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TERMINAL COMPLEMENT COMPONENTS ARE CRITICAL IN THE RELEASE OF CELLULAR RNA IN CIRCULATION

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Despite over 10 years of intense research, the intimate mechanisms responsible for extracellular vesicles (EVs) formation (exosomes and microvesicles) and the release of cellular RNA species (ex RNAs) in circulation are currently known. The complement system is comprised of over 20 soluble and membrane bound proteins with critical roles in recognizing, binding, and removal of foreign particles as well as initiating and regulating innate and acquired immune responses. Activation of the complement system occurs during both, normal (circadian variation), and pathological conditions through either classical, alternative, or lectine pathways leading to the formation and transient insertion of C5b-9/Mac pore complex into cellular plasma membrane. We hypothesize that a) MAC-insertion promotes a sudden, significant and transient water and Ca++ influx, leading to: i) endocytosis of the affected area, followed by delivery of C5b-9/MAC-containing plasma membrane into the multi vesicular body (MVB) and its incorporation into exosomes or ii) exocytosis of the C9 channel/MAC-affected plasma membrane patch followed by micro vesicles (MVs) formation. In addition, the size of the MAC/C5b-9 pore, 12 nm, is large enough to: i) allow cytoplasmic RNA species to be transferred into the MVB following endocytosis of C5b-9/MAC-containing plasma membrane and ii) RNA species located near the plasma membrane to be released in the extracellular space upon C5b-9/MAC insertion. Our results, for the first time implicate MAC/C5b-9 as: i) a possible channel responsible for exosomes and microparticle biogenesis, and ii) loading of cytosolic RNAs into the exosomes, and iii) the direct release of cytoplasmic RNA species into the circulation (ex RNAs).

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