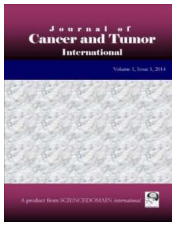

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Could Monocytes Colonized by Circulating Epithelial Cells of the Prostate Gland be a Source of Metastasis of the Adenocarcinoma? A Hypothesis Based on a Previous Study

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Authors' contributions

This work was carried out in collaboration between all authors. Author MN designed the study and wrote the first draft of the manuscript. Author AHL contributed towards image selection and general critiquing of the manuscript. Author LM reviewed and made significant contribution to the manuscript quality. All authors read and approved the final manuscript.

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ABSTRACT

Background: Recently we reported the successful in vitro cultivation of prostatic epithelial and stromal cells from patients with benign prostatic hyperplasia and adenocarcinoma of the prostate by liquid biopsy. In that study we noticed monocytes that were colonized by prostatic epithelial cells; this was confirmed using a monoclonal antibody to prostate epithelial cells. We also detected a deleterious effect exerted on the monocyte cytoplasm by a process yet to be determined.
Aim: To develop a hypothesis that will explain the significance of monocytes colonized by prostatic epithelial cells in the pathogenesis of prostate adenocarcinoma.
Study Design: Retrospective analysis of images in the previous study.
Place and Duration: Kilimanjaro Christian Medical University College, Tumaini University, Moshi, Tanzania. One month.

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Results: We found that all monocytes viewed, without exception, contained intra-cytoplasmic prostatic epithelial cells and most of them presented with apparent cytopathology. The cytopathology presented as strand formation and shrinkage of monocytes. Often the loss of integrity of monocyte cytoplasm could be arbitrarily graded as little to complete loss of cytoplasm.
Conclusion: We hypothesize that epithelial cells invade monocytes and colonize the cytoplasm. Monocytes colonized by epithelial cells then participate in the metastatic process of the prostate adenocarcinoma to different parts of the body. We report for the first time, a monocyte colonized by an epithelial cell of the prostate gland. This could also be an unrecognized phenomenon with other types of cancers.

Keywords: Prostate epithelial cells; monocytes; metastasis; colonization.

1. INTRODUCTION

Macrophages are phagocytic cells that arise from the bone marrow promonocytes, which later differentiate into blood monocytes. When blood monocytes gain entry into tissues they settle and become macrophages. Phagocytic cells phagocytose foreign particulate matter which they may destroy through chemical processes including reactive oxygen or nitrogen intermediates. Monocytes infected by bacteria e.g. Mycobacterium tuberculosis, viruses, e.g. human immunodeficiency virus (HIV) and rickettsia e.g. Anaplasma (Ehrlichia) phagocytophilum are killed by the respective pathogens. Monocytes can also be involved in adaptive immunity by presenting pathogen peptides to antigen presenting cells, which result in the formation of antibodies and cytokines responsible for pathogen elimination. It is an immunological principle that monocytes, neutrophils and eosinophils ingest only foreign material or self material that has been modified enough to be recognized as foreign [1,2,3].

Macrophages can degrade the extracellular matrix upon which cancer cells are placed there by letting them loose to wander and migrate. Additionally, tumor-associated macrophages provide growth factors to cancer cells for their growth and division. The trade off is that cancer cells produce colony stimulating factor which stimulates the growth of the tumor associated macrophages [4].

2. MATERIALS AND METHODS

2.1 Retrospective Examination of Images in the Previous Study

2.1.1 Ethical consideration

This hypothesis is a development from a previous ethically approved study [2]. We studied a total of 20 monocyte culture images from 34 patients afflicted with benign prostatic hyperplasia (BPH) and adenocarcinoma of the prostate (ACP). We chose the 3 most representative images that were clear enough to postulate our hypothesis in a publication. The images were stained by Giemsa stain, H&E stain and anti-androgen receptor monoclonal antibody. The following criteria were used for selection of the images: morphology included presence of nucleus, cytoplasm integrity and presence of prostatic epithelial cells. Control images were monocytes cultured from young men who had no history of benign prostatic hyperplasia or adenocarcinoma.

3. RESULTS

Fig. 1 giemsa-stained 30-day old monocyte culture of a 22 year old participant. Note absence of intra-cytoplasmic epithelial cells in the monocyte cytoplasm. C=cytoplasm, arrows =nuclei; original magnification 40X.

Fig. 2 represents a 13-day old monocyte culture of an 80-year old patient exhibiting moderately differentiated adenocarcinoma, Gleason grade 10 and a plasma total PSA of 8.4ng/ml. Each of the 8 monocytes is overwhelmed by the presence of intra-cytoplasmic epithelial cells appearing as dots in the image. Prostate epithelial cells in monocytes were detected using a monoclonal antibody to androgen receptor (see reference 2). C = cytoplasm, arrows = nucleus. Original magnification 40X.

Fig. 3 shows 4 arbitrarily staged monocytes from a patient aged 70 years presenting with a moderate to poorly differentiated adenocarcinoma, Gleason grade 9. Each monocyte contains many epithelial cells in the cytoplasm. Cell 1 is an invaded monocyte containing epithelial cells in the cytoplasm and strand formation. In cell 2 there are fewer

epithelial cells than in cell 1 with loss of cytoplasm and more progressive strand formation. Cell 3 is a monocyte which also contains epithelial cells and shows more progressive strand formation. Cell 4 shows a monocyte with more advanced cytopathology but weaker staining of cytoplasm and epithelial cells than the previous three. Original magnification 40X.

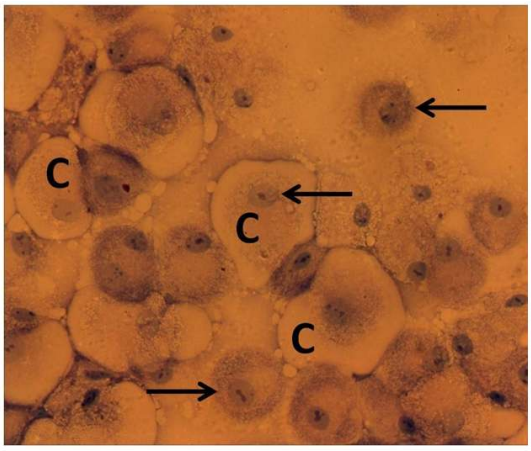

Fig. 1. Giemsa-stained 30-day old monocyte culture of a 22- year old participant. Original magnification 40X

4. DISCUSSION

The adoption of a monocyte cell culture technique to grow prostatic epithelial cells derived from plasma of patients with benign prostatic hyperplasia and adenocarcinoma has been described [1,2]. The technique takes advantage of the property of monocytes to stretch out their cytoplasm when grown in culture on glass or plastic vessels (Fig. 1). When this happens, it becomes possible to detect microorganisms located in the cytoplasm after appropriate staining under light microscopy.

It has been established that the main function of monocytes is the uptake of foreign particulate organisms derived from exogenous sources e.g. bacteria or protozoa [3]. Cells that are specialized for this function are macrophages (in tissue) monocytes, neutrophils and eosinophils (in blood) [4]. Therefore, macrophages and monocytes recognize, engulf and internalize foreign exogenous organisms in their cytoplasm and where successful, destroy such invaders by different methods including use of oxygen or nitrogen intermediates [3,4,5].

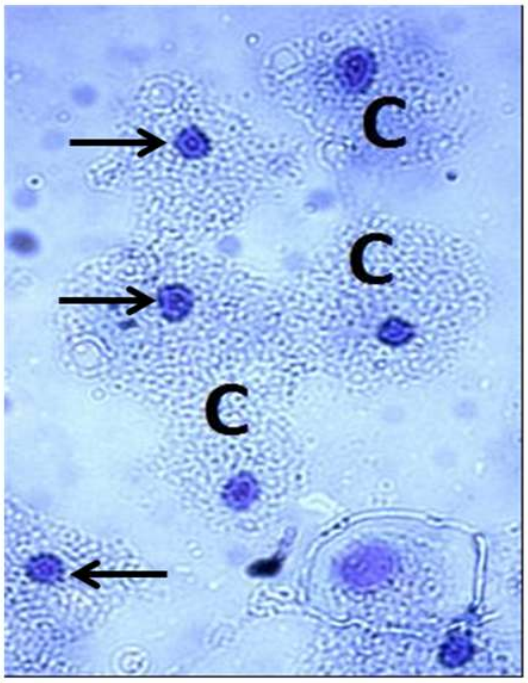

Fig. 2. Represents a 13-day old monocyte culture of an 80-year old patient exhibiting moderately differentiated adenocarcinoma. Original magnification 40X

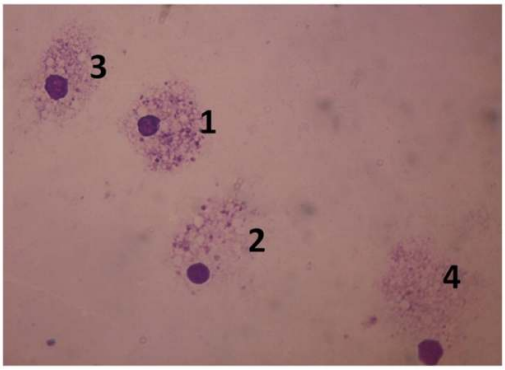

Fig. 3. Monocytes from a patient aged 70 years presenting with a moderate to poorly differentiated adenocarcinoma. Original magnification 40X

Regarding monocytes as macrophage cells of the immune system, two authors will be considered. First, the concern whether tumor cells are recognized as foreign and the body would therefore mount an immune response in an attempt to eliminate the cancer much depends on the type of monocyte present at the site of the cancer. In this regard cancer has been discussed as an inflammatory process [6]. It was

pointed out that the body may react differently to cancer depending on the type of monocyte that gets associated with the cancer. First, M1 macrophages can have a direct cytotoxicity on tumor cells whereas M2 macrophages can promote growth of tumor cells. Second, a question about where macrophages are found on the tumor and what functions they promote in the invasion. Some authors equate macrophages to 'traitor cells' because they are attracted to the tumor where they facilitate cancer cells to migrate out of the tumor, invade blood or lymph and therefore promote invasion. In addition, macrophages also provide growth factors to cancer cells for growth and division. The trade off is that cancer cells provide monocytes with colony stimulating factors for their growth [7]. Therefore the association between cancer cells and monocytes is mutually beneficial, to the detriment of the host. Finally, studies in the mouse inflammatory monocytes show that they may contribute to tumor development [8].

The emerging roles of chemokines has been discussed [9]. It was pointed out that chemokines are produced by the primary tumor cells as well as the site where the cancer has established metastasis. Chemokines are also produced by the stromal microenvironment of the primary tumor site. Monocyte chemo-attractant protein 2 (CCL2), a CC chemokine, is expressed in cells such as macrophages, endothelial cells and smooth muscles. It attracts monocytes to sites of inflammation [10]. Bone marrow endothelial cells have been shown to produce CCL2. Fractalkine, is a CX3C chemokine present in the bone marrow in adult human beings [11]. It promotes adhesion of human epithelial prostate cancer cells to the bone marrow and facilitates their migration toward human osteoclasts. CX3CR1, a receptor for fractalkine, is expressed on epithelial cells. Fractalkine could be an important chemokine responsible for migration of circulating prostate cancer cells to the bone.

The role of monocyte - lineage cells in prostate cancer cell invasion and tissue factor expression has been elucidated through a tissue factor (TF) which is a glycoprotein related to coagulation and inflammation [12]. In a co-culture study utilizing different cell lines and human peripheral blood monocytes it was demonstrated that there was a significant prostate cancer invasion. A significant TF expression was noted in highly invasive prostate cancer cells.

Bone is considered a common site for prostate cancer metastasis [13] Osteoblasts and osteoclasts are specialized cells derived from the monocyte/macrophage hematopoietic lineage which function in bone formation and resorption, respectively [13,14,15]. Metastasis of prostate cancer to the bone is a common finding and osteoblast and osteoclast activation assumes a pathological propensity in prostate cancer. Because of the common lineage between monocytes, osteoblasts and osteoclasts, it is tempting to speculate that osteoblasts and osteoclasts could also be invaded and colonized by prostatic epithelial cells and together with monocytes invaded and colonized by prostatic cells make the metastatic spread of the prostate cancer a formidable phenomenon as discussed by Cook et al. [16].

5. CONCLUSION

The analysis of images used in a previous study revealed important findings: First, all the monocytes presented in the study were colonized by prostatic epithelial cells. Second, there was apparent cytopathology of all the monocytes invaded by prostatic epithelial cells. We were able to arbitrarily grade the cytopathology as to degree of loss of cytoplasm, cell size and apparent cell death in Fig. 3. Third, literature search revealed that cancer is an inflammatory process and that some monocytes can promote cancer growth while others cause death of the cancer cells. We further postulate on the mechanism of these events. Fourth, monocytes may be important cells for the metastasis of cells of prostate adenocarcinoma from the tumor to blood. Fifth, what was revealing and exciting, and probably the most important finding in this study, is that it has shown for the first time that prostate epithelial cells or cancer cells invade, colonize and kill other cells. The mode of metastasis of prostate cancer cells is not known. From our discussion above we hypothesize that monocytes invaded and colonized by prostatic epithelial cells have a role in prostate cancer metastasis especially to bone. Interestingly as shown in Fig. 2 the cytoplasm of each of the 8 monocytes is overwhelmed by prostatic epithelial cell invasion. If these monocytes reach the bone they may form prostatic epithelial metastatic niches.

CONSENT

This hypothesis was developed after the earlier publication (Ref. 2) as per the Belmont report (1979) on ethical principles and guidelines section on informed consent. The verbal consent was authenticated by an attending surgeon.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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