 Activation of neutrophils by opsonized bacteria (S aureus or E coli, at left) causes the release of bacterially induced microvesicles (b-MV; ~500 nm in diameter). After their release, b-MV can aggregate both nonopsonized and opsonized bacteria, leading to reduced bacterial growth. Released b-MV contain antibacterial proteins myeloperoxidase (MPO) and lactoferrin, and express integrins CD11b and CD18 on their surfaces. This is proposed to be a novel bacteriostatic mechanism for host defense against pathogenic bacteria. Indeed, aggregates of b-MV and bacteria can be detected in the sera of bacteremic patients. Professional illustration by Alice Y. Chen.
and contain different types of proteins depending on the trigger used to evoke their production. Each of the MV subpopulations possessed different antibacterial effects. While s-MV had no discernible antibacterial properties, p-MV were moderately effective, and b-MV were most potent at preventing bacterial growth. Intriguingly, the bacteriostatic effects of b-MV were evident regardless of whether bacteria were opsonized or not, even though opsonization of bacteria was required to activate b-MV production from neutrophils in the first place. Proteomic analysis of the MV subpopulations revealed that antibacterial proteins (myeloperoxidase, lactoferrin) were enriched in b-MV, which may be related to their differential effects on bacterial growth. Surface markers for b-MV included the integrins CD11b and CD18, which were necessary for their antibacterial properties (see figure).

A mechanism for the antibacterial properties of b-MV was proposed in which b-MV attach to bacteria via integrins, leading to the formation of aggregates of b-MV and bacteria. Aggregation of bacteria with b-MV did not have a bactericidal effect, but instead prevented their growth, and was therefore bacteriostatic. This antibacterial effect was reduced by treatment of b-MV with water or saponin, and was dependent on Ca$_2^{+}$, energy (glucose), and actin cytoskeletal remodeling, among other processes. The bacteriostatic effect of b-MV was not altered by inhibition of NADPH oxidase, suggesting that superoxide is not required for bacterial aggregation.

The investigators went further to demonstrate that neutrophil-derived MV (CD11b$^+$CD177$^+$) were routinely detected in the serum of healthy donors, and increased 5- to 6-fold in patients with documented $S$ aureus bacteremia. Large CD11b$^+$ aggregates of bacteria and MV were found in blood serum from bacteremic patients, which were rarely detected in healthy individuals.

The effects of MV on bacteria are distinct from those of NETs, which is supported by several comparisons. The formation of NETs is a lengthier process (2–4 hours) while maximum b-MV formation occurred within 20 minutes. The production of NETs is dependent on reactive oxygen species, whereas the formation and activity of b-MV were independent of respiratory burst. NETs do not require energy or other cellular structures, while b-MV were dependent on an intact vesicular structure, cytoskeletal remodeling, and an adequate supply of glucose.

In summary, these findings put forward a novel and important immunologic role for extracellular neutrophil MV in trapping and arresting bacteria. An important aspect of these findings is that neutrophil MV are freely mobile in systemic circulation, with the capacity to attach to bacteria in blood or tissues—even those that may have escaped opsonization. Further studies are anticipated that will investigate the mechanisms underlying b-MV release from neutrophils, which remain unknown.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES
A new way of trapping bugs: neutrophil microvesicles

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