

Signaling Network of Oncostatin M Pathway

Gourav Dey^{1*}, Aneesha Radhakrishnan^{1,2*}, Nazia Syed^{1,2}, Joji Kurian Thomas^{1,3}, Arpitha Nadig⁴, Kotteazeth Srikumar², Premendu Prakash Mathur^{2†}, Akhilesh Pandey⁵, Sze-Kwan Lin⁶, Rajesh Raju¹ and T. S. Keshava Prasad^{1,2,3#}

¹Institute of Bioinformatics, International Tech Park, Bangalore-560 066, India.

²Department of Biochemistry and Molecular Biology, School of Life Sciences, Pondicherry University, Puducherry-605 014, India.

³School of Biotechnology, Amrita Vishwa Vidhyapeetam, Kollam-690 525, India.

⁴Department of Bioinformatics, Kuvempu University, Karnataka, Shankaraghatta-577 451, India.

⁵McKusick-Nathans Institute of Genetic Medicine and Departments of Biological Chemistry, Pathology and Oncology, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.

⁶School of Dentistry, College of Medicine, National Taiwan University, 1 Chang-Te Street, Taipei-10016, Taiwan

*Both authors contributed equally.

†Current address: KIIT University, Bhubaneswar-751 024, India

#**Corresponding author:** Dr. T. S. Keshava Prasad, Ph.D., Institute of Bioinformatics, International Tech Park, Whitefield, Bangalore-560 066

Tel.: +91-80-28416140; Fax: + 91-80-28416132; E-mail: keshav@ibioinformatics.org

GD: gourav@ibioinformatics.org

AR: aneesha@ibioinformatics.org

NS: nazia@ibioinformatics.org

JKT: joji@ibioinformatics.org

AN: arpithanadig02@gmail.com

KS: srikumarprof@gmail.com

PPM: ppmathur@yahoo.com

AP: pandey@jhmi.edu

SKL: sklin7400@ntu.edu.tw

RR: rajesh@ibioinformatics.org

TSK: keshav@ibioinformatics.org

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Abstract

Oncostatin M, a member of IL-6 cytokine family, is involved in inflammation, homeostasis, growth and differentiation of organs, wound healing and tumorigenesis. The role of oncostatin M in cell differentiation and proliferation is complex and varies in response to the microenvironment. Multiple biological effects of oncostatin M make it a biomedically important molecule with immense clinical and therapeutic potential. A comprehensive catalog of molecular reactions and gene regulations induced by oncostatin M, if available publicly, will greatly accelerate molecular research on oncostatin M and its role in multiple human diseases. In view of this, we developed the largest signaling network of molecular events induced by oncostatin M. In the process, we have documented 78 molecules involved in 35 protein-protein interactions, 54 enzyme substrate reactions and 8 protein translocation events. In addition, we have also cataloged 322 gene regulation events by oncostatin M signaling. We have submitted oncostatin M signaling pathway to NetPath, NetSlim and WikiPathways in order to make it publicly available.

Keywords: Angiogenesis, Arthritis, LIF, Oncogenesis, OSMR

Abbreviations

AKT	v-akt murine thymoma viral oncogene homolog 1
JAK	Janus Kinase
LIFR	Leukemia inhibiting factor
MAPK	Mitogen-activated protein kinase
OSM	Oncostatin M
OSMR-beta	OSM receptor-beta subunit
PI3K	Phosphoinositide 3-kinase
PTMs	Post-translational modifications
STAT	Signal Transduction and Activator of Transcription

Introduction

Oncostatin M (OSM), belonging to the IL-6 family of cytokines (Heinrich et al. 2003), was first reported and purified from U937 monocytic cells (Zarling et al. 1986, Ensoli et al. 1999, Hasegawa et al. 1999). In normal physiological condition, OSM is associated with multiple biological processes and cellular responses including growth, differentiation, and inflammation. However, anti-proliferative activity of OSM against breast cancer cell line generated the interest of biomedical community on this molecule (Douglas et al. 1997, Douglas et al. 1998). OSM was also found associated with pathological conditions such as proliferation of ovarian cancer cells (Taga and Kishimoto 1997), prostate cancer 22Rv1 cells (Hoffman et al. 1996), up-regulation of the ER chaperone Grp78/BiP in the liver cells, atherosclerotic lesions, ischemic heart disease and rheumatoid arthritis (Linsley et al. 1990, Dunham et al. 1999). The dual role of OSM in either inducing or inhibiting the proliferation of various types of cells called upon the scientific community to investigate role of OSM in various physiological and experimental contexts in detail. However, diverse molecular level information pertaining OSM signaling is not available in a centralized resource. Therefore, we have systematically gathered and curated molecular information from literature and created a public resource for OSM induced signaling events. We integrated OSM signaling pathway into NetPath (Kandasamy et al. 2010), which is a public resource of human signaling pathways.

OSM is known to mediate its biological effects by binding to two distinct heterodimers of gp130 with either leukemia inhibiting factor receptor (LIFR) or OSM receptor-beta (OSMR-beta) (Thoma et al. 1994). Former heterodimer between gp130 and LIFR is called type I receptor complex and the latter between gp130 and OSMR-beta is called type II receptor complex. Type I receptor can bind to either OSM or leukemia inhibiting factor, whereas type II receptor has more affinity towards OSM (O'Hara, K.A., et al. 2003). The binding of OSM to either gp130/OSMR-beta or gp130/LIFR induces the activation of Janus Kinase family members through tyrosine phosphorylation (Tanaka and Miyajima 2003). The activated JAK family members in turn induce the activation of Signal Transduction and Activator of Transcription (STAT) proteins (Schaefer et al. 2000). Alternately, the activated receptors can also activate mitogen-activated protein kinase (MAPK) pathway (Van Wagoner et al. 2000) and PI3K/AKT pathways (Arita, K., et al., 2008). It was also reported that OSM bring about ligand-induced receptor degradation of gp130, OSMR-beta, and LIFR before enhancing the synthesis of the receptor subunits (Blanchard et al. 2001).

Materials and methods

Literature search was carried out using 'oncostatin' as a keyword. The interpreted information regarding OSM signaling cascade was recorded in 'PathBuilder,' a software utility developed by Kandasamy and colleagues to annotate signaling pathways (Kandasamy et al. 2009). In order to generate an OSM specific signaling pathway, we have considered only those reactions that are specifically initiated by OSM stimulation. Molecular reactions initiated by OSM in combination with other cytokines were thus, not considered in the signaling cascade depicted here. We considered NetPath annotation criteria, as previously described in (Goel et al. 2011, Nanjappa et al. 2011, Raju et al. 2011a) to generate the OSM signaling cascade and for categorizing the

involved reactions into protein-protein interactions, post-translational modifications (PTMs), protein activation-inhibition reactions, protein translocation events and gene regulation events. In case of PTMs, we have mapped site and residue information of the PTMs given in the literature to specific and longest isoform of the corresponding protein as given in the RefSeq database. In addition to the NetPath criteria, we applied more stringent NetSlim criteria to choose more confident and core pathway reactions, among larger set of OSM pathway reactions (Raju et al. 2011b). Using this subset of pathway reactions, we depicted a core signaling cascade map of OSM, using 'PathVisio' (<http://www.PathVisio.org>).

After an initial round of internal review, we uploaded OSM signaling pathway information into NetPath. Further, we requested the 'Pathway Authority,' who has considerable expertise on OSM signaling, for expert opinion. The pathway authority, in this case SKL, who is also a co-author in this manuscript, has reviewed the listed reactions pertaining to the OSM signaling cascade. We have incorporated suggestions and opinion of the pathway authority.

Results and discussion

The information pertaining to OSM signaling was found in over 1,100 scientific research articles. A manual analysis through the available and relevant scientific literature led to the identification of 78 molecules involved in the OSM signaling cascade reactions. Among these, 78 molecules were part of 35 protein-protein interaction and 54 PTM events. OSM signaling pathway was also found to regulate the expression of 322 unique genes in humans. Stimulated by OSM signaling pathway, 8 proteins were found to be translocated between different sub-cellular compartments. We provided these pathway reactions and their associated descriptions in NetPath (http://www.netpath.org/pathways?path_id=NetPath_114). The molecule page in NetPath was made dynamic and informative by linking represented molecules to external repositories including HPRD (Goel et al. 2012, Prasad et al. 2009), OMIM (Hamosh et al. 2005), Entrez Gene (Maglott et al. 2005) and Swiss-Prot (Boeckmann et al. 2003). A graphical depiction of OSM pathway reactions chosen by NetSlim criteria is provided in Fig. 1. The OSM reaction map can also be accessed at NetSlim through the link provided (http://www.netpath.org/netslim/OSM_pathway.html).

Role of OSM in inhibiting and inducing proliferation

OSM was observed to promote and inhibit cell proliferation in different cell types. It was found that OSM employs different downstream elements to bring about these effects. Studies pertaining to OSM induced inhibitory effects in MCF-7 cell lines revealed a STAT3 activated module of signaling. This activation of STAT3 by OSM was in turn found to influence various genes associated with migration and cell differentiation (Zhang et al. 2003). In human proximal tubule cells, OSM was found to have anti-fibrotic effects, through the attenuation of transforming growth factor - β 1 initiated events and inhibition of *CTGF* expression (Sarkozi et al. 2011). In case of SKOV3 ovarian cancer cell line, proliferating effect of OSM have been traced to the phosphorylation and activation of STAT3, MAPK1/2 and p38 signaling cascade (Li et al. 2011). However, proliferative effects of OSM on OSA cell lines were shown to be associated with activation of STAT3, Src and JAK2 cascade and to increased expression of *MMP2* and

VEGF genes, which in turn associates OSM with tumor invasion and angiogenesis (Fossey et al. 2011).

Role of OSM in other pathological conditions

OSM has been associated with multiple sclerosis of microglia and astrocytes through upregulation of associated molecules including intercellular adhesion molecule-1 in human cerebral epithelial cells (Ruprecht et al. 2001). Regulation of transcription of *LDLR* gene by OSM has been associated with the regulation of blood cholesterol level. OSM was also reported to utilize JAK/STAT and MAPK signaling cascades in HepG2 cells and cause a decreased expression of *PCSK9* gene, which influences *LDLR* expression in liver (Cao et al. 2011). *Albasanz-Puig* and colleagues demonstrated the dual roles of OSM, brought about through interplay of STAT1 and STAT3, in both promoting as well as inhibiting atherosclerosis. OSM had also been found to inhibit *VEGF* expression through STAT1, whereas STAT3 module induced by OSM was found to increase the expression of *VEGF* expression (Albasanz-Puig et al. 2012). The ability of OSM to influence different genes including *CYR1*, *PGLF* and *IL6*, in various cells and cell lines, through either JAK/STAT, MAPK or CREB signaling cascades, associated OSM to various pathological conditions in rheumatoid arthritis (Migita et al. 2011, Tu et al. 2012, Kok et al. 2011).

Role of OSM in repair and remodeling

Studies on adult human cardiac myocytes, fibroblasts and bone marrow-derived mesenchymal stem cells showed the recruitment of STAT3 or MAPK1/2 by OSM, which initiated remodeling in pathological conditions such as arthritis and osteoporosis, as well as aiding in repair of fractures (Weiss et al. 2005, Nicolaidou et al. 2012).

Availability of data

OSM signaling pathway data can be freely downloaded from NetPath (http://www.netpath.org/pathways?path_id=NetPath_114) and NetSlim (http://www.netpath.org/netslim/OSM_pathway.html), for unrestricted non-commercial use under the adaptive Creative Commons License (<http://creativecommons.org/licenses/by-nc/2.5>). The data available in both the resources will be periodically updated. We have also submitted OSM pathway to Wikipathways (<http://www.wikipathways.org/index.php/Pathway:WP2374>).

Conclusions

OSM is emerging as an important molecule with potential clinical and therapeutic values in multiple human diseases. However, a variety of biological effects induced by OSM signaling pathway remain poorly defined so far. Therefore, we tried to gather publicly available experimentally derived information on OSM induced events and depicted these molecular events in the form of a signaling pathway. We believe that OSM signaling pathway information, as freely available will soon be integrated into various global resources and gene set enrichment analysis tools, which will allow discovery of biological processes and pathological conditions

where OSM signaling is involved. OSM signaling pathway developed in this study will also provide a platform for biomedical community to design further discovery oriented high-throughput studies for this signaling pathway. OSM pathway map generated by us would aid and accelerate future studies of OSM related processes.

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Conflict of interest The author(s) declared no conflicts of interests.

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Figure Legends

Fig. 1: Schematic representation of Oncostatin M signaling pathway- NetSlim (http://www.netpath.org/netslim/OSM_pathway.html) map generated to graphically represent the different reactions induced by OSM in various cell types.