ADQI 14 Figures

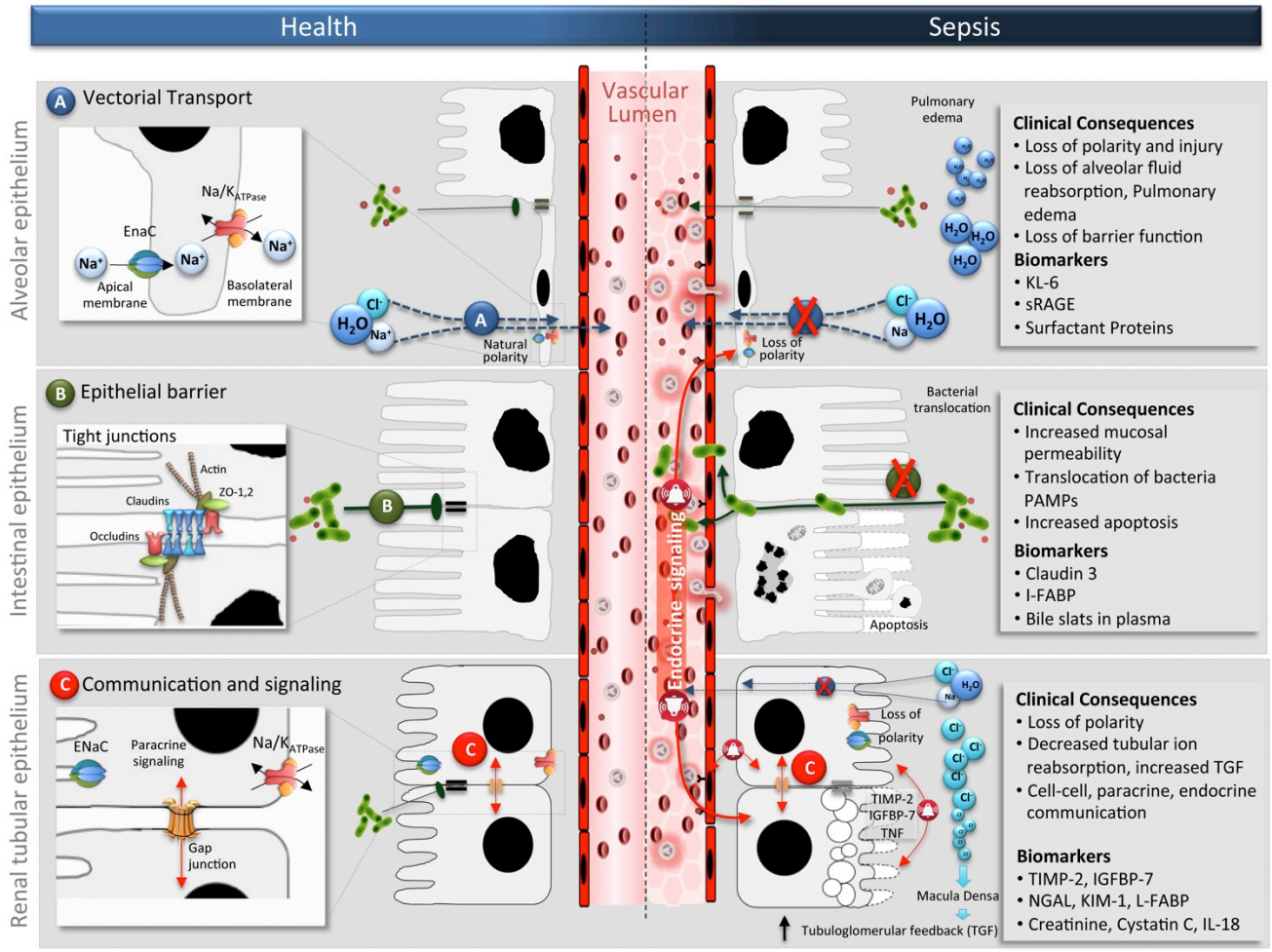

Figure 1. Despite obvious differences in epithelial function across different organs, sepsis alters common features of all epithelia, such as vectorial ion transport, barrier function and communication. The figure shows a simplified representation of these common epithelial functions in the lung (panel A), intestine (panel B) and kidney (panel C) during normal conditions (left hand side), and their alterations during sepsis (right hand side). Importantly, despite these common functions are characteristic of the epithelia of the lung, intestine and kidney, the figure emphasizes only one in each panel in the interest of clarity. *Panel A: Vectorial Transport in the lung*. Sepsis induces alterations in vectorial transport in the alveolar epithelium due to loss of polarity, and endocytosis of the Na/K ATPase pump, resulting in impaired alveolar fluid clearance and thus in pulmonary edema. In addition, the alteration in the Na/K ATPase pump has been associated with loss of tight junctions, impairing the important barrier function of the alveolar epithelium. *Panel B. Barrier Funciton*: The epithelial barrier function is also severely impaired in the intestinal mucosa. Claudin-3 has been recognized as an important component of the tight junctions, and has been shown to be excreted in urine after intestinal mucosal injury. *Panel C. Communication and signaling*: Sepsis may induce increased cell-to-cell, paracrine and even endocrine communication, and organ cross-talk. Panel C also shows how alterations in vectorial transport in the renal tubular epithelial cell due to loss of polarity and endocytosis of epithelial ion channels (Epithelial sodium channel or ENaC), may induce increments in delivery of chloride to the macula densa, triggering tubuloglomerular feedback (TGF), and resulting in the clinical AKI phenotype.

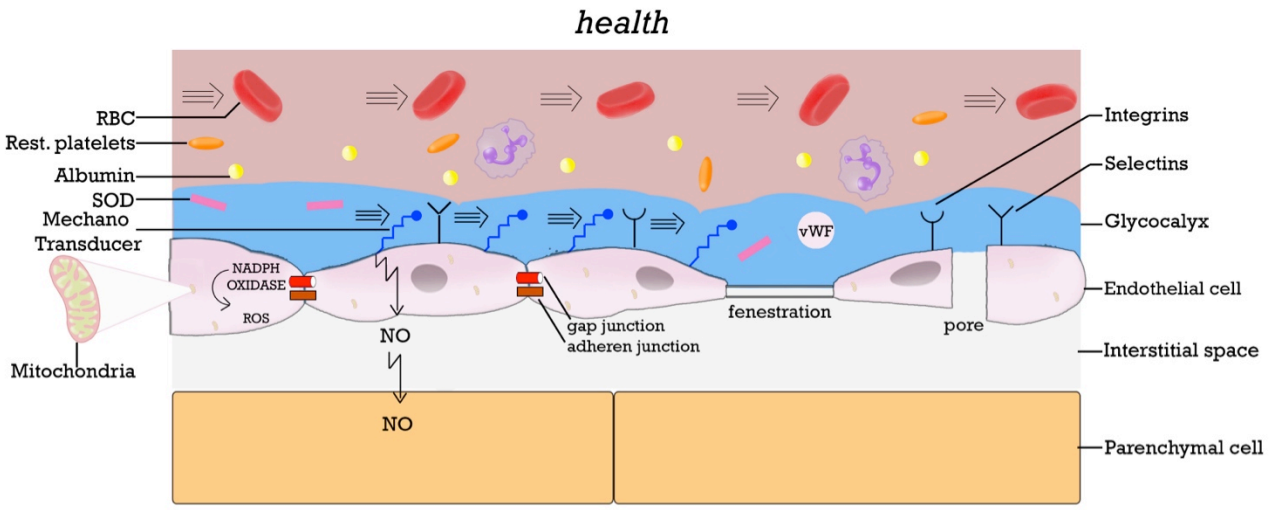

Figure 2. The endothelium in health: This figure shows a number of the key elements of the endothelium in health responsible for its key role in its interface between circulating blood and the parenchymal cells. Elements relating to it function as a vascular barrier, vascular regulation, transcellular signaling, and hemostasis are shown. Highlighted are the endothelium glycocalyx housing various molecules including mechanotransducers (and its transductory role between sensing sheer stress and inducing NO affective for smooth muscle vasodilation, inactive adhesion molecules embedded in the glycocalyx, molecules essential for hemostatic, and antioxidant defense molecules such as SOD. Intra and transcellular elemnts of the endothelial shown include mitochondria with its contribution to ROS generation and oxidative phosphorylation, Transcellular elements present include gap junctions for electrical communication for upstream vascular regulation and intercellular tight junctions important for maintaining vascular barrier. Morphological elements shown include transcellular fenestrations and pores.

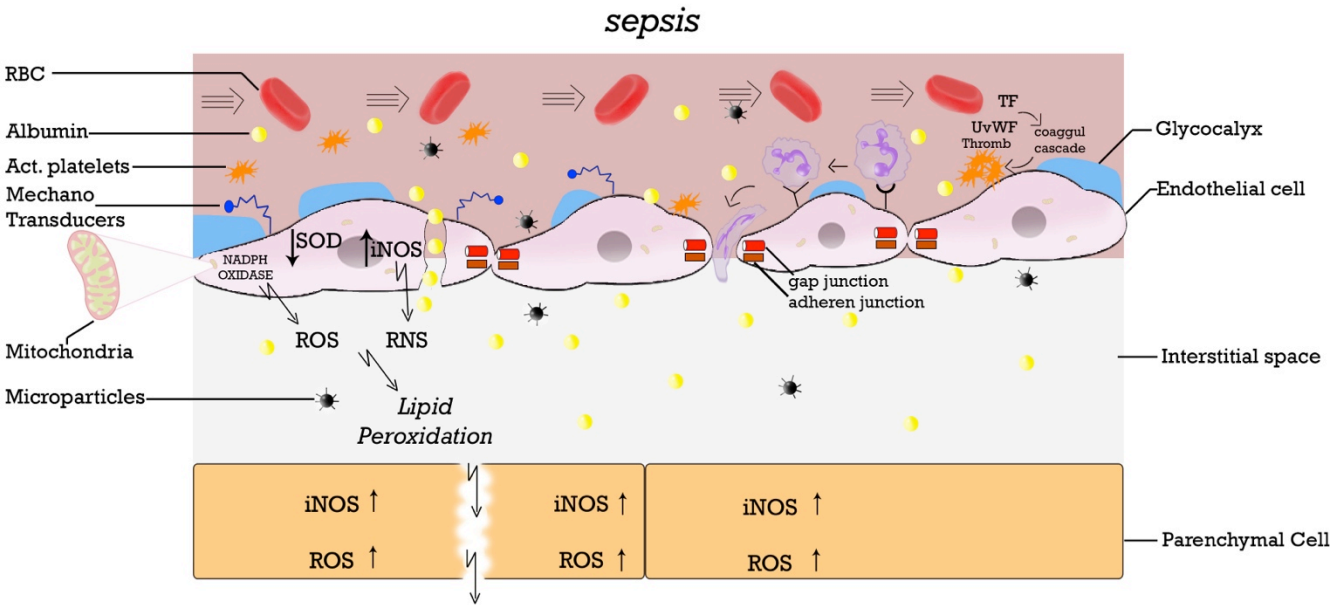

Figure 3. The endothelium in sepsis: This figure shows the pathogenic effect of sepsis on the various elements of the ECL resulting in its functional impairment in terms of its function as a vascular barrier, a regulator of vasotone and its hemostatic function. The destruction of the glycocalyx results among many other effects, in the exposure of adhesion molecules resulting in the trapping (selectins) and transmigration (integrins) of activated leucoytes, activation of hemostatic compounds in favour of a pro-coagulatory state and the loss of mechanotransductory function due to these molecules losing their natural environment essential for the sensing of sheer stress. The barrier function of the ECL is compromised by direct membrane destruction due to lipid peroxidation induced by ROS/RNS as well the decomposition of molecules such as tight junctions anchoring the EC together. The role of the EC as a vasomotor tone regular is lost due to the loss of function of the mechanotransductory system, the over production of iNOS mediated NO and the loss of transcellular gap junction essential for an integrative control of vasotone along the ECL. Endothelial destruction also results in the release of microparticles contributing to the pathogenic effect of EC dysfunction.

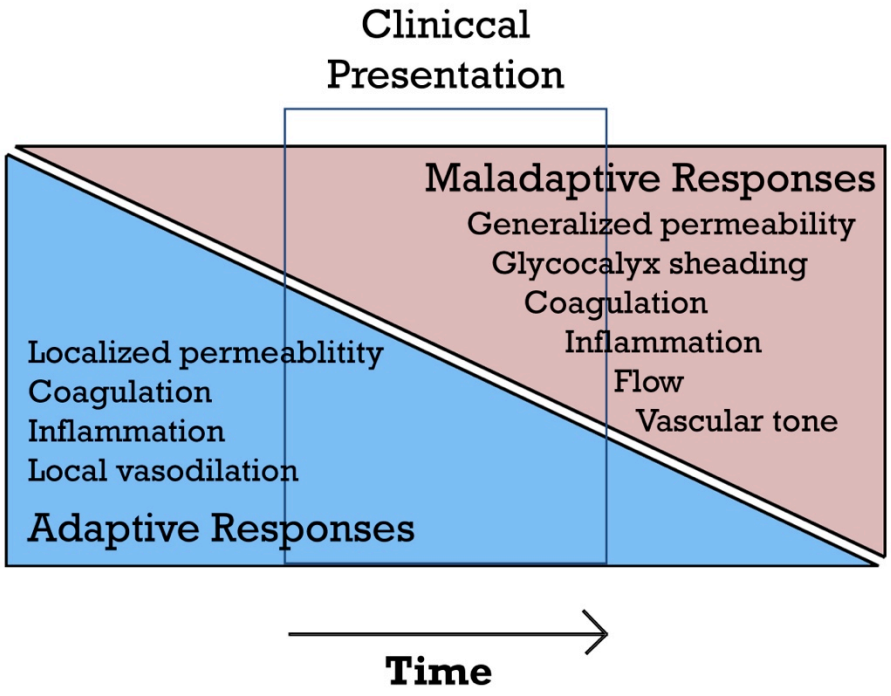

Figure 4. Conceptual framework of adaptive vs. maladaptive responses to the septic insult.

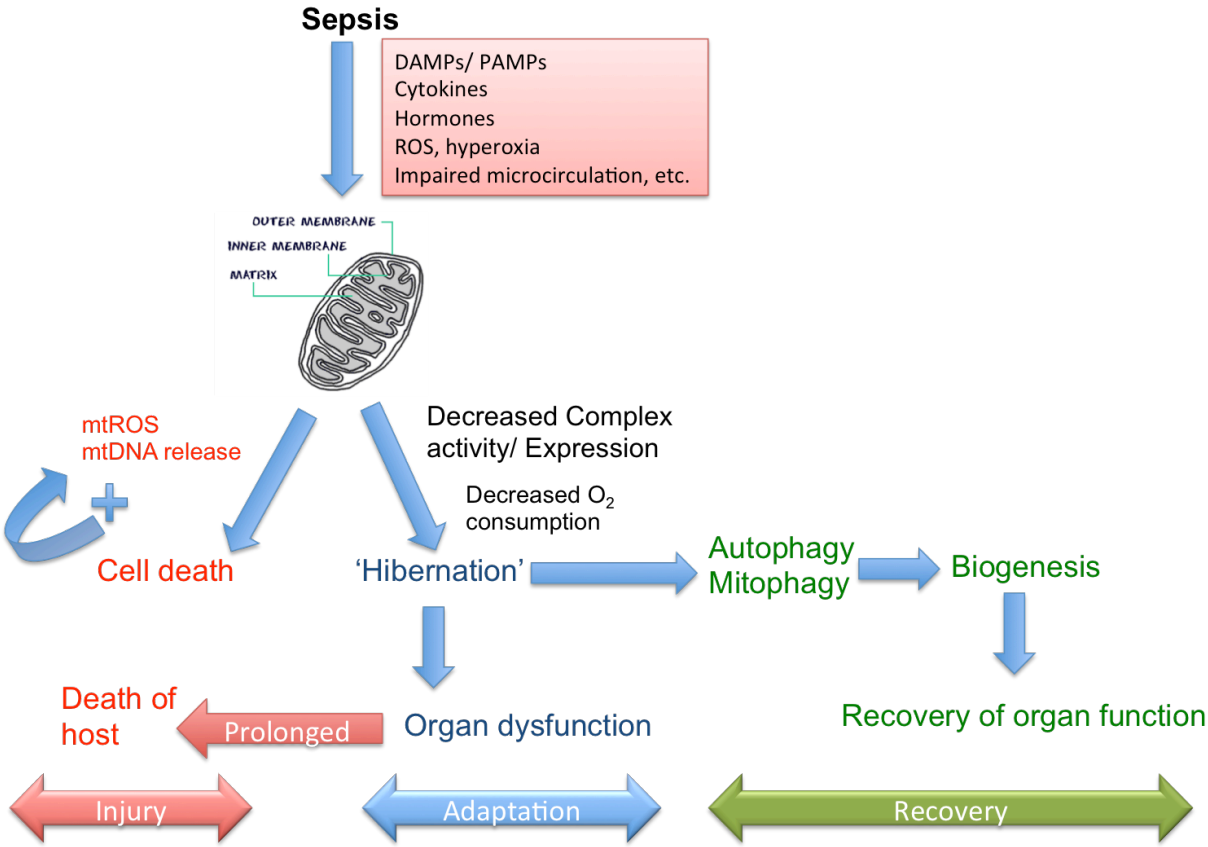

Figure 5. Conceptual framework of the role of mitochondrial function in the response to sepsis.

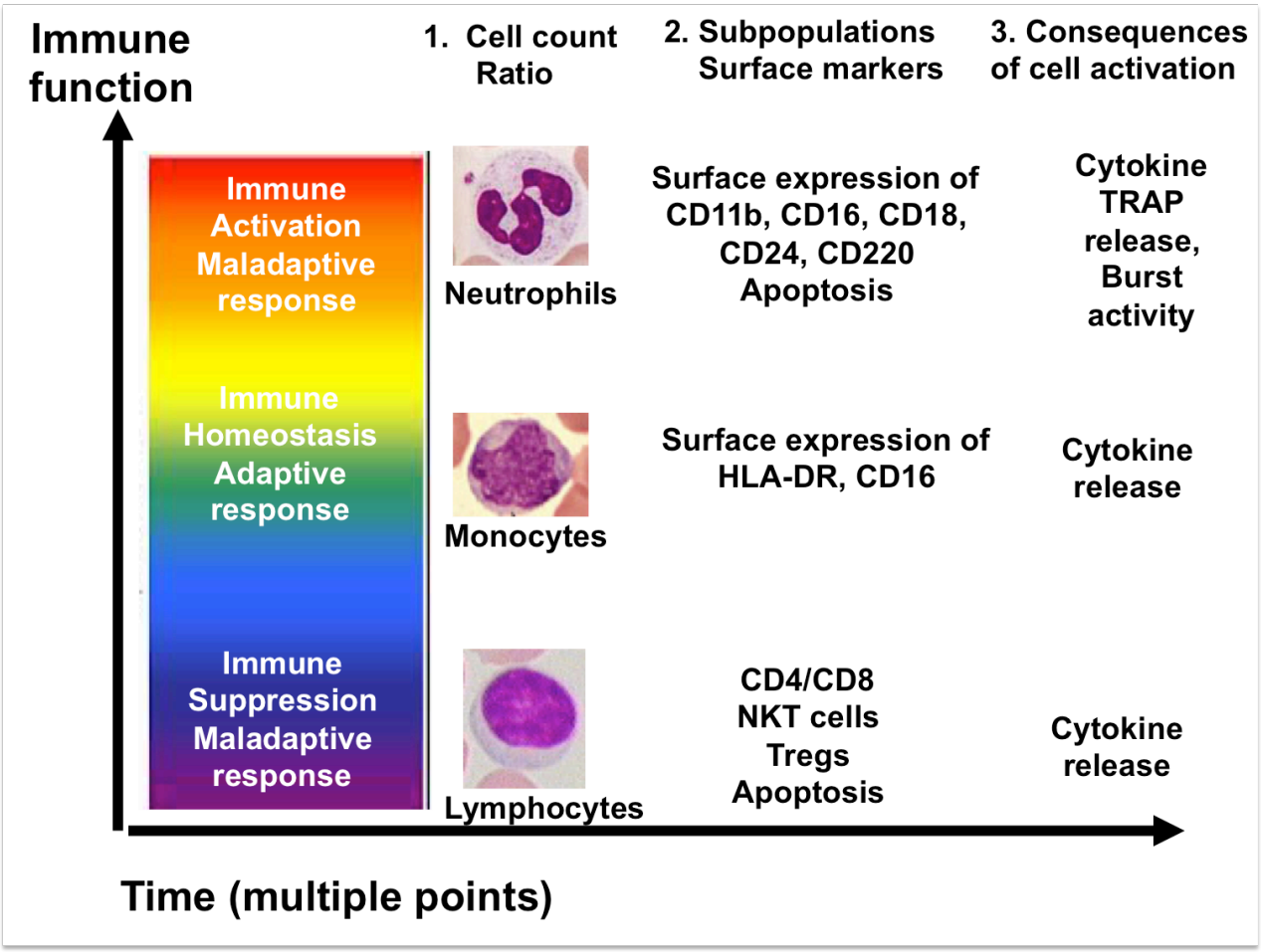

Figure 6. Multi-step evaluation of immune cell activation, suppression and homeostasis. FACS can identify on neutrophils, monocytes and lymphocytes: 1) cell count ratio; 2) specific sub-population surface markers; 3) biological consequences of cell activation.

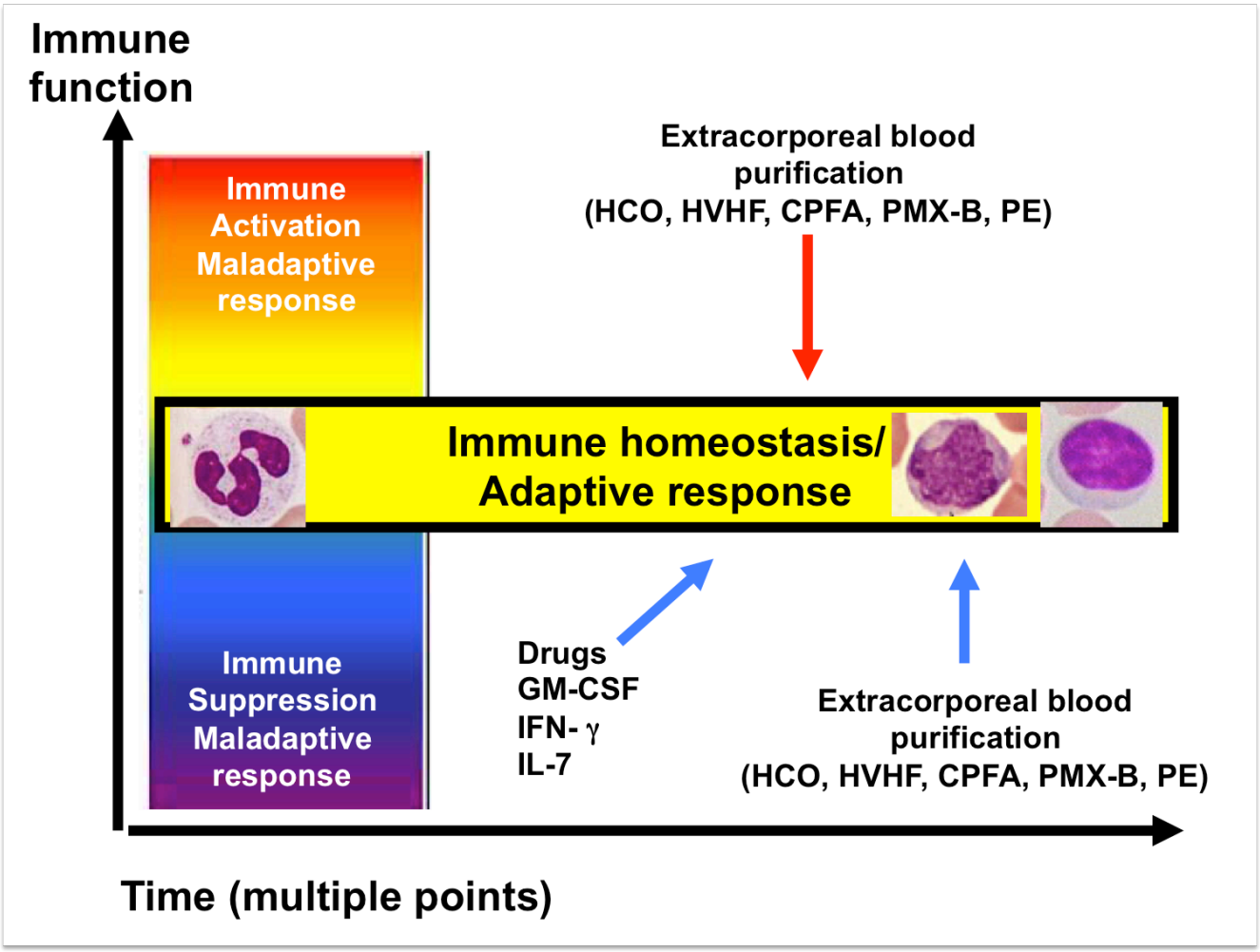

Figure 7. Possible biological effects of different drugs and of extracorporeal blood purification therapies on immune system activation, suppression and homeostasis. HCO: high cut-off; HVHF: high volume hemofiltration; CPFA: coupled plasma filtration adsorption; PMX-B: polymyxin B hemoperfusion; PE: plasma exchange; GM-CSF: granulocyte-macrophage colony-stimulating factor; IFN-γ: interferon gamma; IL-7: interleukin 7.