RESEARCH HIGHLIGHT

Posttranslational modifications of CXCR4: implications in cancer metastasis

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CXCR4, the most widely expressed chemokine receptor in solid malignancies, has been implicated in cancer metastasis. However, how the activity of CXCR4 is regulated during carcinogenesis especially at the metastatic stage remains largely unknown. As with other G protein-coupled receptors, CXCR4 is subjected to posttranslational medications such as phosphorylation, ubiquitination, glycosylation, and sulfation. These posttranslational modifications contribute significantly to the heterogeneity of CXCR4 in terms of intracellular location, signaling, and functionality. We have shown that the difference in the sulfation level of CXCR4 is responsible for, if not all, the difference in the activities of CXCR4 between the highly metastatic and non-metastatic nasopharyngeal carcinoma (NPC) cell lines. Molecular mechanistic studies revealed that the Epstein-Barr virus-encoded oncoprotein LMP1 induces the expression of tyrosylprotein sulfotransferase 1 (TPST-1) through nuclear translocation of the epidermal growth factor receptor. This LMP1-regulated TPST-1 expression accounts for tyrosine sulfation of CXCR4 and is associated with the metastatic phenotype of NPC cell lines. Finally, in NPC patient specimens, there was a positive correlation between the expression of LMP1 and TPST-1 and the metastatic potential of NPC. Our findings provide the first evidence that the posttranslational modification of a chemokine receptor plays a role in cancer metastatic progression. Understanding the role of posttranslational modifications of chemokine receptors in cancer biology may provide new insights for developing attractive therapeutic targets in cancer therapy.

Keywords: Chemokine receptors; CXCR4; Posttranslational Modifications; Cancer metastasis

***Abbreviations*:** CXCR4, CXC-chemokine receptor 4; EGFR, Epidermal growth factor receptor; GPCR,G protein-coupled receptor; LMP1, Latent membrane protein 1; NPC, Nasopharyngeal carcinoma; SDF-1, Stromal cell-derived factor 1; TPST, Tyrosylprotein sulfotransferase

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Introduction

Chemokines are a family of small-molecular-weight chemoattractant cytokines that promote directional migration (chemotaxis) of leukocytes, endothelial, and epithelial cells. To date, more than 50 chemokines have been discovered, which are classified into CXC, CC, XC, or CX3C chemokines based on the positioning of the conserved cysteine residues [1]. As their names suggest, the primary function of chemokines is to orchestrate cell trafficking and, in particular, the movement of pro-inflammatory cells to the site of inflammation. In addition to a role in inflammation, it is now clear that the release of chemokines is involved in quite a wide range of other physiological and pathophysiological processes, including wound healing, angiogenesis, and the development and metastasis of tumors [2].

Chemokine receptors are seven-transmembrane G protein-coupled receptors (GPCRs), all with their N-terminus outside the cell surface, three extracellular and three intracellular loops as well as a C-terminus in the cytoplasm. To date, at least 20 chemokine receptors have been identified. One of the intracellular loops of the chemokine receptors couples with a heterotrimeric G protein, which initiates a cascade of intracellular signaling events [3, 4]. One of the most intriguing and perhaps important roles that chemokines and the chemokine receptors have is in regulating cancer metastasis. We now know that chemokines engage in nearly all aspects of tumor metastasis, from detachment of the tumor cell from the primary site, to 'in-transit' survival and evasion of immune surveillance, and attachment to the target organ and prospering of the tumor in the new environment [5, 6].

CXCR4, a 352-amino acid rhodopsin-like GPCR, is one of the best studied chemokine receptors, primarily due to its role as a co-receptor for HIV entry [7]. Of particular importance to CXCR4 is its ability to influence the survival and proliferation and mediate the metastasis of a variety of cancers. CXCR4 is widely detected in human cancers and is the most widely expressed chemokine receptor in solid malignancies investigated thus far [8, 9]. Pioneering work by Müller and colleagues identified an important role for the SDF-1/CXCR4 axis in metastatic breast cancer by showing that CXCR4 was highly expressed in human breast cancer cells, malignant and metastatic breast tumors and that SDF-1, the natural ligand for CXCR4, was found at very high levels in sites of preferential metastasis for breast cancers. Furthermore, they demonstrated that administration of neutralizing antibodies to CXCR4 significantly reduced metastases of the CXCR4-positive, human breast carcinoma cell line MDA-MB-231 to lung and lymph nodes [10]. In addition, a growing body of evidence now shows that the SDF-1/CXCR4 axis plays a role in the process of angiogenesis, epithelial-to-mesenchymal transition (EMT), and stem cell mobilization [11, 12].

As with other GPCRs, CXCR4 is subject to tightly regulated posttranslational modifications such as phosphorylation, ubiquitination, glycosylation, and sulfation. These posttranslational modifications contribute significantly to the heterogeneity of CXCR4 in terms of intracellular location, signaling, and functioning. Here, we discuss how CXCR4 is processed posttranslationally and how these posttranslational modifications impact the functionality of this chemokine receptor with an emphasis on our recent findings of the role of tyrosine sulfation of CXCR4 in cancer metastasis.

Posttranslational Modifications of CXCR4

1. Dimerization

It has been suggested that CXCR4 has the ability to undergo homodimerization in a ligand-dependent [13] or -independent [14] fashion. Heterodimerization of CXCR4 with other cell surface receptors such as CCR2 [15, 16], CCR5[17], CXCR7 [18], or CD4 [19] has also been reported. The functional consequences of homo- or heterodimerization are currently not well understood but may be of great significance [20]. It has been suggested that homodimerization of CXCR4 is necessary to elicit G protein-independent activation of JAK/STAT as well as enhance the response of CXCR4 to SDF-1. Heterodimerization may be a means of achieving an additional level of regulation of the receptor activity.

2. Phosphorylation and Ubiquitination

Upon ligand activation, CXCR4 is rapidly phosphorylated and internalized. The phosphorylation events of CXCR4 mostly occur on serine residues located at the C-terminus of the receptor. Removing the 45 amino acid C-tail of CXCR4, which contains 15 serine and 3 threonine residues, eliminates agonist-promoted phosphorylation [21] and attenuates receptor internalization [22]. Increased phosphorylation of Ser339 was also observed following treatment with SDF-1, EGF, or phorbol ester [23]. Mutation of Ser339 resulted in reduced SDF-1-promoted phosphorylation of CXCR4 as did truncation of the C-terminal 7 amino acids, which removes 5 serine residues from the tail [24]. These observations suggest that Ser339 may be a major phosphorylation site on CXCR4. Other phosphorylation sites may include Ser324, Ser325, and Ser330 at the C-terminus. Mutation of these serine residues to alanine partially or completely inhibited degradation of CXCR4 with or without affecting receptor internalization [25].

One of the functional consequences of GPCR

Table 1. Posttranslational modifications of CXCR4 and their functional consequences

Type of posttranslational modification	Partners or sites involved	Functional consequences	References
Dimerization	CXCR4, CCR2, CCR5, CXCR7, CD4	Activation of JAK/STAT; Enhanced response to SDF-1	13-19
Phosphorylation	Ser339, Ser324, Ser325, Ser330	Internalization	21-25
Ubiquitination	Lys327, Lys331, Lys333	Degradation	25-27
Glycosylation	Asn11, Asn176	Binding of SDF-1	28-31
Sulfation	Tyr7, Tyr12, Tyr21	Binding of SDF-1; Cancer metastasis	38-42

phosphorylation is receptor internalization. Upon internalization, GPCRs can be recycled back to the plasma membrane or sorted to the lysosome for degradation [26]. CXCR4 has been shown to be ubiquitinated, sorted to the lysosome, and degraded, a process mediated by the E3 ubiquitin ligase AIP4, a member of the Nedd4 family of E3 ubiquitin ligases [27]. Of note, CXCR4 is most likely mono-ubiquitinated on one of three lysine residues (Lys327, Lys331, or Lys333) at the C-terminus. Mutation of these residues to arginine eliminates ubiquitination and degradation of the receptor [25]. Taken together, these observations suggest that phosphorylation of specific residues on CXCR4 may dictate the fate of the receptor following internalization.

3. Glycosylation

There are two potential *N*-linked glycosylation sites, Asn11 and Asn176, within the extracellular domain of CXCR4 [28]. Both sites undergo glycosylation when CXCR4 is expressed in insect cells; however, only Asn11 appears to be glycosylated in mammalian cells [29]. Mutation of Asn11 to glutamine [30] or leucine [31] disrupts SDF-1 binding and diminishes signal transduction. Thus, glycosylation of CXCR4 is important for binding of its cognate ligand.

4. Sulfation

Sulfation is the most abundant posttranslational modification of tyrosine residues in multicellular eukaryotes [32]. Tyrosine sulfation has been shown to be important for protein-protein interactions during the intracellular transport of proteins and upon their secretion. Tyrosine sulfation is mediated by tyrosylprotein sulfotransferases (TPSTs), which reside in the trans-Golgi network [33]. These enzymes catalyze the transfer of sulfate from the universal sulfate donor adenosine 3'-phosphate 5'-phosphosulfate (PAPS) to the phenolic hydroxyl group of a tyrosine residue, resulting in the formation of a tyrosine *O*-sulfate ester and adenosine 3',5'-diphosphate (3',5'-ADP) [34]. In mammals, two highly homologous TPST enzymes, TPST-1 [35] and TPST-2 [36], have been identified. Both TPST isoforms are broadly expressed in human and murine tissues and also co-expressed in the majority of cell types [37]. Due to the cellular localization of the TPST enzymes, tyrosine sulfation can only occur in proteins that transit the trans-Golgi network and, therefore, is limited to secretory or transmembrane proteins.

In the extracellular domain of CXCR4, three potential sulfation sites, i.e., Tyr7, Tyr12, and Tyr21, have been identified. Tyr21 is considered as the main sulfation site on CXCR4, accounting for the majority of sulfate incorporation [38]. The sulfate group at Tyr21 contributes substantially to the ability of CXCR4 to bind its ligand, SDF-1. The structural basis for sulfotyrosine-SDF-1 interaction reveals that sulfotyrosine 21 binds to a specific site on SDF-1 that includes Arg47 [39]. Nevertheless, the mechanisms of TPST-1 activation and the functional consequences of CXCR4 sulfation in cancer remain enigmatic.

The posttranslational modifications of CXCR4 and their functional consequences are summarized in Table 1.

Regulation of CXCR4 Sulfation by LMP1 and its Role in Cancer Metastasis

Previously, we have demonstrated that the expression of functional CXCR4 is associated with the metastatic

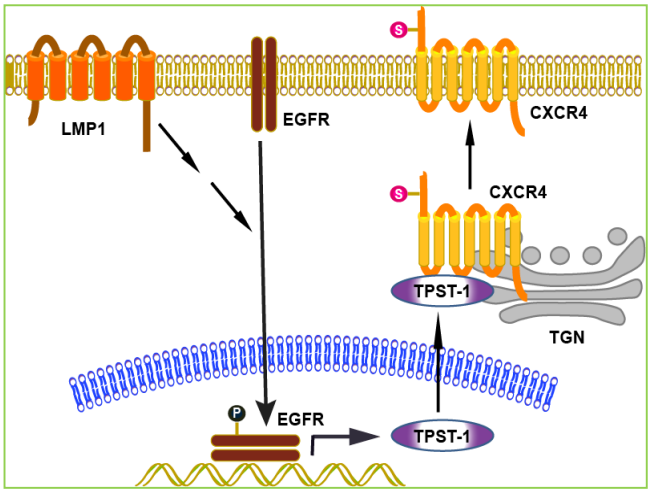

Figure 1. Proposed model for LMP1-induced tyrosine sulfation of CXCR4 in nasopharyngeal carcinoma cells. Epstein-Barr virus-encoded LMP1 induces phosphorylation and nuclear translocation of EGFR [41], which binds the promoter region and induces the expression of TPST-1. Increased TPST-1 expression, in turn, induces tyrosine sulfation of CXCR4 [42]. Sulfation of CXCR4 is assumed to occur in the trans-Golgi network, followed by translocation to and assembly in the plasma membrane. LMP1-induced tyrosine sulfation of CXCR4 is associated with increased cell motility and invasiveness of nasopharyngeal cancer cells. Abbreviations: LMP1, latent membrane protein 1; EGFR, epidermal growth factor receptor; TPST-1, tyrosylprotein sulfotransferase 1; TGN, trans-Golgi network.

potential of nasopharyngeal carcinoma (NPC), a head-and-neck malignancy with a high incidence in Southeast Asian countries [40]. However, how the function of CXCR4 is regulated during NPC carcinogenesis is an unsolved issue. We have shown that the oncoprotein latent membrane protein (LMP1) encoded by Epstein-Barr virus, a DNA virus which is etiologically associated with NPC, induced phosphorylation and nuclear translocation of the epidermal growth factor receptor (EGFR) in cultured NPC cells [41]. Bioinformatic analysis revealed that the TPST-1 gene contains a putative EGFR binding site, TGTTT, in the 5' UTR region. Therefore, it is plausible to speculate that LMP1-induced nuclear translocation of EGFR might regulate the expression of TPST-1, which will influence the sulfation status and function of CXCR4.

Using the labeling and immunoprecipitation technique, we were able to demonstrate that LMP1 could indeed induce tyrosine sulfation of CXCR4, which was associated with increased cell motility and invasiveness in a NPC cell line HNE2. As expected, LMP1 induced the expression of TPST-1 and tyrosine sulfation of CXCR4, which were inhibited by transfection with EGFR siRNA and TPST-1 siRNA, respectively. Next, we used a chromatin immunoprecipitation (ChIP) assay to show that EGFR could bind to the TPST-1 promoter under the control of LMP1. A reporter gene assay further indicated that the activity of the TPST-1 promoter could be suppressed by deleting the binding site between EGFR and TPST-1 [42]. These results highlighted the importance of EGFR and TPST-1 in LMP-1-induced tyrosine sulfation of CXCR4.

Does tyrosine sulfation have an impact on the activity of CXCR4 and does this pose any clinical significance? The answers to these questions have been positive through our studies. Our *in vitro* experiments revealed that although both the highly metastatic NPC cells 5-8F and the non-metastatic cells 6-10B expressed similar levels of CXCR4 mRNA and protein, functional CXCR4 was only found in cells with high metastatic potential, which was correlated with a high level of CXCR4 sulfation as compared with the non-metastatic cells [40]. Furthermore, the tyrosine sulfation level of CXCR4 was positively correlated with the motility and invasiveness of NPC cell lines [42]. In a panel of human NPC patient specimens, immunohistochemical staining revealed that there was a positive correlation between the expression of LMP1 and TPST-1. Significantly, the expression of TPST-1 was positively correlated with the metastatic potential of NPC. Based on these observations on cell culture models and patient samples, we propose that LMP1 regulates tyrosine sulfation of CXCR4 through EGFR-mediated TPST-1 expression, which corresponds with the metastatic potential of NPC tumor cells [42]. The signaling events that account for LMP1-induced sulfation of CXCR4 in NPC cells are summarized in Figure 1.

Concluding Remarks

Our findings provide the first evidence that the posttranslational modification of a chemokine receptor plays a role in the metastatic process of cancer. This represents the first step on the long journey of demonstrating the importance of posttranslational modifications of chemokine receptors in cancer metastasis. For future research on the role of CXCR4 sulfation in cancer metastasis, the following areas will need to be investigated: 1) the exact sulfation site on CXCR4 and the detailed sulfation process; 2) the role of TPST-2 in CXCR4 sulfation; 3) the role of CXCR4 sulfation on cancer metastasis *in vivo*; and 4) the signaling transduction pathways connecting CXCR4 sulfation and the invasive/metastatic phenotype of cancer cells. Understanding the precise mechanisms regulating posttranslational modifications of chemokine receptors and their biological significance may provide new insights for developing attractive therapeutic targets in cancer therapy.

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Conflict of interest

The authors declare that they have no conflict of interest.

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