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Survey

Oncostatin M and interleukin-31: Cytokines, receptors, signal transduction and physiology

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ABSTRACT

Oncostatin M (OSM) and interleukin-31 (IL-31) are two cytokines belonging to the IL-6 family which share a common signaling receptor subunit, the OSM receptor beta (OSMRβ). Both of them are released by monocytes/macrophages, dendritic cells and T lymphocytes in inflammatory situations and upon binding to their respective receptor complexes they signal mainly via the JAK/STAT pathway. Besides sharing many biochemical properties, both display divergent physiological functions. This review summarizes aspects of cytokine transcription and biosynthesis, cytokine–receptor interactions, cross-species activities, signal transduction and physiology delineated from recent findings in genetic mouse models for both cytokines, OSM and IL-31.

Contents

1. Oncostatin M (OSM)

Even though the discovery of OSM dates back 25 years [1], its physiology and involvement in disease development are still incompletely understood. Initially discovered as a cytokine released from U937 cells which has cytostatic activities on the growth of melanoma cells, hence its name oncostatin M, it is now becoming clear that OSM has multiple functions in hematopoiesis, mesenchymal stem cell differentiation, liver regeneration, heart remodeling, nociception, inflammation and metabolism (Fig. 1).

1.1. Transcription, biosynthesis and secretion of OSM

Within the last two decades the orthologues of human (h), bovine (b), murine (m) and rat (r) OSM have been cloned [1–4]

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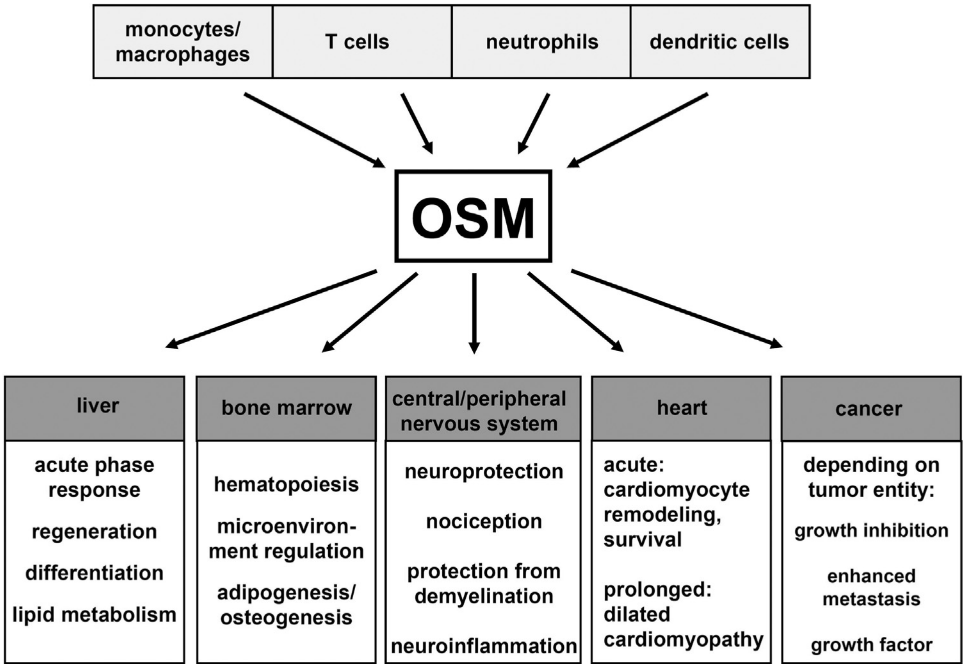

Fig. 1. Main producers, target tissues and activities of OSM. Summary of some described target tissues of OSM as well as an excerpt of its physiological and pathophysiological functions.

(Tables 1 and 2). With the number of sequenced genomes increasing, further sequences are available for many more species (https://www.ncbi.nlm.nih.gov/gene, ortholog_gene_5008[group]). The exon–intron structure of the gene encoding OSM is identical between species with three exons separated by two introns. Interestingly, in all species the *OSM/Osm* gene is located in direct proximity to the gene encoding leukemia inhibitory factor (LIF) which might indicate that both have originated from a gene duplication [5,6].

For human and murine OSM the promoters have been characterized and indicate that *OSM/Osm* transcription is controlled by C/EBP and GC-rich elements for basal activity, but that STAT5 response elements are crucial for stimulus-dependent increase in transcription. Transcriptional silencer(s) located between nt −194 and −109 in the proximal human *OSM* promoter appear to assure cell-specific control of OSM expression [3,7,8]. Indeed, stimulation of many hematopoietic cell types with cytokines activating STAT5, like IL-2, IL-3, EPO, GM-CSF, results in a strong expression of OSM. Not surprisingly, OSM was then identified as an amplifier of cytokine production and bone marrow remodeling in myoproliferative neoplasms carrying oncogenic JAK2 mutations (TEL/JAK2 and JAK2-V617F) which result in constitutive activation of STAT5 [9,10]. Recently, a number of studies have shown that OSM transcription is upregulated in response to prostaglandin E2 in a cAMP-dependent manner [11–14]. Major cell types secreting OSM upon stimulation are activated monocytes/macrophages, neutrophils, dendritic cells and T-lymphocytes [15–20]. Furthermore, mOSM mRNA is present in the bone marrow to a much higher extent than in the spleen which points to a role of OSM in hematopoiesis and/or osteogenesis [3]. Hematopoietic cells in the bone marrow were identified as source of OSM [21]. Its expression is, however, undetectable in liver, lung, ovary, small intestine, kidney and brain [3,21].

The more than 1000 nt long 3′ untranslated regions (3′ UTR) of the human and murine OSM mRNAs contain several AU-rich sequences which are known to be involved in the regulation of mRNA stability of several cytokines including e.g. IL-6 [22] (reviewed in: [23]). Regarding the hOSM mRNA it was recently

Table 1
Processing and posttranslational modifications (PTM) of OSM and IL-31 orthologues as well as topology and PTM of OSMRβ and IL-31RA orthologues (according to www.uniprot.org).

Cytokine	Full-length protein	Signal peptide	C-terminal prodomain	Mature protein	Disulfide bonds	N-glycosylation sites (predicted)
hOSM	252 aa	25 aa	32 aa	195 aa	2	2
bOSM	245 aa	26 aa	40 aa	179 aa	2	1
rOSM	239 aa	25 aa	32 aa	182 aa	2	–
mOSM	263 aa	24 aa	58 aa	181 aa	2	3
hIL-31	164 aa	23 aa	–	141 aa	1	2
mIL-31	163 aa	23 aa	–	140 aa	1	3
Receptor	Full-length protein	Signal peptide	Extracellular region	TM domain	Intracellular region	N-glycosylation sites (predicted)
hOSMRβ	979 aa	27 aa	713 aa	21 aa	218 aa	5
mOSMRβ	971 aa	23 aa	714 aa	21 aa	213 aa	14
rOSMRβ	962 aa	28 aa	710 aa	21 aa	203 aa	5
hIL-31RA (main isoform)	732 aa	19 aa	500 aa	21 aa	192 aa	10
mIL-31RA	716 aa	18 aa	481 aa	21 aa	196 aa	4

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