Seminars in Cell & Developmental Biology 19 (2008) 379–384

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Conditional gp130 deficient mouse mutants

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ARTICLE INFO

Article history:
Available online 17 July 2008

Keywords:
gp130
Interleukin-6
Interleukin-11
Interleukin-27
Ciliary neurotropic factor
Leukemia inhibitory factor
Oncostatin M
Cardiotrophin-1
Cardiotrophin-like cytokine
Neuropoietin
Cre recombinase
Conditional mouse mutants

ABSTRACT

The common cytokine receptor chain, gp130, controls the activity of a group of cytokines, namely, IL-6, IL-11, IL-27, ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin M (OSM), cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC) and neuropoietin (NPN). This family of cytokines is involved in multiple different biological processes, including inflammation, acute phase response, immune responses and cell survival. To analyze the different components of the gp130 network, mouse mutants for the single cytokine were generated by conventional gene targeting. However, since the cytokines of the IL-6 family show redundancy, it does not reveal the complete picture. Therefore, the study of mice with a cell type specific inactivation of the gp130 receptor chain is an approach that will subsequently allow the dissection of the cellular cytokine network. Here, we summarize the experimental results of the conditional gp130 mutants published so far.

Contents

1. Introduction

Since its discovery, gp130 has been the focus of many investigations and has been shown to be involved in several biological processes. One feature of this receptor and its cytokines is the redundancy of the signals, since the lack of one of the cytokines can still lead to functional signaling [1]. Inactivation of gp130 in mice leads to lethality at birth or shortly after. The generation and analysis of a conditional gp130 mouse mutant mouse have highlighted the multiple functions of this receptor *in vivo*. The phenotypes of the published mutants are described in this review (Fig. 1).

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doi:10.1016/j.semcdb.2008.07.001

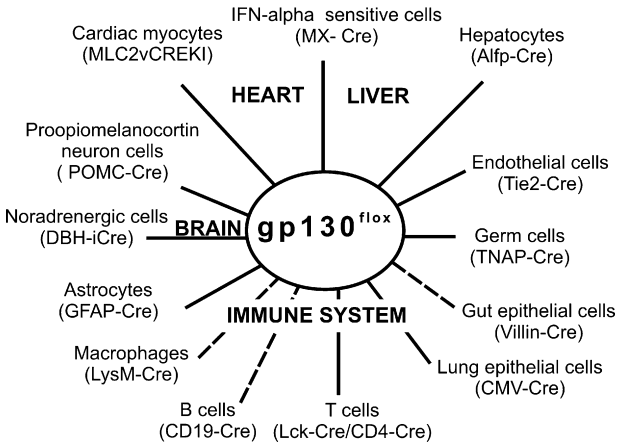

Fig. 1. Representation of the Cre mouse mutants used to analyze the role of gp130 in cell or tissue specific manner. Dashed lines correspond to unpublished mutants and continued lines are published Cre-specific gp130 conditional mouse strains. Details are covered in the text.

2. IL-6 family of cytokines

The IL-6 family of cytokines consists of IL-6, IL-11, ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin M (OSM), cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC) and neuropoietin (NPN) [2–4]. These proteins often have overlapping biological effects, since they all share the same common signal transducer for signaling, the glycoprotein 130 (gp130) [5]. The demonstration of the necessity of gp130 was shown by experiments on IL-6R, which contains a relatively short cytoplasmic region of only 82 amino acids. When this region of IL-6R was truncated, IL-6 was still able to mediate signals, thereby indicating that the cytoplasmic region of IL-6R is not involved in signaling [6]. Indeed, a complex of IL-6 and IL-6R must associate with a non-ligand-binding gp130 receptor in order to signal. Moreover, IL-31 was recently added to the IL-6 family. However, IL-31 does not bind to gp130 but to the gp130-like monocyte receptor or IL-31Rα, which heterodimerizes with oncostatin M receptor β to form the IL-31R signaling complex [7,8]. In addition to the IL-6 family of cytokines, a member of the IL-12 family, IL-27, also utilizes gp130 as its signaling subunit [9]. Since the members of the IL-6 family signal through a common receptor, they also show redundancy. For example, acute phase proteins can be induced by IL-11, OSM and LIF, in addition to IL-6 [10]. The gp130-dependent cytokines also share pleiotropic activities and are produced after an inflammatory stimulus by diverse cells [11]. Although they are highly redundant in their capacity to mediate biological functions, their main difference resides in the homodimerization or heterodimerization of the signal transducer gp130 and the binding to the receptor subunit α, which is specific for each cytokine. To transduce its signals, IL-6 first binds to IL-6R and then the complex associates to a gp130 homodimer. This homodimer is also used by IL-11 for its signaling. Similarly to IL-6, IL-11 binds to IL-11R and then to gp130 [12]. Both IL-6 and IL-11 do not necessarily need a membrane-anchored receptor to signal, since soluble forms (sIL-6R and sIL-11R) can substitute membrane IL-6R and IL-11R [13]. In contrast, LIF and OSM utilize heterodimers for signaling. LIF binds to LIFR with low affinity and require a heterodimer of LIFR and gp130 to mediate signals [14]. OSM can signal either through the LIFR/gp130 or to OSMR/gp130 complexes [15]. CNTF and CT-1 utilize the LIFR/gp130 heterodimer after binding to their specific receptors CNTFR (or soluble CNTFR) and CLF-1(NR6), respectively [16]. Similarly to CNTF, NPN first binds to CNTFR and then to the LIFR/gp130 complex [3]. Finally, IL-27 signals through a heterodimer consisting of gp130 and IL-27Rα (WSX-1) [9]. Since gp130 is expressed widely including liver, lung, spleen, heart, kidney, placenta and brain, binding to a second, cytokine-specific receptor allows the regulation of the signaling and of the biological activities. Indeed and as stated above, soluble forms of IL-6R and IL-11R are able to make cell responsive to IL-6 and IL-11, even if membrane IL-6 and IL-11 are not expressed. However, since IL-6 and IL-11 signals through a homodimer, they are strictly dependent on gp130, while the cytokines using the heterodimer gp130/LIFR or gp130/OSMR can use LIFR or OSMR to transduce their signals, at least in part.

3. Mice deficient in one cytokine of the IL-6 family

Mice deficient in one of the members of the IL-6 family show milder phenotypes than expected, certainly due to the redundancy of the gp130-dependent cytokines. For instance, LIF$^{-/-}$ female mice are sterile due to a defect during blastocyst implantation and show abnormalities in hematopoiesis [17,18]. IL-6$^{-/-}$ mice exhibit defects in hematopoiesis, acute phase protein synthesis, antigen-specific antibody production, chemokine induction and leukocyte recruitment and hepatocyte regeneration [19–21]. In addition, they display increased susceptibility to infections [22]. CNTF$^{-/-}$ mice develop progressive mild motor neuron degeneration, while OSM$^{-/-}$ mutants have a defect in the development of a subtype of nociceptive neurons [23,24]. The only cytokine-deficient mouse mutants showing a lethal phenotype are CT-1$^{-/-}$ mice, which have an increased loss of motoneurons [25].

4. Mice deficient in one receptor of the IL-6 family

Mice deficient in a receptor of the gp130 family display more severe phenotypes. gp130$^{-/-}$ mice die 12.5 days postcoitum, exhibiting disrupted placental architecture, hypoplastic development and a decrease in fetal liver hematopoiesis [26] and highlighting a role for gp130 signaling during development. Mice lacking LIFR, a part of the receptor complex for LIF, CNTF and CT-1, show lethality characterized by placental defects and loss of motor neurons [27,28]. CNTFR$^{-/-}$ mice die perinatally and display loss of motor neurons [29]. Mice deficient in the specific receptor for CLC, CLF-1(NR6), display a lethal phenotype with reduced number of hematopoietic progenitor cells [30]. Finally, two mouse models show less severe phenotype: IL-11R$^{-/-}$ female mice are sterile due to a defect in the decidua formation, while OSMR$^{-/-}$ mice have defects in hematopoiesis [31–33].

5. gp130 signaling pathway and mouse models

After the cytokines bind to their specific receptor and then to gp130, signaling involves the activation of the JAK/STAT pathway [34]. gp130 has been shown to activate the Janus kinases JAK1, JAK2 and TYK2 [35]. These protein kinases induce the phosphorylation of distinct intracellular tyrosines (Y) present on the cytoplasmic domain of gp130 and act as docking sites for the initiation of the downstream pathway. The activation of the STAT pathway is mediated by phosphorylation of the four distal tyrosines (Y765, Y812, Y904, Y914) [36]. STAT3 is most potently activated, while STAT1 has been shown to be induced following binding of IL-27 to the WSX-1/gp130 complex [37]. In addition to the STAT1/3 pathway, the SHP-2/ERK MAPK pathway can be activated and only requires the phosphorylation of a single tyrosine, Y757 (Y759 in human gp130) [38]. These two signaling cascades are under the tight control of negative feedback mechanisms [39]. Two members of the suppressor of cytokine signaling (SOCS) family, SOCS1 and SOCS3, regulate these processes by binding directly to the phosphorylated JAK or to