Editorial Commentary

The emerging role of trogocytosis in the evasion of cancers and parasitic protists from immune cells

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The word of "trogocytosis" started to be used in immunology since 2003. The word "trogo" means "nibble" or "chew" in Greek, and trogocytosis represents a mode of internalization of a part of a neighboring cell, which is a distinct manner from conventional "phago"cytosis, meaning, as we understood, "eat" with one bite. After the report in 1972 (1), in which transfer of major histocompatibility complex II (MHC class II) from B to T cells was observed, a similar mode of transfer of surface molecules has been reported for a variety of immune cells such as T, B, natural killer (NK), and dendritic cells (2-5). However, it remained elusive whether or not and, if so, how surface molecules such as transmembrane receptors were transferred to other cells. The hypothetical idea of the nibbling of surface membranes was proposed by Hudrisier and colleagues in 2001 (6). In this study, it was shown that surface lipids and proteins were acquired with peptide-loaded MHC and T cell receptor and the phenomenon was named "trogocytosis" (3,6). After their findings, the concept has been generally accepted that surface receptors are transferred between immune cells via trogocytosis. In the recent publication by Hamieh and colleagues, a new role of trogocytosis in immune evasion has been demonstrated, in which tumor cells escape from killing during immune therapy by chimeric antigen receptors (CARs) (7).

CARs are artificially designed receptors that harbor one extracellular single chain variable fragment (scFv) domain that recognizes target cells and one to three cytosolic intercellular signaling domains derived from CD3ζ, costimulatory proteins such as CD28, and 4-1BB. Recognition of the target tumor cells by CAR-expressing T cells via the scFv domain causes activation of the signaling domains, which in turn elicit downstream effector activity, such as secretion of perforin, granzyme, and stimulation of Fas, to eliminate tumor cells. Adoptive transfer of CAR-expressing T cells showed impressive efficacy to B cell malignancies and was considered as a promising therapeutic measure (8). However, even though complete remission of tumor cells was observed, relapse was reported to occur because of loss or reduction of the tumor antigen on the leukemia cells and exhaustion and elimination of CAR T cells (9,10). Hamieh and colleagues showed that CD19, a B cell antigen, on the acute lymphoblastic leukaemia (ALL) cells (NALM6) was taken up by CAR T cells via trogocytosis and it is caused reduction of the tumor antigen (7). Subsequently, trogocytosed CD19 in the CAR T cell was transferred onto the CAR T cell surface. This B cell antigen expressing CAR T cell was recognized as malignant B cells and killed by other CAR T cells and it is called T cell fratricide (meaning "murdering one's brother") and eventually exhaustion of the CAR T cells (7). Although other mechanisms were reported for immune evasion of tumors from CAR T cells, such as antigen loss on the tumor cells caused by genetic mutation, alternative splicing,

epitope shedding, or lineage switching (11), regulation of trogocytosis could be one of the potential therapeutic strategies.

Trogocytosis is not restricted to mammals. There were a number of reports that described trogocytosis in a wide range of eukaryotes from protists (synonymous to protozoa) to mammals (12). As early as in 1979, Brown and colleagues demonstrated by electron microscopy that the cytopathic mechanism, which was also referred as "trogocytosis", of the free-living amoeba, *Naegleria fowleri*, by which the amoeba nibbled mouse embryonic cells (13). Similar trogocytosis-like ingestion of the target cells and trogocytosis-mediated cytopathic mechanisms have been reported from other free living and parasitic amoebas, such as *Acanthamoeba*, *Dictyostelium*, and *Entamoeba* (12,14). In addition, in the multicellular organisms, trogocytosis has also been reported to be involved in retinal development in *Drosophila* (15), primordial germ cell development in Caenorhabditis elegans (16), remodeling of synapses in *Mus musculis* (17), communication between mesenchymal stroma/stem-like cells and cancer cells in *Homo sapiens* (18), and spread of a intercellular pathogen *Francisella tularensis* between macrophages (19). In contrast to the cytopathic consequence of trogocytosis by protists, trogocytosis by multicellular organisms usually does not lead to killing of target cells. The concept is now well accepted that trogocytosis in multicellular organisms in general serves for intercellular communications. However, there are several notable exceptions. Trogocytosis was implicated in cytopathy by neutrophil and macrophages against cancer cells and the human genital parasitic protist, *Trichomonas vaginalis* (20-23).

A series of the reports on trogocytosis in various organisms suggest the sporadic existence of trogocytosis at least among the supergroup Unikonta (containing Opistokonta and Amoebozoa) of eukaryotes. Does trogocytosis in protists and multicellular organisms differ in the context of mechanisms and functions? A recent study on trogocytosis in the human intestinal protist, *E. histolytica*, the causative agent of amebiasis, demonstrated that amoebic trogocytosis may also serve for immune evasion (24). It was shown that an *E. histolytica* trophozoite which had trogocytosed Jurkat T cell was decorated with Jurkat T cell-derived membrane proteins such as class I MHC (24). *E. histolytica* trophozoites are exposed to complement during invasion and thus, protection from complement is indispensable for survival. This finding suggests trogocytosis in protists also serves as intercellular communication mechanism and way of decorating their surface with molecules stole form their neighbors.

To improve CAR T cell therapy, one potential approach will be regulating trogocytosis of CAR T cells. To this end, understand the molecular mechanisms is indispensable. Unfortunately, molecular basis of trogocytosis is not well clarified except for trogocytosis specific AGC family kinase in *E. histolytica* (25), most of the report showing molecules shared with phagocytosis (26). Studies of molecular basis of trogocytosis in model organisms and protists will provide novel drug target.

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