculate that CXCL14 may be required for the establishment of neural circuits that are closely linked with feeding behaviour (Fig. 2).

CXCL14 mRNA has been shown to be produced in a subset of microglia and GABAergic neurons in the CNS of mice (*39*). Very recently, Banisadr *et al*. (*40*) reported that *CXCL14* is expressed in GABAergic interneurons in the dentate gyrus of adult mice and inhibits the tonic and phasic effects of synaptically released GABA in neural stem/progenitor cells. In contrast, they also showed that such GABAergic transmission on the same cells is enhanced by the CXC chemokine CXCL12. Thus CXCL14 and CXCL12 oppositely act on the GABAergic interneurons, although an underlying mechanism remains elusive. *Cxcl14* and *Cxcl12* mRNA are co-expressed during early embryogenesis and in the fetal brain of mice, chickens (*8*, *41*) and carp (*7*). It has been shown that CXCL12 and its receptor CXCR4 are essential for neurogenesis during late gestation via the recruitment of neuronal stem/precursor cells (*42*, *43*). Therefore, when and where these two primordial chemokines are produced are critical for the proper development of the CNS. Presumably, the action of CXCL14 on neural progenitor cells during that stage may be integral for establishing the neuronal circuits that support feeding behaviour in a novel environment.

CXCL14 has also been reported to be expressed in Schwann cells of the sciatic nerve in mice (*44*). CXCL14 inhibits the proliferation of primary cultured

Schwann cells and up-regulates the expression of myelination-associated genes. Consistently, the expression level of CXCL14 is elevated in the transgenic mouse model of Charcot-Marie-Tooth disease type 1A, which is characterized by myelin degeneration. However, CXCL14-KO mice do not appear to suffer from detrimental neuropathy in either the CNS or the peripheral nervous system.

CXCL14 as an Anti-microbial Peptide

The antimicrobial activity of CXCL14 has been highlighted in recent reports (*45*, *46*). The epithelial cell layers in the skin constitute a physical barrier against environmental microbes that present a potential threat to the host. Two types of bacteria reside in the skin: commensal bacteria (*Finegoldia magna*) and virulent bacteria (*Streptococcus pyogenes*). CXCL14 is constitutively expressed in the skin; however, its expression is specifically suppressed at the earliest stages of infection. CXCL14 is capable of killing commensal bacteria more efficiently than virulent bacteria at a concentration of approximately 100 nM (*46*). Whereas the amount of CXCL14 in the skin is locally decreased during the earliest stage of infection, the total number of the commensal bacteria is inversely increased. SufA protease released from the commensal bacteria then digests CXCL14 to generate a partial fragment that possesses a strong bactericidal activity against virulent pathogens (*46*). Subsequently, the numbers of bactericidal peptides against virulent bacteria such as β-defensin, CCL20 and midkine are produced. In this way, skin integrity is maintained in conjunction with permanently residing bacteria and anti-microbial peptides.

Role of CXCL14 in the Uterus during Pregnancy

CXCL14 also appears to play a role in supporting the reproductive process in females. First, *CXCL14* expression is up-regulated in the endometrium during the mid to late secretory phases of the menstrual cycle (*21*). Moreover, the expression of *CXCL14* is enhanced by the binding of progesterone to the −2028/−2007 and −722/−697 DNA regions upstream of the transcriptional initiation site. Since the number of uterine NK cells increases after ovulation, and peaks in the late secretory phase, target responsive cells of CXCL14 might be residual NK cells in the uterus.

Second, CXCL14 is expressed at embryo implantation sites and inhibits the outgrowth of trophoblasts via the down-regulation of matrix metalloproteinase-2 and -9 (*47*, *48*). This function may be related to the receptive status of the endometrium for implantation and establishment of pregnancy. However, CXCL14 is not essential for pregnancy in mice, as CXCL14-KO female mice were able to conceive and deliver pups (*37*).

The CXCL14 Receptor and Signal Transduction Pathway

The CXCL14 receptor molecule has not yet been identified. Thus, the intracellular signaling events elicited by CXCL14 stimulation are not fully understood in any species. Human monocytes acquire CXCL14-responsiveness and lose their chemotactic response to a control chemokine (CCL2) after PGE2 treatment (*11*), suggesting that the putative CXCL14 receptor may be distinct from those of other inflammatory monokines. Since CXCL14-stimulated calcium influx in PGE-treated monocytes was abrogated by pertussis toxin (PTX) (*11*), it has been postulated that a specific subgroup ($G_{\alpha i}$) of GPCRs is involved in CXCL14 signal transduction, similar to other chemokines. Nevertheless, CXCL14 does not seem to use typical CXC-type receptors CXCR1, 2, 3 and 4, since their ligands (CXCL8, CXCL10 and CXCL12) did not compete with the high-affinity binding of CXCL14 in iDC cells (*18*). In addition, tumour-suppressive activity and metabolic functions are specifically observed in CXCL14 but not in other CXC chemokines, and T cells are not responsive to CXCL14. Based on these observations, it is speculated that CXCL14 utilizes a distinct type of receptor molecule.

Lack of a sensitive bioassay has made the search for the CXCL14 receptor difficult. We recently discovered that the CXCL14-mediated chemotaxis of THP-1 cells and human iDCs is greatly enhanced in the presence of the anti-CXCL14 monoclonal antibody, MAB730 (*49*). THP-1 cells possess high-affinity ($K_d = 10$ nM) and low-affinity ($K_d > 500$ nM) binding sites for ^{125}I-labeled CXCL14. As is the case with many other chemokines, binding of the latter is mediated by a heparan sulfate moiety on proteoglycans on the cell surface, and MAB730 partially blocks the heparin binding of CXCL14. This bioassay system will be very useful in the search for the CXCL14 receptor and screening of CXCL14 inhibitors.

As described in the previous section, CXCL14-mediated signals cross-talk with insulin-elicited signal transduction pathways in skeletal muscle. Therefore, myocytes should express CXCL14 receptors. Recently, we found that the binding capacity and chemotactic response of C2C12 myoblastic cells to CXCL14 were significantly enhanced by forskolin treatment (T. Hara, unpublished data). Forskolin-treated C2C12 cells were chemoattracted by CXCL14 in a PTX-dependent manner (T. Hara, unpublished data), as is the case in human monocytes. However, MAB730 antibody-assisted CXCL14 chemotaxis of THP-1 cells was not inhibited by PTX (T. Hara, unpublished data). Thus, it appears that the activation of CXCL14 receptors is a complicated and cell type-dependent process. Efforts to clone the CXCL14 receptor cDNA are ongoing in our laboratory.

With respect to the mechanism of action of CXCL14, Pelicano *et al.* (*14*) recently reported that CXCL14 and the inositol 1,4,5-triphosphate receptor are physically associated inside breast cancer cells and act together to modulate intracellular calcium concentrations. Interestingly, NIH3T3 or MCF7 cells

expressing CXCL14 are more migratory than control parental cells (*14*, *28*). Thus, CXCL14 inside the cells might play a unique role in regulating cell motility.

Future Directions of CXCL14 Research

Research on the roles and regulation of CXCL14 began in 1999. Over the past 12 years, our knowledge of the physiological roles of this mysterious member of the CXC chemokine family has increased incrementally. CXCL14-mediated chemoattraction of iDCs and NK cells could strengthen the immunological barriers against malignant cancer cells. However, under some circumstances, CXCL14 is a pro-tumourigenic factor. It must be determined whether cancer incidence in various organs is increased or decreased in CXCL14-KO mice.

Now we know that CXCL14 is involved in the regulation of body weight as well as of glucose metabolism. Elucidation of the CXCL14 receptor structure and signal transduction machinery will be crucial for understanding the mechanisms by which CXCL14 affects the CNS and peripheral tissues. This will also be an important step toward the development of novel anti-obesity and anti-diabetes drugs. If specific inhibitors and activators of CXCL14 become available, it might be possible to modulate the *in vivo* trafficking of various types of immune cells, suppress the malignant growth and invasiveness of cancer cells and control appetite and blood glucose levels.

Finally, the bactericidal activity of CXCL14 in the skin is a receptor-independent function. Since the expression levels of CXCL14 are higher in mucosal tissues, including the lungs, small intestine and tongue, it will be important to determine whether CXCL14 plays a significant role in the regulation of microflora and mucosal immunity in these tissues. The function of CXCL14 in digestive organs might be closely related to systemic glucose metabolism and feeding behaviour, and may contribute to ensuring the intake of a sufficient amount of energy for locomotion and intellectual activities.

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Conflict of interest

None declared.

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