International Journal of Surgery 72 (2019) 214–215

Contents lists available at ScienceDirect

International Journal of Surgery

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

Invited Commentary

A Commentary on “Clinico-pathological and prognostic significance of CXCR4 high expression in renal cell carcinoma: A meta-analysis and literature review” (Int J Surg 2019; 71:12–18)

ARTICLE INFO

Keywords:
CXCR4
Renal cell carcinoma
Significance
Meta-analysis

The expression of CXCR4, a G-protein coupled chemokine receptor encoded on chromosome 2, is either low or absent in several healthy tissues [1].

High expression of CXCR4 has been documented across a diverse range of human tumours including melanoma, ovarian cancer, triple negative breast carcinoma, clear-cell renal cell carcinoma, Non small cell lung cancer, prostatic adenocarcinoma, neuroblastoma, gastric carcinoma, colorectal carcinoma and pancreatic ductal adenocarcinomas [2,3].

Binding of CXCR4 to its ligand CXCL12 promotes gene transcription, cell adhesion and cell survival, angiogenesis, interaction between tumour cells and their microenvironment, invasion and proliferation. This axis also contributes to metastatic potential as CXCL12 expression is highest in common metastatic sites such as liver, lung, brain [3].

In a comprehensive meta-analysis of CXCR4 in renal cell carcinoma (RCC) done by Si et al. [4], 14 eligible studies from 2002 to 2014 were included which contained data from 1203 patients. This meta-analysis showed higher CXCR4 expression in RCC than in the normal renal tissue with $p < 0.0001$. Nuclear localization of CXCR4 promotes nuclear accumulation of Hypoxia-Inducible-Factor-1α (HIF-1α) and RCC tumourigenicity by forming a feed-forward loop. Aberrant expression of CXCR4 was found to be higher in higher Fuhrman grades than lower grades and in patients with metastatic RCC vs non-metastatic RCC. This could suggest a role for CXCR4 and HIF-1α in the promotion of invasiveness, metastasis and prognostic outcomes.

In a study of 225 patients with clear cell RCC by An et al. [5], CXCR4 staining intensity was found to correlate positively with disease progression from TNM stages I to IV and indicated reduced overall survival and a poor outcome. This study had its limitations owing to a small sample size [5].

Si et al. [4] further concluded that CXCR4 expression was associated with increased risk, pathological grades, metastatic status, prognosis and overall survival and its expression was not found to be associated with gender or clinical stage.

The study by Si et al. [4] is significant with respect to the expression of CXCR4 in RCC and its variants as it has analysed a large cohort of patients and has used CXCR4 expression as a predictor of grade, stage and patient outcomes. The limitations of the meta-analysis were discussed in detail and issues of varied immunohistochemical staining pattern, statistical heterogeneity and publication bias were addressed. Nine out of fourteen studies included in the meta-analysis were from Asia (China) which could have led to selection bias and skewed data. Si et al. [4] concluded that CXCR4 expression is correlated with the risk of RCC development and that it could be a potential biomarker of prognosis. CXCR4 was also suggested to be a potential therapeutic target for personalized cancer therapy [4].

In conclusion, more studies are needed to provide insight into the role of CXCR4 in patients with RCC and its variants. Relation of CXCR4 to patient risk stratification, staging, syndromic associations and personalized treatment options remains to be determined.

Provenance and peer review

Invited Commentary, internally reviewed.

Funding source

None declared.

Declaration of competing interest

None declared.

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DOI of original article: https://doi.org/10.1016/j.ijsu.2019.08.021

https://doi.org/10.1016/j.ijsu.2019.10.053
Received 25 October 2019; Accepted 31 October 2019

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