

## The CCL5 in Breast Cancer is Platelet CCL5- A Hypothesis

**Pushpam Kumar Sinha\***

*Independent Researcher, 101, Vijayshree Complex, Kankarbagh Main Road, Kankarbagh, Patna- 800020, India*

**\*Corresponding Author:** Pushpam Kumar Sinha, Independent Researcher, 101, Vijayshree Complex, Kankarbagh Main Road, Kankarbagh, Patna- 800020, India.

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### Abstract

CCL2 and CCL5 are the two chemokines plentifully expressed in Breast Cancer (BC). Close associations between CCL2 and CCL5 have been hypothesized; and both have been demonstrated to confer metastatic potential to the BC cells. Hence understanding the biology of either will shed light on the other. And in this paper I choose to investigate the source of CCL5 (in BC cells). Pin-pointing the source of CCL5 will lead to focused therapeutic intervention against BC metastasis. Through the analysis of connections between CCL5 and Interleukin 8 (IL8), I hypothesize that the CCL5 in BC is platelet CCL5. As a result of this hypothesis Aspirin seems to be the focused drug against BC metastasis. But there are challenges with using this drug in BC patient who is also simultaneously not suffering from any cardiovascular disorder.

**Keywords:** Chemokines; Milieu of Tumor Cells; Monocytes; Macrophages; Platelet suspension

### Introduction

Out of a plethora of mechanisms and or molecules that can be held responsible for the movement of monocytes from peripheral blood to the primary site of solid tumor, CCL2 and CCL5 are the chemokines that definitely play this role in tumor biology [5]. Both CCL2 and CCL5 are plentifully expressed in Breast Cancer (BC) both in the tumor cells and the other cells in the Milieu of Tumor Cells (MTCs) where as in healthy breast they are expressed in limited amount [6]. This differential expression of CCL2 and CCL5 between the tumor state and the non-tumor state of breast points out to the possibility of these molecules being involved in tumor development. Post localization of monocytes to tumor cells, the monocytes differentiate into sub-populations of differentially polarized macrophages the most important of which is Tumor-Associated Macrophages (TAMs). TAMs also themselves produce CCL2 and CCL5 [5], and (TAMs) are the most important players governing metastasis in its several stages [7]. CCL2 and CCL5 may also be bound in loop [6]; hence out of the two I focus in this paper on CCL5. You will find abundant literature stating the expression of CCL5 in tumor cells and MTCs, but hardly any literature that talks about the source of CCL5 (or any other pro tumor biology chemokine/cytokine for that matter) in tumor. In this paper I seek the source of CCL5 in BC from a very important result published in the paper [2].

Hence, in conclusion CCL5 is the main chemokine that populates the tumor cells and the MTCs with TAMs. In addition to indirectly promoting metastasis (through TAMs), CCL5 also promotes metastasis directly by influencing the architecture of extra cellular matrix [5]. So an ideal preventive therapeutic against metastasis would be the one that targets CCL5. With this goal in mind for Breast Cancer metastasis, I venture out in this paper to find answer to the question, "Where do CCL5 (in BC) comes from ?", so that I prevent the source of CCL5 itself from producing CCL5. The significance of this work is clear in the last section "Discussion" when I am able to suggest a certain possible preventive therapeutic against Breast Cancer metastasis, and the challenges involved. The method used in

this paper is literature review of a handful of papers on Breast Cancer/Breast Cancer Metastasis/Metastasis [1-7].

### ***CCL5 and IL8***

The link between CCL5 secretion (in MTCs) and Interleukin-8 (IL8) expression (by monocytes in peripheral blood) has been established with the former causing the latter [5]. Contrastingly it has been shown in [2] that in BC Akt and IL8 are components of the same Akt signaling pathway (ASP) with the latter somewhere downstream of Akt. This led me to question myself, "Is there any connection between CCL5 and ASP?" I searched literature and found [1]. In [1] the drug Cordycepin down-regulated CCL5 in Ovarian Cancer Cells which prevented the activation of ASP and thereby caused the subsequent down-regulation of Nuclear Factor-kappa B transcription factors. This result was specifically for Ovarian Cancer Cells, but even otherwise the paper [1] states that CCL5 is one of the molecules that influence ASP positively. I assume here that the same relation between CCL5 and ASP holds for BC. Thus CCL5 and IL8 may also be tied together through ASP apart from several other possible signaling mechanisms operating inside cells.

### ***Source of CCL5 in BC***

Platelet has neither nucleus nor genes, but it is a storehouse of hundreds of biologically relevant molecules. One of the molecules contained in platelets is CCL5 [4] which is so important for metastasis [5]. In [2] platelets were first isolated from human subjects and treated with aspirin in-vitro, which thereafter were used as suspensions for certain cultured breast cancer cell lines. This experiment demonstrates clearly that aspirin blocks the release of several molecules from platelets which deactivates ASP leading to the diminished expression of IL8 from breast cancer cells. The breast cancer cells with reduced expression of IL8 showed the loss of invasive capability. Invasion is the first step in multi-step metastatic process [3]. If the source of CCL5 known to be highly expressed in BC is other than the platelets, the experiment in [2] in light of the knowledge disseminated in section "CCL5 and IL8" would not have led to the impairment of invasive capability of breast cancer cells because the diminished expression of IL8 would have been rescued by the non-platelet CCL5 through ASP. Hence it is suggested that the CCL5 in BC is platelet CCL5.

### **Discussion**

How does one prove the above hypothesis? Use the same experimental platform as that in [2], and while suspending the breast cancer cell lines in aspirin-treated platelets mix the molecule CCL5 from outside in this platelet suspension. If this variation of experiment outlined in [2] proves my assumption that the CCL5 influences ASP positively in BC, the above hypothesis is proved.

What is the therapeutic implication of this work? CCL5 seems to be a good target to prevent metastasis in BC. From what has been discussed so far in this paper, Aspirin seems to be a good treatment strategy for BC. But there are problems even with this. The experiment in [2] was not on human subjects, but the platelets of the human subjects were treated with aspirin in-vitro. This restricted aspirin to only those platelets that are going to come in contact with breast cancer cells. But if you administer aspirin orally to a BC patient, how will you ensure that the deactivation of only those platelets happen that are engaged in cross-talk with cancer cells? This is a challenge. Aspirin in a BC patient will affect all the platelets in circulation in the patient blood, and hence even the platelets involved in healthy response, like for example in wound repair at the site of wound, would be affected. It would not be advisable to administer aspirin orally to the BC patient to treat BC alone unless the BC patient also suffers from cardiovascular disorders. Being a patient also of the cardiovascular disorders will be a boon in disguise for the BC patients. Aspirin has long been known to be the drug of choice against cardiovascular disorders [2].

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