Letter to the Editor
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Cell-in-Cell Phenomena or Tumor-APCs? A Pathologist's Perspective

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Dear Editor,

Among the myriad fascinating aspects that play critical roles in carcinogenesis, tumor immunity and the loss of antigen presentation are paramount. Significant advances have been made in understanding the molecular mechanisms underlying both phenomena, leading to the recent development and application of cancer immunotherapies.[1] Efforts to enhance tumor antigen presentation through dendritic cell-based interventions have sought to generate antitumor T cells (CD4 and CD8). However, in cancer patients, dendritic cells often exhibit deficiencies or a tolerogenic state, thus limiting the efficacy of such strategies. Consequently, research has pivoted towards reprogramming tumor cells into antigen-presenting cells (APCs).[2] Tumor cells have been successfully reprogrammed into antigen-presenting cells (tumor-APCs) by transducing transcription factors PU.1, IRF8, and BATF3. It is now established that tumor-APCs can effectively present their antigens, activating an immune response that eliminates them. These cells can present endogenous tumor antigens on MHC-I, facilitating targeted destruction by CD8+ T cells.[3] They secrete inflammatory cytokines, cross-present antigens to naïve CD8+ T cells, and demonstrate the ability to engulf and process proteins and dead cells.[3] The engulfment capacity of tumor-APCs, involving either live or dead cancer cells, warrants further examination in the context of the cell-in-cell phenomenon, notably observed in oral squamous cell carcinoma.

Cell-in-cell phenomena, such as cannibalism (cancer cells engulfing neighboring cancer cells) and efferocytosis (the engulfment of apoptotic cells), are well-documented in cancer biology.[4,5] These phenomena have been observed in oral squamous cell carcinoma, exhibiting some unusual histopathological features.[6] Interestingly, cancer cell cannibalism and efferocytosis have

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been associated with nutritional demands and the clearance of apoptotic cells, respectively, rather than antigen presentation or immune function. Despite their distinctiveness, the cancer cells involved in these processes often express dendritic cell markers like CD68,[3,4,7] a heavily glycosylated glycoprotein predominantly found in macrophages and other mononuclear phagocytes. Thus, it is plausible to consider that cancer cells engaged in cannibalism and efferocytosis could be participating in the engulfment and degradation of cells. Moreover, metastatic tumor cells frequently express CD68 as a mechanism to evade macrophage-mediated phagocytosis and the lethal effects of cytotoxic CD8+ T cells during invasion into everyday tissue microenvironments.[8]

Considering the established capabilities of tumor-APCs in engulfing and processing materials such as apoptotic bodies and cancer cells for antigen presentation,[3] a pivotal question emerges: Could cellular cannibalism and cancer cell involvement in efferocytosis be indicative of previously unrecognized tumor-APCs? Are these phenomena merely aspects of engulfment and processing for antigen presentation, or do they coexist with tumor-APCs in cancer patients, complicating morphological differentiation? These queries necessitate further investigation to elucidate these matters, as cellular cannibalism and tumor-APCs represent distinct phenomena.

To date, the detection and quantification of tumor-APCs rely on techniques targeting markers (surface, cytoplasmic, or nuclear), gene expression analyses, and functional assays. Differentiating between tumor-APCs, cellular cannibalism, and efferocytosis poses a significant challenge. Advances in single-cell analysis methods could provide invaluable insights into the heterogeneity and diversity of cell populations within the tumor microenvironment. Examining transcriptional profiles and antigen-presentation machinery at the single-cell level may offer a more comprehensive understanding of these phenomena. We advocate for a clinical study aimed at identifying and quantifying tumor-APCs in tumor masses (biopsy samples) using markers such as CD11c, CD11b, CD40, CD80, etc., and correlating these findings with patient prognosis to reinforce the concept of tumor-APCs as both a prognostic and therapeutic model. Tumor-APCs could also influence intra-tumoral heterogeneity, potentially affecting the outcomes of immunotherapies designed to enable cancer cells to process and present endogenous tumor antigens. Future research should focus on distinguishing between tumor-APC, cellular cannibalism, and efferocytosis at the tissue level to deepen our understanding of carcinogenesis.

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Authors' Contribution

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Conflict of Interest

None declared.

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