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Letter to the Editor

The Non-canonical Mechanism of Immune Escape in Cancer: Intercellular Transfer of Immune Checkpoint Molecules

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Recently, immunotherapy based on the blockade of immune checkpoint proteins has shed a light of hope on cancer patients with a range of clinical trials demonstrating inspiring clinical efficacy, including melanoma,[1] urothelial bladder cancer,[2] lung cancer,[3] *etc.* Nevertheless, several obstacles have seriously limited the further benefits from immune checkpoint blockade (ICB) therapy, which has mainly focused on great individual heterogeneity, the formation of immune resistance during treatment, innate immune insensitivity, and so on. Although constant efforts have been made by researchers to resolve these problems, limited effect was produced. Gradually, we realized that not only should we explore more novel and effective immune checkpoint proteins for synergizing therapeutic efficacy, more importantly, we ought to return to the regulatory mechanisms of previously identified classical immune checkpoint proteins and elucidate their immune modulatory patterns we had underestimated or undiscovered before.

Classically, the interaction between the crucial immune checkpoint proteins, such as PD-1/PD-L1, CTLA-4/CD80 or 86, CD47/SIRPα, and MHC-I/LILRB1, has been mostly dependent on the direct interaction between the receptors and ligands following cell-to-cell contact. Intriguingly, a recent study found a novel molecular mechanism regulating the cell-surface expression of PD-1 on natural killer (NK) cells.[4] This process involved the formation of an immunological synapse of the NK cell and capture of fragments of the cell membrane from the tumor cell, which helped transfer the PD-1 protein from the cell membrane of the tumor cell to the surface of the NK cell. This biological process is called trogocytosis.[5] In short, trogocytosis endowed the NK cells with the ability of an exogenous acquirement of PD-1, which was primarily unable to be expressed on the NK cells. Notably, this process could be hijacked by tumor cells as an alternative pathway to escape the innate immune surveillance exerted by the NK cells. Herein, based on this research,[4] we would like to highlight some points regarding the intercellular exchange of the immune checkpoint proteins as a crucial immune escape regulatory function exerted by cancer cells. The basic mechanisms and characteristics of trogocytosis and other cytosis forms are shown in Figure 1.

Firstly, the immune checkpoint proteins transferred intercellularly by trogocytosis are far more than PD-1, but also include MHC-I[6] and CTLA-4,[7] which are both key immune checkpoint proteins for innate and adaptive immunity, respectively. This could provide the tumor micro-environment with an even more complex exchange network of immune checkpoint proteins, which may further induce the formation of the adaptive immune resistance during ICB treatment. Importantly, we would need to focus on those immune cells, which would express the negative immune checkpoint proteins exogenously and utilize multiple preclinical models to verify the potential intercellular molecule exchange mechanisms.

Secondly, other cell contact modes concerning membrane fusion or swap would need to be identified for they could also mediate intercellular material exchange. In addition to close direct cell-cell contact patterns, the remote intercellular communication also required sufficient attention. PD-L1 was found to be able to be loaded as cargoes in the exosomes to suppress the immune function of the $CD8^+$ T cells in melanoma, which impaired the efficacy of anti-PD-1 therapy.[8] Moreover, the MHC-I structure was found to be able to be capsuled in the exosomes in the form of disulfide-linked MHC I dimers and thus became recognized by the immune cells following the exosome releasing.[9] Notably, MHC-I expressed on the cellular membrane of cancer cells could be sensed by the LILRB1 receptor and thereby served as a "don't eat me" signal to protect the tumor cells against phagocytosis.[10] However, whether the cancer cells could also utilize this innate immune checkpoint pathway to induce immune evasion remains unknown and would require further investigation. More recently, Schwich *et al*.[11] demonstrated that the human leukocyte antigen-G loaded by the exosomes could interact with the inhibitory receptor immunoglobulin-like transcript receptor-2 in the blood micro-environment, which was represented by the upregulation of a range of immune checkpoint molecules, including PD-1, CTLA-4, TIM3, *etc.*

To conclude, the regulatory network of the immune checkpoint molecules has been largely expanded along with the development of accurate molecular identification and tracking technology. An in-depth understanding of the mechanism and logic of tumor immune escape through non-canonical modulatory functions would therefore be urgently required under the background of the ICB era.

Keywords: ICB; Immune escape; Exosome; Intercellular communication; Trogocytosis.

Abbreviations: ICB, immune checkpoint blockade; NK cell, natural killer cell.

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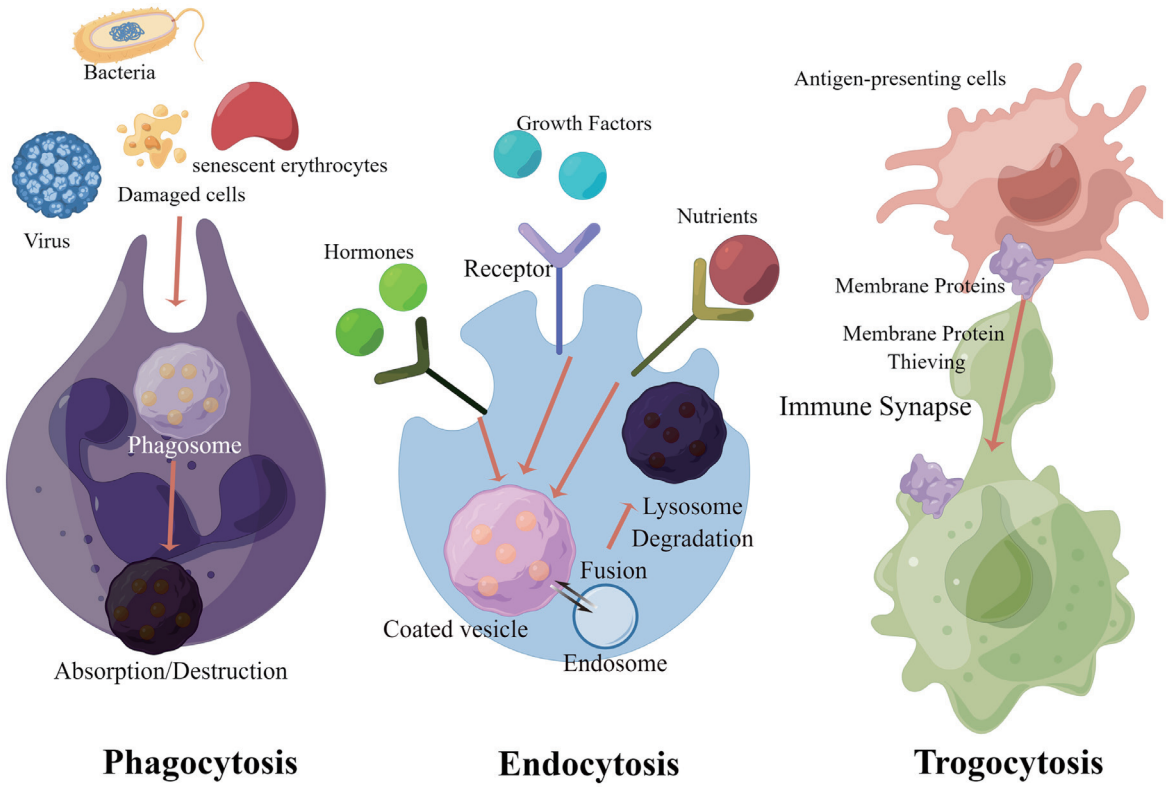

Fig. 1. The graphical diagram showing the functioning mechanisms and characteristics of the three cytosis forms. The phagocytosis of the immune synaptic cells swallows or eats the pathogenic source and particles. At ordinary times, phagocytes travel around the human body to search for the cause of disease and move to specific sites under the recruitments. Once the pathogenic source is swallowed by the phagocytes, it is encapsulated in intracellular particles called phagosomes, and then the phagosomes and lysosomes fuse into phagosomes. The pathogenic source would be degraded by enzymes or killed by free radicals. Receptor mediated endocytosis is a special type of endocytosis, which is mainly used to ingest special biological macromolecules, *e.g.*, different proteins, including hormones, growth factors, lymphokines, and some nutrients. Trogocytosis is dependent on the formation of the immune synapse, which would "capture" the fragment of the cellular membrane of the target cells and express the specific membrane expressed proteins from "theft". Figure produced by and permission obtained from Figdraw: http://www.figdraw.com

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study concept and design (THL, XYL), acquisition of relevant materials (THL), drafting of the manuscript (THL, XYL), and critical revision of the manuscript for important intellectual content (XYL). All authors have made a significant contribution to this study and have approved the final manuscript.

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