Review of: "[Review] Investigating the Role of Urokinase in Cancer Metastasis: A Review"

Lifang Zhang[1]

1 Case Western Reserve University

Potential competing interests: No potential competing interests to declare.

Comments for the review article:

This is an excellent report and very thorough summary on the role of Urokinase in cancer metastasis. It demonstrates the current state of understanding of this topic, as about 60% of its citations are to articles published within 10 years and 30% to reports from the last 5 years. It provides sufficient knowledge to the audience interested in this subject, and gives deeper understanding of how cancer cells interact with and manipulates the surroundings to promote spread of disease.

This review article has an overall very good structure on describing the impact of Urokinase on different aspects of cancer metastasis, and incorporated sufficient research findings from published articles to demonstrate the function of Urokinase. First, it briefly introduced the scientific finding that Urokinase levels were elevated in many types of cancers and the overexpression might associate with a worse prognosis and higher metastasis. These facts led to the hypothesis that Urokinase plays an important role in cancer metastasis. Immediately afterwards, the author showed the audience an overall image of the impact of Urokinase on different aspects of cancer metastasis. Urokinase, based on its protease activity, promotes cancer metastasis through the regulations of extracellular matrix protein degradation, cancer cell invasion and migration, cancer cell proliferation and survival, and cancer cell stemness and chemo-resistance. Then it was followed by evidence-based and detailed statements of Urokinase functions in different aspects of cancer metastasis. Naturally led to the demonstration of researches on Urokinase inhibitors as a possible therapeutic for treating cancer metastasis. Finally gave a conclusion that targeting the Urokinase system via inhibitors, antibodies, gene therapy and other strategies, may be a promising approach for preventing and treating cancer metastasis.

It is a well-organized review, but still there are some areas for improvement:

There are repeated paragraphs in the article. For example: The second half of the second paragraph under the title **Role of uPA in Cancer Cell Proliferation and Survival** is the same with the first paragraph under the same title. These two parts can be combined into one.

The second half of the second paragraph under the title **Role of uPA in Cancer Cell Proliferation and Survival**:

"*Through its capacity to control the activities of cell cycle regulators like cyclin D1 and **c-Myc**, uPA also encourages the proliferation and survival of cancer cells. Key proteins involved in controlling the cell cycle, cyclin D1 and c-Myc, have been discovered to be overexpressed in a variety of cancers. Studies have demonstrated that uPA can boost the expression of cyclin D1 and c-Myc, which promotes cancer cell survival and proliferation. For instance, a research by*

Hamurcu et al., 2018 [86] discovered that cyclin D1 may be upregulated by uPA in breast cancer cells, increasing cancer cell survival and proliferation. Moreover, it has been discovered that uPA increases the growth and survival of cancer cells through regulating the activity of apoptotic regulators such Bcl-2 and Bax. Key apoptosis-regulating proteins Bcl-2 and ***Bax*** *have been discovered to be changed in a variety of cancers. The activity of Bcl-2 and Bax can be modulated by uPA, according to studies, which increases cancer cell proliferation and survival and decreases cancer cell death. For instance, a research by Ye et al., 2012 [87] found that uPA can increase the proliferation and survival of cancer cells by downregulating Bax and upregulating Bcl-2 in ovarian cancer cells*."

The first paragraph under the title **Role of uPA in Cancer Cell Proliferation and Survival** "*One way that uPA encourages cancer cell survival and proliferation is through controlling the activity of proteins connected to the cell cycle, such Cyclin D1 and* ***CDK4****. Proteins called Cyclin D1 and CDK4 that are essential for controlling the cell cycle have been discovered to be overexpressed in a variety of cancers. According to studies, uPA can stimulate Cyclin D1 and CDK4 activity, which boosts the growth of cancer cells. For instance, Lee et al,. 2016 [79] discovered that uPA can upregulate Cyclin D1 in breast cancer cells, increasing the proliferation of cancer cells. Similar to this, Jiang et al., 2008 [80] discovered that uPA can upregulate CDK4 in lung cancer cells, which increases the proliferation of cancer cells. The activity of anti-apoptotic proteins like Bcl-2 and* ***Bcl-xL*** *is regulated by uPA, which is another way it encourages cancer cell survival and growth. The proteins Bcl-2 and Bcl-xL, which are essential for controlling cell survival, have been discovered to be overexpressed in a variety of cancers. According to studies, uPA can boost the activity of Bcl-2 and Bcl- xL, which increases the survival of cancer cells. For instance, according to a research by Schuyer et al., 2001 [81] uPA can increase Bcl-2 in ovarian cancer cells and aid in the survival of cancer cells*."

The proteins c-Myc and Bax in second paragraph and CDK4 and Bcl-xL in first paragraph, are the only things that differ between these two parts. The citations are different but the contents are the same.