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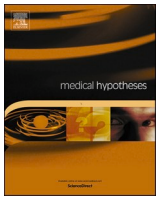

Delivery of magnetic nanoparticles to lung cancer cells via polarized macrophages: A riveting tale of a bio-inspired phenomenon

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ABSTRACT

Macrophages critically influences the tumor progression. The bio-carriers like macrophages have proven successful in circumventing this mammoth challenge by selectively infiltrating cancerous cells with anticancer drugs. Moreover, macrophage phenotypes have been found to have a key role in early phage of angiogenesis in the lungs. Phenotypic macrophages will serve to billet the iron, which has been found to have cancer cell-killing proficiency. Recent studies have shown the modulation of the molecular mechanism for tumor suppression by iron oxide (IO) nanoparticles. In addition, previous research focus on the interlink connections of iron and macrophages concerning macrophage polarization and consequent tumor suppression. However, we found that the initiation of the molecular response by external macrophages carrying anticancer agents has an exceptional breach in current drug delivery technology. We assume that macrophages carrying IO nanoparticles prepared by insemination-like formulation strategy to initiate the three-way response 1) directly invading the tumors with *in vitro* polarized macrophages; 2) Simultaneously delivering IO nanoparticles to augment the tumor suppression, and 3) IO deposition in TME further encourages polarization from M2 to proinflammatory M1 macrophages. Therefore, in the present study, we hypothesize that magnetic nanoparticles that are entrapped in phenotypic polarized macrophages will have striking potential to target lung cancer. In this hypothesis, we discussed the molecular interplay of iron and macrophages, *in-vitro* internalization of iron nanoparticles, and *in vivo* release inside the tumor cell.

Introduction

The second highest malignancy prevalence in the world is lung cancer [1]. A major challenge in treating lung cancer is drug resistance. As cancer advances, the tumor microenvironment (TME) may become resistant to drugs [2]. The bio-carriers like macrophages have proven successful in circumventing this mammoth challenge by selectively infiltrating cancerous cells with anticancer drugs[3–5]. In lung cancer, macrophages portray a crucial role in the pulmonary defense and inflammatory response that restrain the initial tumor growth[6]. At the beginning of tumorigenesis, alveolar macrophages (AMs) are found in the airspaces of the pulmonary voids and be present in the lower respiratory tract[7]. According to the research, the specific phenotype of AMs appears to have a significant role in the early phases of angiogenesis in the lungs[8]. Macrophages differentiate into proinflammatory M1 cells in response to precursors like iron[9]. A study by Costa da Silva, Milene revealed that patients with non-small cell lung cancer (NSCLC) who have detectable iron in their TME have smaller malignant cells

Abbreviations: TIME, Tumor immune microenvironment; TME, Tumor microenvironment; AMs, Alveolar macrophages; NSCLC, Non-small cell lung cancer; MRI, Magnetic Resonance Imaging; CXCL, Chemokine Ligand; ROS, Reactive oxygen species; TLR_4, Toll-like Receptor 4; MAPK, mitogen-activating protein kinase; LPS, Lipopolysaccharide; IFN, Interferon; JAK, Janus Kinase; STAT1, Signal Transducer And Activator Of Transcription 1; IRF3, Interferon Regulatory Factor 3; iNOS, Inducible Nitric Oxide Synthase; DAMP, Damage-Associated Molecular Pattern; THP-1, Tamm-Horsfall Protein 1; RPMI, Roswell Park Memorial Institute medium; AFM, Atomic Force Microscopy; FTIR, Fourier Transform Infrared; MMAD, Mass Median Aerodynamic Diameter; FPF, Fine Particle Fraction; BAL, bronchoalveolar lavage; FPN, Ferroportin; DMT1, Divalent Metal Transporter 1; MZF1, Myeloid Zinc Finger 1; Nrf2, Nuclear Factor Erythroid 2-related Factor 2; LIP, Labile Iron Pool; EGFR, Epidermal Growth Factor Receptor; TfR1, Transferrin Receptor 1; E1A, Early Region 1A Gene Tumor immune microenvironment.

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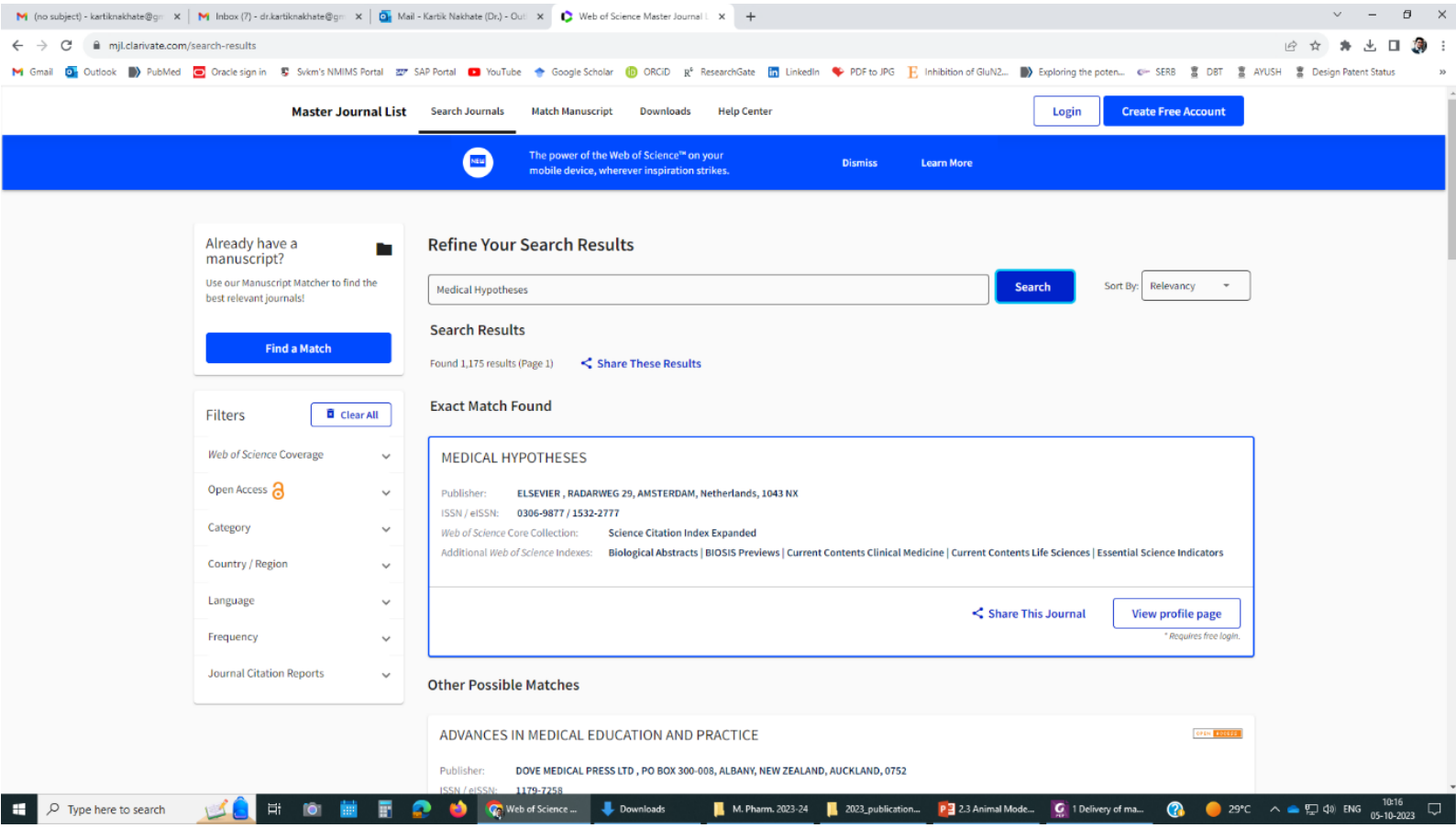
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