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Review

The cell secretome, a mediator of cell-to-cell communication

Joseph Zullo, Kei Matsumoto, Sandhya Xavier, Brian Ratliff, Michael S. Goligorsky*

Departments of Medicine, Pharmacology and Physiology, Renal Research Institute, New York Medical College, Valhalla, NY 10595, USA

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ABSTRACT

We are witnessing the emergence of a novel type of biological regulation, namely, the communication between cells via their secreted substances, the secretome. This brief overview is based on the available published data and our own experience. We discuss three vignettes illustrating the importance of communication via the secretome: (1) the secretome of stem cells and its effects in sepsis and systemic inflammatory response; (2) the profibrotic secretomes partially responsible for development of fibrotic complications; and (3) the contribution of senescence-associated secretory products to the propagation of the senescence phenotype. Considering the richness of secretomes of different cells under diverse conditions, it becomes imperative to gain insights into their individual components in an attempt to harness cell secretomes for therapeutic purposes.

Contents

On this 50th anniversary of Ettore Majorana Foundation and Centre for Scientific Culture (EMFCSC), that has started as a meeting place for theoretical physicists, but later opened its doors to other sciences, it would be appropriate to discuss a subject of significant interdisciplinary interest, namely, the communication. The relationship between the local and the global regulatory factors is steadily gaining additional layers of complexity. This subject percolates through diverse fields of knowledge, from sociology to theoretical physics, where it is described as Mach's Principle. In the field of biology the ideas of plants communicating with each other or the microbiome of the soil have deep historic roots and gave rise to the concept of *allelopathy*, study of plant-released chemicals that influence growth and survival of neighboring organisms. Positive and negative allelopathy is distinguished on the basis of whether these chemicals are supportive or harmful to the neighbors. Quite similar principles are operant in the field of communication in the animal kingdom and between various cells. The century-old ideas of the hierarchical regulation by the central nervous system and endocrine hormones describe the control mechanisms governing local functions through the central regulators. In parallel with those, there is growing awareness that the local regulators per se determine or modulate local functions and that these regulatory mechanisms can spill over to the distant organs to achieve the global impact. This latter trend was initiated by the discoveries of eicosanoids with their local and systemic organismal functions. More recently, a fledgling realization of the fact that secretory products of individual cells within an organ affect their own behavior, as well as that of the neighboring cells and distant organs has gained experimental recognition.

1. General concept of the secretome

In parallel with the completion of genome sequencing, a host of further "-omics" questions has emerged: What are the

* Corresponding author. Tel.: +1 914 594 4730.
E-mail address: Michael_goligorsky@nymc.edu (M.S. Goligorsky).

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transcriptome, translatome or proteome, and how those affect the secretome of a particular cell [1]. The authors of this 14-year-old original paper illustrated their case with the comparative analysis of transcriptome and translatome (http://bioinfo.mbb.yale.edu/what-is-it). The consensus based on this "–omics" tree defines the cell secretome as a portion of proteins secreted to the extracellular space, which in humans constitutes 13–20% of the entire proteome [2]. More recently, proteins present in microvesicles (100 nm–1 μm in diameter) and exosomes (<100 nm in diameter), both organelles secreted by cells and containing up to 42% of the secretome [3] (see ExoCarta database of exosomal proteins in http://exocarta.ludwig.edu.au), have been incorporated into the original term. Obviously, the secretome of individual cells and tissues is specific, and this secretome signature changes in response to fluctuations in physiologic states or pathologic conditions. Not surprisingly, therefore, studies of the secretome are considered of significant importance as a way to discovery of diagnostic tools for cancer, infectious diseases, senescence-messaging, to name a few, and could serve as a pathfinder of therapeutic strategies and of stem cell adaptive transfer [4]. The field, however, remains immature. Here, we shall describe a few examples of communication via the secreted substances (with the full understanding that these are mere vignettes representative of more numerous studies and our own interest) to illustrate recent advances in this type of information exchange. It should be mentioned that lipid mediators, as important as they are, do not strictly fit the definition of the secretome (part of the proteome) and are not discussed below.

2. Sepsis and effects of bone marrow stromal cells on macrophages

The switch of the cell secretome from a modest baseline to the activated state occurs in response to diverse pathological stressors. For instance, hypoxia induces a sharp increase in the release of several pro-angiogenic cytokines (HGF, VEGF, bFGF, PlGF and TGF-β) [5]. LC–MS/MS analysis of the secretome of mesenchymal stem cells stimulated by TNF-α revealed increased expression of IL-6, IL-8, MCP-1, MMPs, PTX3 and cathepsin L [6]. Some of the components of the secretome have cardioprotective effect, as judged by the improved ischemic heart function upon infusion of MSC-conditioned medium, even without MSC themselves [7]. Administration of single cytokines, like G-CSF, GM–CSF, erythropoietin or IGF-1, however, was ineffective [4], arguing in favor of combination therapy.

Analysis of mechanisms responsible for the improved survival of mice with experimental sepsis and receiving transplantation of bone marrow-derived stromal cells revealed that these adoptively transferred cells secrete prodigious amounts of PGE_2 [8]. In turn PGE2 produced by transplanted cells activates prostaglandin EP1-EP4 receptors to reprogram infiltrating macrophages to increase their IL-10 production. This mechanism, according to Nemeth et al. [8], underlies the protective effect of stem cell transplantation in sepsis.

Our own observations [9] supplement this data with findings obtained in septic mice receiving a combination therapy with mesenchymal stem and endothelial progenitor cells, each acting via the secretome to elicit beneficial effect. The cyto-/chemokine release from embedded stem cells was examined including effects on modulating the polarization and release of proinflammatory molecules from macrophages (Fig. 1). EPC–MSC co-culturing improved stem cell viability during LPS exposure, an effect augmented by MSC hypoxic preconditioning. Delivery of co-embedded EPC with hypoxic preconditioned MSC to AKI mice demonstrated additive improvement (as compared to EPC delivery alone) in medullary RBF and proteinuria, with no differences observed for serum

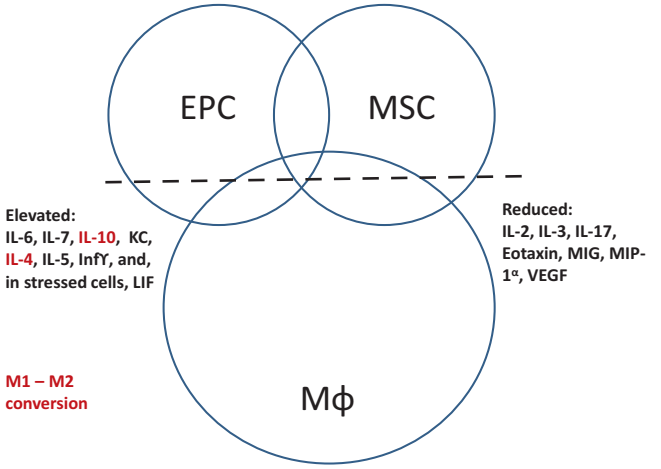

Fig. 1. Differential profile of the secreted cyto- and chemokines by macrophages alone or co-incubated with endothelial progenitor and mesenchymal stem cells. Note that the secretion of interleukins −4 and −10 is elevated by co-incubation with stem cells, and this change in the secretome could be responsible for conversion of M1 to M2 macrophages.

creatinine, MAP or angiogenesis. Exposure of proinflammatory M1 macrophages to EPC–MSC conditioned culture medium changed their polarization to anti-inflammatory M2 macrophages, while EPC–MSC delivery to endotoxemic mice elevated levels of circulating M2 macrophages. Incubation of co-embedded EPC–MSC with macrophages altered their release of cyto-/chemokines including enhanced release of anti-inflammatory IL-10 from macrophages [9].

3. Waves of secreted products in acute ischemic injury are responsible for the local and systemic inflammatory responses

Cell stress induces a rapid activation of xanthine oxidoreductase followed by increased generation of uric acid, one of the earliest "danger" signals [10,11]. Uric acid release after IRI unleashes a cascade of secondary events. The relatively fast damage response is accomplished via Toll-like receptors (TLR) −4 and −2-mediated exocytosis of Weibel–Palade bodies [11]. Exocytosis of Weibel–Palade bodies represent the second wave of response to noxious stimuli. These endothelia-specific organelles contain von Willebrand factor, IL-8, angiopoietin-2, eotaxin, endothelin-1 and big endothelin-1 together with endothelin-converting enzyme, among other biologically active molecules. Exocytosis of Weibel–Palade bodies releases to the bloodstream these normally sequestered substances. Kuo et al. documented release of angiopoietin-2, eotoxin and IL-8 to the systemic circulation. In general, exocytosis of Weibel–Palade bodies results in the release of components that possess either pro-inflammatory or pro-regenerative properties. The biological role of the pro-inflammatory components is dominant in the acute phase of an injury, whereas the role of the pro-regenerative components appears to play a role in the long-term outcome: inhibition of exocytosis of Weibel–Palade bodies, while ameliorating acute renal dysfunction after the insult, tends to exaggerate the chronic fibrotic consequences [12]. Considering the plethora of biologically active constituents of Weibel–Palade bodies, it is possible that they can exert mutually opposing actions. It would be a future goal to analyze each of them separately and replenish those which are necessary for regeneration, while suppressing those which exacerbate inflammation.

Next, we reasoned that the surge in uric acid after acute renal injury may also lead to exocytosis of other internal storage pools