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MINIREVIEWS

Noncanonical intercellular communication in immune response

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Abstract

The classical view of signaling between cells of immune system includes two major routes of intercellular communication: Through the release of extracellular molecules or a direct interaction between membrane bound receptor and its membrane bound ligand, which initiate a cascade of signaling in target cell. However, recent studies indicate that besides these canonical modes of signaling there are also noncanonical routs of intercellular communications through membrane stripping/membrane exchange/trogocytosis, extracellular traps, exosomes and ectososmes/microparticles. In this review we discuss what are the components of noncanonical pathways of signaling and what role they play in immune cells interactions.

Key words: Trogocytosis; Membrane stripping; Extracellular traps; Exosomes; Ectososmes; Microparticles

Core tip: Noncanonical routes of intercellular communications through membrane stripping, trogocytosis, extracellular traps, microparticles and exosomes and their function in immune response are highlighted.

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INTRODUCTION

For many decades general belief has been that during an immune response the immune cells communicate either by a direct contact between molecules anchored at the plasma membrane of adjacent cells (juxtracrine signaling) or *via* short (autocrine and paracrine) or long (endocrine) distance signaling using various cytokines or hormones and their cognate receptors systems (Figure 1). However, recent years studies, amounting to hundreds of publications, indicate that besides these well-known (canonical) signaling pathways there is a cornucopia of nonclassical (noncanonical) signaling mechanisms, which modify behavior of immune cells and shape the immune response. Below we give a brief overview of features and functions of these noncanonical signaling pathways.

MEMBRANE STRIPPING/MEMBRANE EXCHANGE/TROGOCYTOSIS

The trogocytosis - the nibbling (gnawing) off the fragments of live cells is probably an ancient mechanism applied by feeding amoebas[1,2]. However, in contrast to amoebic trogocytosis, which ultimate goal is devouring, and death of cellular pray, the immune cells developed mechanisms of vital trogocytosis or membrane stripping or exchange (Figure 2). During such a process, upon close contact between cells, the recipient cells acquire (borrow) foreign molecules, which they normally do not produce, and the donor cells either completely lose given molecules or the level of these molecules become, at least temporarily, reduced[3,4]. Recent studies indicate that the membrane exchange between various cell types, including immune cells, is a much more common and frequent phenomenon than previously thought. The *in vitro* and *in vivo* studies in different model systems showed that upon disengagement from immunological synapse with antigen presenting cells (APCs) or from a direct contact with other target cells, the activated $CD4^+$, $CD8^+$ T cells, regulatory T cells, helper T cells, macrophages, B cells, monocytes, granulocytes and natural killer (NK) cells, are able to internalize fragments of APCs/target cell membrane together with monoclonal antibodies, antigens, ligands, major histocompatibility complex (MHC), adhesion or co-stimulatory molecules[5-18]. For example, studies of Baba *et al*[19] showed that OX40 ligand (OX40L) expressed by COS-1 cells is transferred to $CD4^+$ T ($OX40L^-$, $OX40^+$) cells, and that the acquired OX40L is functionally active. Other studies showed that the trogocytic acquisition of m157 (the murine cytomegalovirus-encoded ligand for the Ly49H-activating receptor) from target cells regulates NK cells function making them hypo-responsive both *in vivo* and *in vitro*[8]. In contrast, acquisition of anti-CD19 chimeric antigen receptors by NK cells enhances their cytotoxicity against the B-cell acute lymphoblastic leukemia cells[7]. Trogocytosis can also lead to acquisition of the MHC complexes by the non-APCs, which in turn may reinforce and/or propagate immune response, and activate or regulate T cells[4]. There are indications that trogocytosis/membrane internalization depends on GTPase TC21 and RhoG-dependent phagocytosis pathway (Figure 2)[16,20]. Membrane internalization not only leads to the acquisition of novel qualities by recipient cells but may also down-regulates the MHC/antigen/co-stimulatory molecules level in bestower APCs[11,16]. There are also instances of multicellular exchange and serial trogocytosis when immune cells acquire novel molecules from multiple sources and then transfer them to other recipient cells. For example the membrane bound molecules from multiple cancer cells can be acquired by $CD4^+$ and $CD8^+$ T cells and monocytes through multiple trogocytosis[21]. It has been shown that monocytes are able to transfer these molecules to other T cells[21]. Thus, trogocytosis/membrane exchange/stripping leads to acquisition/depletion of molecules and their cognate functions in recipient/donor cell, and ultimately modify or modulate an immune response (Figure 2)[3,4,6,18,22,23]. Trogocytosis and its outcomes can be either beneficial or harmful for the organism. Depending on circumstances and cell partners involved the trogocytosis may either promote or prevent development of various pathological conditions or diseases. For example trogocytosis is involved in the ablation of red blood cells in autoimmune hemolytic anemia[24] but when it removes antibodies binding to self-antigens it can prevent autoimmune diseases[25]. Another example of harmful trogocytosis is "oncologic trogocytosis" occurring between ovarian epithelial cancer cells and stromal cells allows cancer cells to acquire multiple drug resistance protein and thus chemoresitance[26].

EXTRACELLULAR TRAPS

Extracellular traps (ETs) were discovered in 2004 in neutrophils and thus have been named Neutrophil Extracellular Traps (NETs)[27]. The process of ETs and NETs formation is called ETosis and NETosis, respectively. ETs consist of filamentous network of chromosomal and/or mitochondrial DNA, which is released from the cell after the break of nuclear/mitochondrial membrane (Figure 3). Because the process of ETosis involves nuclear/mitochondrial/plasma membrane breakage it usually leads to a suicidal, distinct from apoptosis or necrosis, death of ETs' producing cells[28]. However, there are instances of non-suicidal (vital) NETosis, when nucleus-deprived neutrophils retain motility and chemotactic and phagocytic functions[29,30]. Another example is the vital mitochondrial NETosis when neutrophils primed, for example, with granulocyte/

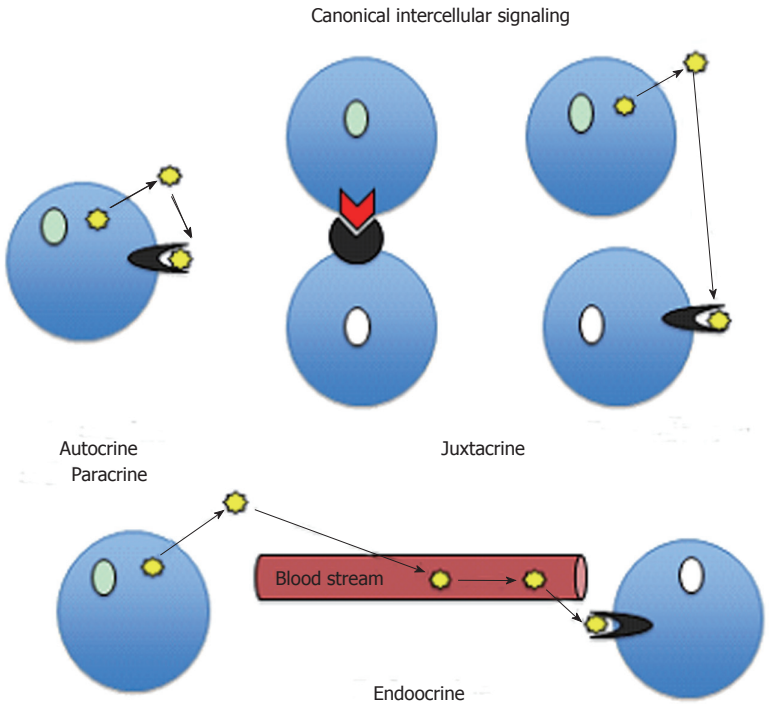

Figure 1 Types of canonical signaling. In autocrine signaling, the cell regulates itself (autoregulates) through internally produced signaling molecules, which after release from the cell bind to cell's own receptors. The examples are: Interleukin-1 produced by monocyte in response to external stimuli binds to its own receptor on the same monocyte; IL-2 released from activated T cell binds to its own receptor leading to self-stimulation. The juxtacrine signaling occurs between closely apposing cells when signaling molecule attached to one cell interacts with its receptor on adjacent cells or when signaling molecule excreted to the intercellular matrix of one cell binds to the receptor on neighboring cell. In juxtacrine signaling the signaling molecules do not diffuse freely between cells. The examples include cytokine signaling in immune system and Notch pathway signaling. In paracrine signaling, released signaling molecules such as, for example, cytokines or retinoic acid diffuse at short distances and act on the cells located in vicinity. In endocrine signaling, signaling molecules such as hormones or cytokines are transported through the circulation to the target cells.

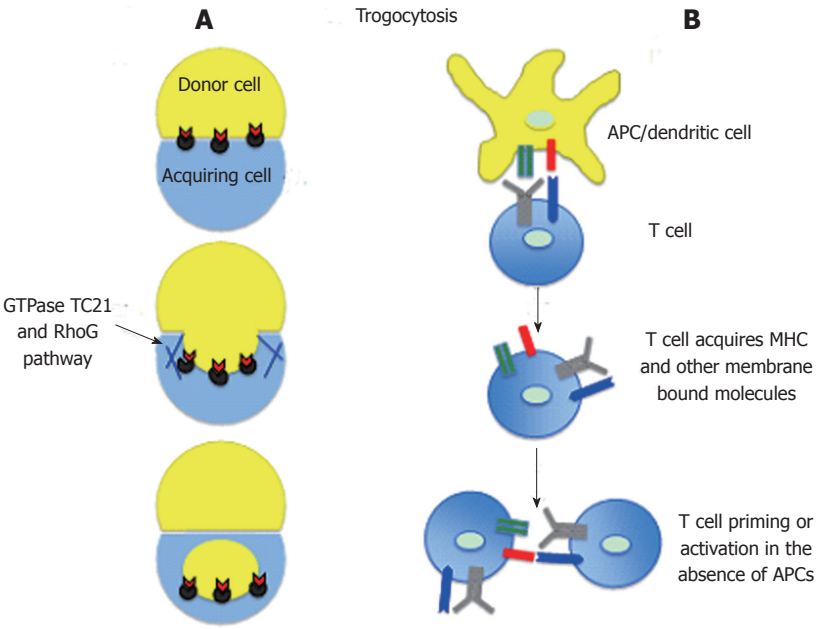

Figure 2 Trogocytosis/ membrane exchange/stripping. A: During trogocytosis the recipient cell acquires membrane bound molecules from donor cell. The process of internalization of donor cell membrane is similar to phagocytosis and depends on actin ring contraction and small GTPases; B: During APC/T cell interaction the T cell may acquire MHC/peptide complexes and co-stimulatory molecules. Subsequently, such T cells can prime/activate naïve T cells in the absence of APCs, and/or by interacting with activated T cells lead to propagation of immune response[16,20]. APC: Antigen presenting cell; MHC: Major histocompatibility complex.

macrophage colony-stimulating factorand stimulated with short-term toll-like receptor 4 or complement factor 5a receptor retain intact nucleus and produce NETs containing exclusively mitochondrial DNA[31].

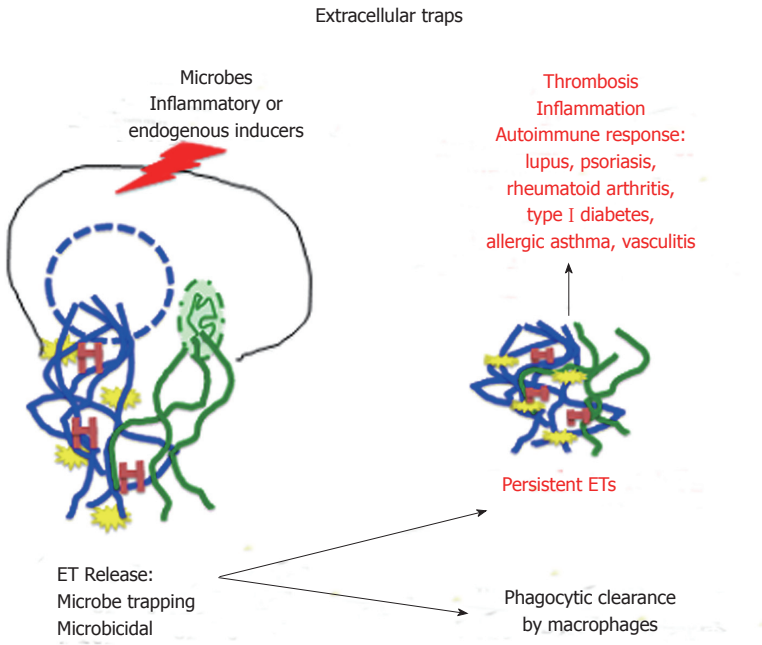

Figure 3 Extracellular traps formation and side effects. Various external or internal inducers may lead to the breakage of nuclear or mitochondrial (or both) membranes and release of extracellular traps (ETs). The ETs contain network of nuclear/mitochondrial DNA (blue/green), antimicrobial compounds (yellow) such as LL37, myeoloperoxidase (lysosomal protein) and elastase (chymotrypsin-like protease), and deiminated (citrullinatied) histones (red H). Under normal circumstances the ETs are promptly removed by macrophages, however if the ETs persist they can lead to inflammatory and autoimmune response[31,32].

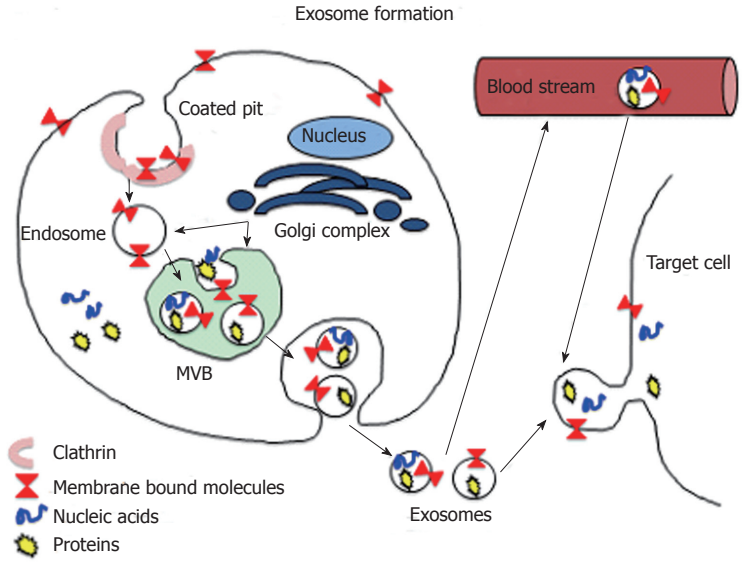

Figure 4 Exosome pathway. Exosome forms through endocytosis, which starts from the invagination of clathrin coated domain of plasma membrane (coated pit) bearing the receptors and other membrane-bound molecules. After entering cell interior, the coated vesicle loses clathrin coat and becomes the endosome. Subsequently, after acquiring variety of other molecules from Golgi apparatus and cytoplasm, the endosome membrane undergoes inward budding resulting in the formation of multivesiular multivesicular body (MVB) containing exososmes. Ultimately, the MVB fuses with plasma membrane and in the process of exocytosis releases exosomes outside the cell. The exososmes either fuse with the membrane of neighboring target cell or enter blood stream to be transported to distant targets. In the alternative outcome (not shown here), which serves as the pathway degradation pathway, the MVB fuses with lysosomes, which degrade its content[67,69].

Besides DNA, the ETs contain various histones (which by themselves have antimicrobial properties) and a plethora of antimicrobial enzymes (Figure 3)[32-35]. The main role of ETs is the immobilization of microbes, which prevents dissemination, and exposing them to a high concentration of antimicrobial agents. Interestingly, many microbes developed defense mechanisms allowing them to escape from or neutralize ETs or ETs producing cells. For example Staphylococcus and Vibrio cholera produce endonucleases, which digest NETs, or/and convert NETs' DNA into toxic metabolite (deoxyadenosine), which induces apoptosis and promotes death of immune cells[35-37]. The fact that ETosis occurs in many different cell types, and not only in vertebrates but also in invertebrates and plants, suggests that ETs are one of the primordial

and evolutionary ancient mechanism of host defense. Studies of molecular pathways involved in initiation and execution of NETosis indicate that stimulation with microbes, inflammatory molecules or endogenous inducers leads, *via* protein kinase C and NADPH oxidase, to the production of reactive oxygen species and nitrix oxide[35]. These, in turn, induce nuclear/mitochondrial/granule membrane rapture, followed by proteolytic cleavage, deamination (citrullination) of histones, chromatin decondensation and eventual release of NETs[38]. It has been shown that besides consistent presence of DNA the other components of ETs vary, as they are stimulatory signal-specific and cell type-specific[32]. Although ETs play beneficial role in host defense, the presence of DNA and various enzymes makes ETs harmful, especially if they persist for long period of time; they become a very potent inducer of autoimmune response and various pathological conditions, such as lupus, psoriasis, vasculitis, rheumatoid arthritis, type I diabetes, allergic asthma and deep-vein thrombosis (Figure 3)[33,35,39]. It has been also shown that, at least *in vitro*, ETs influence the behavior of immune cells. NETs are able to down regulate lipopolysaccharide-induced activation of monocyte-derived dendritic cells, inhibit their capacity to activate proliferation of $CD4^+$ T lymphocytes and to polarize naïve $CD4^+$ T cells toward Th1/Th17 phenotypes, promoting Th2 response instead[40]. In addition, prolonged exposure to NETs can induce macrophage and dendritic cells death, which may limit ongoing inflammation[41]. However, it is still unknown, which components of NETs are responsible for these effects. The fact that persisting ETs can modify molecular and cellular components of immune system indicates that fast clearing of ETs is extremely important for proper functioning of immune response[42]. Recent studies indicate that macrophages serve as such clearing agents. Thus, macrophages seem to have a dual role; they can produce ETs and also remove them through phagocytosis[35]. Macrophage ETs, named METs, were discovered in 2010 in murine RAW 264. 7 (Abelson murine leukemia virus transformed macrophages) cell line and since then have been described in many different macrophage types[35,43]. In contrast to the neutrophils where the NETs formation is their main strategy (neutrophils are short-lived "by design") the formations of METs in macrophages, which are long-lived cells, is an auxiliary strategy and is (regardless of stimulation) self-limited to less than 25% of total macrophage population[35]. Recently, the eosinophil extracellular traps (EETs) and their role in allergic diseases such as human eosinophilic chronic rhinosinusitis and eosinophilic otitis and eosinophilic esophagitis have been described[44,45]. Eosinophil traps released during local cytolysis contain DNA/histone H1 complex, which form globular fibers ticker than those present in neutrophil-derived traps. The EETs can trap fungi and bacteria and at least in eosinophilic esophagitis (characterized by esophageal epithelial barrier defects) can guard against pathogens infiltration through the impaired esophageal wall[45].

Table 1 Molecular content of exosomes[49,55-61,74,75]

Nucleic acids	Exosome lumen proteins	Exosome membrane proteins	Lipids
mRNA	Actin	Annexins	Cholesterol
miRNA	Cofillin	Channels	Diglycerides
tRNA	GAPDH	EGFR	Eicosanoids fatty acids
rRNA	Hsp70	FasL	Gangliosides
mitochondrial	Rab	I-CAM1	Lyso-phosphatidylcholine
DNA	Tubulin	Integrins	Lyso-bis phosphatidic acid
retrotransposons		LBPA/CD63	Phosphatidylcholine phosp
		LAMP1/2	hatidylethanolamine
		MHC	Phosphatidylserine
		PD-1L	phosphatidylinositol
		Tetraspanins	Sphingomyelin
		Tsg 101	

GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; I-CAM1: Intercellular adhesion molecule 1; EGFR: Epidermal growth factor receptor; LBPA: Lactoferrin-binding protein; LAMP1/2: Lysosomal-associated membrane protein 1; MHC: Major histocompatibility complex; PDL-1: Programmed death 1.

EXOSOMAL AND ECTOSOMAL/ MICROPARTICLE SIGNALING

Exosomes are small (30-150 nm) endocytic membranous vesicles, which are produced by various cell types including immune cells[46]. They were discovered over 30 years ago and for many years they were believed to be the non-functional cell debris or debris disposal vehicles. However, over the last several years numerous studies have proven that exosomes are an important component of intercellular communication circuit and as such play a crucial role in initiation and/or modulation of immune response[46-54]. Exosomes form inside the cell through endosome/mulitvesicular body (MVB) pathway in which they acquire various cytoplasmic, membrane bound and/or nuclear components (Figure 4). Fully matured exosomes released (*via* exocytosis) from a founder cells deliver, sometimes over long distances, various molecules to their targets. Exososmes may contain a variety of molecules such as: (1) genetic material: retrotransposomal DNA, mitochondrial DNA, mRNAs, miRNAs, rRNA, tRNA; (2) lipids; and (3) proteins: Cytoskeletal proteins, heat shock proteins, channels and transporters, adhesion proteins, tetraspanis and various receptors (Table 1), listed in Exocarta database http://www.exocarta.org[49,55-61]. There are many studies showing how exososmal signaling can influence and modify immune cells and immune response. For example the exosomes released by B cells and dendritic cells contain functional MHC - antigenic peptide complexes, which induce adaptive immune responses *in vitro* and *in vivo*[62,63]. Andreola *et al*[64], showed that death-inducing Fas ligand - bearing exosomes secreted by tumor cells induce lymphocyte apoptosis, which

in turn suppress anti-tumor response. In addition, other studies showed that exosomes derived from B lymphocytes expressing FasL can kill T helper (TH) lymphocytes[65], and that antigen-specific suppression of immune response is exerted by microRNA-150 (miRNA-150)-containing exosomes derived from T $CD8^+$ suppressor (Ts) cells[66]. There are also studies showing that exosomes participate in the signaling between pathogens and immune cells. For example exosomes derived from Schistosoma japonicum worm induce macrophage differentiation into M1 subtype[67] and Leishmania-derived exosomes deliver Leishmania specific molecules into the host macrophages and induce secretion of IL-8[68]. Bhatnagar *et al*[69] showed that pathogen-associated molecular patterns (PAMPs)-rich exosomes secreted from macrophages infected with various mycobacteria are able to stimulate proinflammatory response in naïve macrophages, and when transferred into mice they stimulate synthesis of IL-12 and TNF-α and promote infiltration of lungs with neutrophils and macrophages. Authors suggest that PAMPs-containing exosomes play a major role in immune surveillance[69]. Because exosomes' content is cell/pathogen specific and they are able to carry and deliver biologically active molecules to the target cells there is also tremendous interest in application of exosomes as biomarkers and the custom engineered exosomes as an immune and anti-cancer therapeutics[70-75].

Besides exosomes, various cells are able to release another type of membranous vesicles called the ectosomes/microparticles (MPs). The MPs are 0.2-2 mm in diameter and unlike exosomes they bud off the plasma membrane without the involvement of endosome/MVB pathway. The MPs contain a variety of bioactive molecules such as procoagulation compounds (for example P-selectin glycoprotein ligand-1 and tissue factor TF) and/or oncogenic proteins, mRNAs and micro RNAs[76-78]. Similar to exososmes, the circulating MPs may promote/inhibit inflammation, immune response, resistance to chemotherapeutics or activate oncogenic pathways[76-78].

CONCLUSION

One of the most fascinating aspects of noncanonical signaling is the fact that its cellular processes such as trogocytosis/membrane exchange, ETs, exosomes and microparticles are evolutionary ancient (amoebic trogocytsosis, ETs in acoelomate) and conserved in plants, invertebrates and vertebrates[79]. This indicates that noncanonical processes served as the primordial defense mechanisms and canonical signaling had developed later in evolution adding a new and more sophisticated quality to the ancient safeguards. Ironically, the existence of these ancient noncanonical pathways has been discovered much latter than canonical pathways, and only in recent decade they have been recognized as an extremely important regulators of innate and adaptive immunity and inflammatory responses.

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