

# Role of Stat3 in nasopharyngeal carcinoma

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## Abstract

### Introduction

Nasopharyngeal carcinoma is an Epstein-Barr virus-associated head and neck cancer which is most common in eastern Asia. Epstein-Barr virus infection, environmental factors and genetic susceptibility play important roles in nasopharyngeal carcinoma pathogenesis. Correlation of signal transducer and activator of transcription-3 (Stat3) overexpression with poor prognosis for nasopharyngeal carcinoma provides evidence that it is involved in the tumorigenic process. In this review, we highlight recent advances in studies on the oncogenic role of Stat3 in nasopharyngeal carcinoma and its potential as a therapeutic target for this cancer.

### Conclusion

Despite different approaches to identify small molecules that effectively inhibit Stat3 signalling, further studies will be needed to make these molecules more effective for improved clinical outcomes.

### Introduction

Nasopharyngeal carcinoma (NPC) is a head and neck cancer with remarkable ethnic and geographic distribution<sup>1</sup>. This Epstein-Barr virus (EBV)-associated epithelial malignancy is relatively rare in most parts of the world but is a significant disease burden in Southern China, Southeast Asia, Northern Africa and Alaskan Inuits

with an annual incidence of about 20 per 100,000 people in endemic areas<sup>1</sup>. The incidence of NPC is also high in some areas of northern Africa<sup>2</sup>. Every year, 80,000 new cases of NPC are diagnosed worldwide, and 50,000 individuals die of NPC<sup>3</sup>.

Radiotherapy and chemotherapy are currently considered as the main treatment for NPC patients and have improved NPC survival rates<sup>4</sup>. However, the prognosis for metastatic NPC remains poor, even with combined radiotherapy and chemotherapy, with relapse rates as high as 82%<sup>5</sup>. Unfortunately, the majority of NPC cases are diagnosed at an advanced stage because of nonspecific presenting symptoms, delay in seeking treatment after the onset of symptoms, and the difficulty of performing a thorough nasopharyngeal examination. Successfully identifying the pivotal molecular mediators of NPC progression and tumour resistance is therefore critical to improve overall survival of NPC patients<sup>3</sup>.

Emerging evidence suggest a signal transducer and activator of transcription-3 (Stat3) signalling pathway is critically involved in the pathogenesis of NPC<sup>6,7</sup>. Therefore, in this review, we provide an overview of the role of Stat3 in NPC tumorigenesis and summarise recent findings that highlight the novel roles of Stat3 in this process. Furthermore, we summarise approaches to inhibit Stat3 expression and suggest that Stat3 is a promising therapeutic target in combating human NPC.

### Discussion

The author has referenced some of his own studies in this review. The protocols of these studies have been approved by the relevant ethics

committees related to the institution in which they were performed.

### Signal transducer and activator of transcription-3 signalling

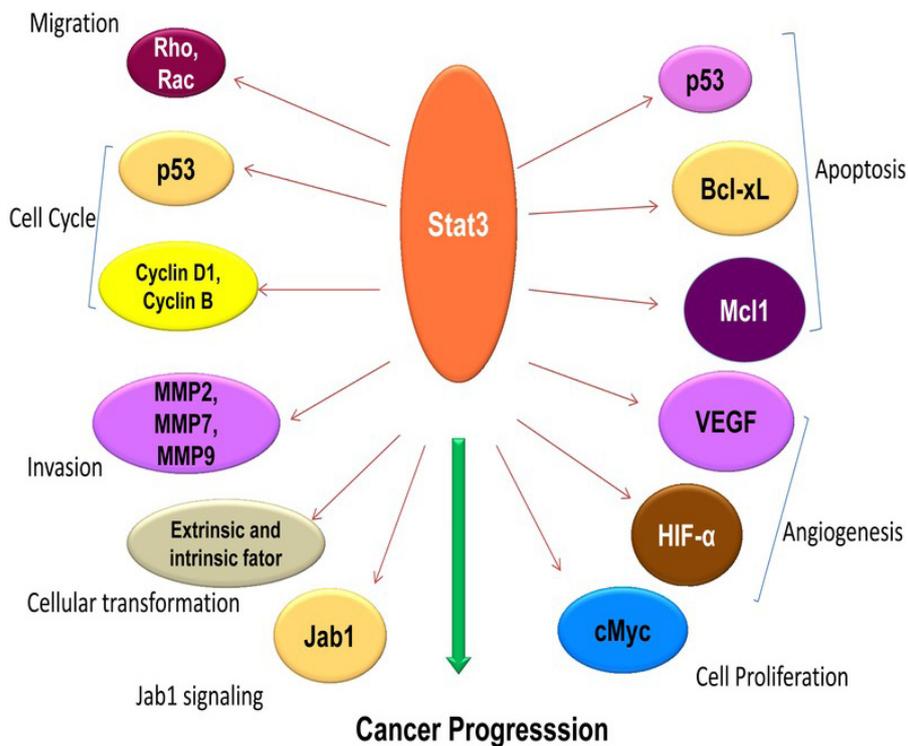
Stat3 is a member of the Stat family of cytoplasmic transcription factors that are activated by many cytokine and growth factor receptors and downstream substrates (e.g. EGFR, c-Met and IL-6)<sup>8,9</sup>. Stat3 is phosphorylated and then forms homodimers or heterodimers with other members of the STAT family. The activated Stat3 complex will then translocate into the nucleus to initiate transcription of Stat3 target genes (Figure 1)<sup>10,11</sup>. A constitutively activated Stat3 can cause transformation of murine fibroblasts and tumour formation in nude mice<sup>8</sup>. Additionally, Stat3 has been shown to be constitutively activated and required for cellular transformation by the viral oncogene, v-Src<sup>12</sup>, whereas blockade of Stat3 signalling by dominant-negative mutants of Stat3 inhibits Src-induced cellular transformation of mouse fibroblasts<sup>12</sup>.

Persistent activation of the JAK2/Stat3 signalling pathway has been documented in a wide range of human cancers and is commonly associated with worse prognoses<sup>13</sup>. Among the tumour-promoting activities ascribed to persistent Stat3 signalling are those involved with cell proliferation, metastasis, angiogenesis, host immune evasion and resistance to apoptosis<sup>14,15</sup>. The role of Stat3 in tumorigenesis has been well established in a wide range of human cancers including multiple myeloma, leukaemia, lymphoma, breast cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer and NPC<sup>7</sup>.

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**Figure 1:** Regulation and targets of Stat3. Stat3, signal transducer and activator of transcription-3; VEGF, vascular endothelial growth factor; MMP, matrix metalloproteinase.

### Role of Stat3 in progression of NPC

A growing body of evidence strongly suggests that Stat3 plays critical roles in head and neck tumourigenesis<sup>13,16</sup>. Emerging evidence has also revealed that Stat3 plays important roles in cell growth, apoptosis, cell death and metastasis in human head and neck cancer cases<sup>17</sup>. However, the molecular mechanism or mechanisms by which Stat3 facilitates NPC progression remain largely elusive. Here, we describe some recent advances in understanding the role of Stat3 in NPC progression. Specifically, in the following sections, we summarise the results of emerging studies of Stat3 as well as its therapeutic implications for NPC.

#### Stat3 activation in NPC

Stat3 activation (phospho-Stat3 expression or nuclear Stat3 expression) or overexpression is observed in more

than 75% of NPC tumours in endemic regions<sup>18</sup>. The study by Buettner et al.<sup>19</sup> showed that in a Germany cohort of 20 NPC tumours, nuclear phospho-Stat3 was detected in 18/19 cases (95%)<sup>19</sup>. In agreement with the clinical evidence, we also examined the Stat3 expression in NPC cells. Immunoblotting showed strong total Stat3 and phosphorylated Stat3 expressions in NPC cells but not in normal keratinocyte cells, where weak Stat3 expression was detected, indicating that Stat3 is overexpressed in NPC<sup>20</sup>.

Further clinical data suggest Stat3 activation may be important for NPC progression as overexpression of activated Stat3 was found to be clinically associated with advanced stages of NPC<sup>18</sup>. This result supports a potential causal role of Stat3 activation in driving NPC progression and metastasis, which agrees with the *in vitro* finding that Stat3 blockade inhibited NPC cell invasion<sup>7</sup>.

#### Stat3 promotes NPC cell growth and invasion

Evidence indicates that constitutive Stat3 signalling upregulates cyclin D1 and cMyc expression which are required for regulation of the G1 phase of the cell cycle<sup>21</sup>, contributing to accelerated cell-cycle progression. Stat3 has also been shown to up-regulate the expression of growth-promoting gene pim-1<sup>22</sup>. Consistent with its role in cellular proliferation, researchers demonstrated that Stat3 signalling provides survival signals and suppresses the apoptosis in cancer cells. These effects are mediated through its target genes such as Bcl-XL, Bcl-2, Mcl1, surviving and c-IAP<sup>23</sup>. In addition, Stat3 negatively regulates the expression of p53, which is the most common inhibitor of cellular proliferation and inducer of apoptosis<sup>24</sup>. In contrast, it was reported that Stat3 can also act as a pro-apoptotic factor, a decrease in apoptosis and a dramatic delay of involution occurred in Stat3 null mammary tissue<sup>25</sup>. Some studies indicated that loss of Stat3 promotes cellular proliferation and transformation in glioblastoma<sup>26</sup>, indicating that Stat3 plays opposing roles in glial transformation depending on the genetic background of the tumour, providing the rationale for tailored therapeutic intervention in cancers. However, transient overexpression of Stat3 in NPC cells HONE-1 was able to enhance cell proliferation and invasion, whereas specific inhibition of Stat3 by siRNA inhibited NPC cell growth and invasion<sup>7</sup>. Similarly, Stat3 inhibitors, such as Cucurbitacin I and Stattic, were able to inhibit cell growth and invasion and induce apoptosis in NPC cells *in vitro*<sup>20,27</sup>, whereas *in vivo* study showed that Cucurbitacin I treatment can inhibit the growth of NPC xenografts *in vivo*. These findings establish the role of Stat3 in NPC cell growth, invasion and tumour formation.

### *Stat3 involved in NPC metastases*

Invasion to extracellular matrix is one of the important steps in tumour growth and metastasis formation. Several studies strongly implicate that Stat3 plays a critical role in this complex multistep process by regulating the matrix metalloproteinases (MMPs). In cutaneous squamous cell carcinoma, overexpression of phosphorylated Stat3 correlated with increased invasion, and metastasis<sup>28</sup>. In contrast, inhibition of Stat3 blocks tumour growth, invasion and metastasis formation in a variety of cell lines both *in vitro* and *in vivo*<sup>29</sup>. Furthermore, Stat3 knockdown using shRNA reduced pancreatic cancer cell invasiveness and MMP-7 expression in nude mice<sup>30</sup>. Constitutively activated Stat3 protein in melanoma could directly bind to the promoter of the MMP-1, MMP-2 and MMP-9 genes, promoting their expression<sup>31,32</sup>.

Stat3 also plays a role in NPC metastases since Stat3 activation was found to be associated with the advanced diseases (stage III and stage IV)<sup>18</sup>. This is also supported by a study by Guang-Wu et al.<sup>33</sup> that vascular endothelial growth factor (VEGF) expression (a target gene of Stat3) is correlated with metastatic NPC. In their studies, the percentage of positive expression of VEGF in NPC tissue was higher than those in benign tumour tissue and nasopharyngeal tissue without tumour, and NPC tissue with distant metastasis showed a higher percentage of positive expression of VEGF than that with local lymphatic metastasis. These data indicated VEGF is involved in NPC metastasis, which could potentially be mediated by Stat3 activation in NPC. All these data show that Stat3 actively promotes cellular invasion.

### *Stat3 and NPC microenvironment*

Tumour cells often adapt to and modify their surrounding microenvironment. It was reported that tumour

cells having constitutively active Stat3 signalling recruit immune cells and subvert their function for self-benefit<sup>34</sup>. Several studies indicated that inhibition of Stat3 activation promotes the release of pro-inflammatory cytokines, whereas a mutant having constitutively active Stat3 in fibroblasts suppressed the lipopolysaccharide-induced pro-inflammatory response<sup>35</sup>. This suggests that Stat3 activation negatively regulates the activity of immune stimulating molecules. Reports suggested that the tumour cells lacking Stat3 activation could efficiently produce the pro-inflammatory factors that promote the maturation and antigen presenting ability of dendritic cells. Additionally, stromal cells, in response to surrounding tumour cell secretions, upregulate their SDF-1/CXCL12 receptors which results in infiltration of endothelial progenitor cells that enhance metastatic spread of tumour cells<sup>34</sup>. Thus, all these indicate the fact that Stat3 mediates a bidirectional communication with immune cells.

The inflammatory nature of NPC seems to suggest the potential involvement of inflammation in carcinogenesis. Stat3 is recently reported to be involved in the modulation of inflammatory responses in cancer by regulating the release of inflammatory cytokines<sup>15</sup>. Additionally, Stat3 signalling in tumour cells can also affect the adaptive immune response by promoting tumour cell production of factors such as VEGF and IL-10, which negatively affect functional maturation of dendritic cells<sup>15</sup>. Although the role of EBV-induced Stat3 activation in immune regulation in NPC patients remains to be elucidated, it is plausible that it is involved in protecting NPC cells from immune responses and thereby promoting NPC tumourigenesis.

### *Stat3 and Epstein–Barr virus infection in NPC*

As described above, EBV infection is the most distinct aetiologic feature

of NPC. It has been postulated that EBV plays a critical role in transforming nasopharyngeal epithelial cells into invasive cancer<sup>1</sup>. Cumulative evidences strongly indicate that Stat3 activation is linked to EBV infection. Recent studies provided direct evidences that introduction of the EBV genome into NPC cells or nasopharyngeal epithelial cells can induce Stat3 activation<sup>7</sup>, which is associated with an increase in cellular invasiveness<sup>27</sup>. Phosphorylated Stat3 has been detected in an EBV-converted HeLa cell line and CNE2-LMP1<sup>36</sup>, a stable LMP1-infected cell line derived from CNE-2 cells. In both of these EBV-associated cell lines, the p-Stat3 levels were elevated when compared with the respective parental cell lines without EBV or LMP1, indicating that Stat3 activation can be directly driven by EBV infection or LMP1 expression. In agreement with these findings, ectopic expression of LMP1 in NPC cell lines can markedly increase the level of activated Stat3<sup>27</sup>. Altogether, these findings agree with previous findings in B cells that this EBV oncoprotein, LMP1 is critical for EBV-mediated transformation of B cells<sup>37</sup>. Kung et al.<sup>38</sup> also demonstrated that LMP1 activates multiple signalling pathways including Stat3. This LMP1-mediated Stat3 activation is recently confirmed in a transgenic mouse model with specific epithelial expression of LMP1, in which activation of Stat3 was observed<sup>39</sup>. Although the direct roles of LMP proteins in NPC tumourigenesis remain to be biologically defined, transgenic mouse studies in papilloma and squamous cell carcinoma demonstrate that LMP1 and LMP2 double transgenic mice showed increased incidence of squamous cell carcinomas accompanied by the high levels of Stat3 activation<sup>40</sup>. In addition to LMP1, the EBV-encoded latency protein, the Epstein–Barr nuclear antigen 2 (EBNA2), has also been shown to interact with Stat3 and enhances

the transcriptional activity of Stat3 by enhancing its DNA-binding activity. Moreover, EBNA2 cooperatively acts on Stat3 activation with LMP1 by augmenting LMP1-induced Stat3 activation<sup>41</sup>. Therefore, EBV infection and EBV proteins can activate Stat3. The recent finding that specific knockdown of Stat3 by siRNA can inhibit the expression of EBV genes LMP1 and LMP2B in NPC cells<sup>7</sup> does imply that Stat3 may alter EBV infection or latency.

#### *Stat3 inhibition as a novel therapeutic strategy against NPC*

Emerging evidence strongly suggests that Stat3 plays a role in the pathogenesis of several tumours<sup>42</sup>. Patients with Stat3 overexpression had poorer overall survival, and patients with lymph node metastasis and Stat3 overexpression had poorer disease-free and overall survival rates<sup>43</sup>. Recent studies have also shown that depletion of Stat3 inhibits the growth of cancer cells. For example, inhibition of Stat3 inhibited proliferation and induced apoptosis in several cancer cells<sup>42</sup> and, in our research, NPC cells<sup>20</sup>.

Given the prominent antineoplastic potential of Stat3, the development of specific, effective and safe Stat3 inhibitors is likely to have a significant impact on cancer treatment<sup>44</sup>. Cucurbitacin I, a selective inhibitor of JAK/Stat3, can reduce the NPC cell *in vitro* clonogenicity and *in vivo* NPC tumour growth<sup>27</sup>. Our recent studies also demonstrated that Stat3 inhibitor, Stattic, exhibits potent antitumour activity and induces chemosensitivity and radiosensitivity in NPC<sup>20</sup>. Inhibiting the Stat3 signalling pathway may be an effective strategy in the treatment of NPC.

#### **Conclusion**

We have provided succinct information on the state of knowledge of the role of oncoprotein Stat3 in NPC. Stat3 is a novel target for the prevention and treatment of human cancers.

Therefore, the development of agents specifically targeting Stat3 inhibition is likely to have a significant impact on cancer treatment. Despite different approaches to identify small molecules that effectively inhibit Stat3 signalling, further studies will be needed to make these molecules more effective for improved clinical outcomes.

#### **Abbreviations list**

EBV, Epstein-Barr virus; MMP, matrix metalloproteinase; NPC, nasopharyngeal carcinoma, VEGF; vascular endothelial growth factor.

#### **Acknowledgements**

YP was supported by the fellowship from China Scholarship Council (No. 2010638087), the fund from the National Natural Science Foundation of China (No. 81372816), the University Cancer Foundation via the Sister Institution Network Fund at the University of Texas MD Anderson Cancer Center and the Project funded by China Postdoctoral Science Foundation (2014M550449).

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