A Plea for an Extended Concept of the Cell

For a better understanding of the bewildering diversity in immunomodulation we must extend our strictly cell orientated knowledge.

Just as every other discipline, medicine approaches reality, i.e. the phenomenon of illness, with specific kinds of questions. Ever since the so-called Galilean Revolution in the 17th century these specific kinds of questions have been marked by linear thinking of cause and effect. In the field of medicine, in contrast for example to the field of physics, the resulting questions about nature in terms of numerical measurement could not be made use of until the cell was discovered as the 'smallest denominator' of organisms by Schwann and Schleiden at the beginning of the 19th century. It is reflected as a paradigm of modern medicine in Virchow's cellular pathology. Kybernetics (Wiener), that emerged in the 1950s and the development of the theory of 'thermodynamics of open energetic systems' (Prigogine) have, however, shown that biological systems are not linear, but rather highly cross-linked and subject to a biological steady state. That means that biological systems are open energetic systems and are thus able to exchange energy and material with their surroundings. The old concept of the cell is not able to include this aspect until extended by the ground substance. It is a fact that it is necessary to define the individual conditions in a causal-analytical method, but due to the increase of chronic diseases, conditions for an overriding principal of order must be sought, that serves as a basis for the striving for preservation of organisms.

This principal is provided for by the ground substance and its regulating mechanisms (Pischinger). Correspondingly, the ground substance pervades the extracellular spaces of the whole organism, reaches every cell and always reacts in the same way. Where the extracellular space is reduced to minimal fissures in epithelial cell groups or in the brain mass, the ground substance forms the intercellular substance. Biochemically speaking, it forms a network consisting of highly polymerized sugar-protein complexes in which the proteoglycans predominate, followed by structural glycoproteins (collagen, elastin, fibronectin, laminin, among others). These form a molecular sieve through which the whole metabolic process must pass (transit route) from the capillaries to the cells and vice versa. Molecules over and above a certain size and/or membrane potential are subject to an exclusion effect. The size of the pores in the filter is determined by the individual concentration of proteoglycans in the relevant tissue compartment, by its molecular weight and by electrolytes and the resulting pH value. The negative potential of the proteoglycans is of decisive functional importance in this process, whereby they are able to bind water and act as ion exchanger of monovalent to bivalent cations. They are thus guarantors for isoionia, isoosmia and isotonia in the ground substance (Hauss). The electrostatic base tonus thus established reacts with fluctuations of potential to each variation in the ground substance. The information that has been coded in this way can then pass itself on as fluctuations of potential in the glycocalyx (superficial film of sugar) to the cell membrane and there, if they are strong enough (selection of information) lead to a reaction in the cells through depolarisation of the cell membrane (e.g. muscle and nerve cells) or as in the case of all other kinds of cells through activation of membrane-based secondary messengers (cyclic

adenosine monophosphate, inosine triphosphate, among others) that transfer the coded information in the ground substance to cytoplasmic enzymes. These reach the nucleus of the cell and can in the end have contact with the genetic material of the nucleus at a suitable point. Thereupon the transcription of relevant DNA-parts (genes) takes place to the various RNA-types. Following the transfer into the cytoplasm the various RNA-types commence the translation of the information on the tubes of the endoplasmic reticulum into products of the cell itself. Since the ground substance is connected to the system of endocrine glands through the capillaries and to the central nerve system through the peripheral vegetative nerve fibres that end blindly in the ground substance, and since the two systems are connected with each other in the brain stem, overriding regulation centres can be influenced via the ground substance. Capillaries, vegetative nerve fibres and the cells of the connective tissue regulating the ground substance, that can influence each other with 'information' via wandering cells of connective tissue (macrophages, leukocytes, mast cells) about products released from the cells (prostaglandin, interleukins, interferons, proteases, protease inhibitors, among others), make up an extremely complex cross-linked humoral system, the historical predecessor of which is to be found in the classical humoral doctrine.

The advantage of such cross-linked systems lies in the considerable increase of adaptability and efficiency and the possibility of newly emerging characteristics appearing again and again, that are not to be achieved by simple addition of the individual characteristics of the components. The ground substance is regulated in a compensating way by an original system of cells: the fibrocyte-macrophage system. Whereas fibrocytes are able to react correctly to a situation within seconds with a quantitatively and qualitatively adapted synthesis of proteoglycans and structural glycoproteins, macrophages for their part can normally disintegrate ground substance by phagocytosis. As the fibrocyte is not able to distinguish between 'good and evil', when it is chronically altered it develops more and more an unphysiological ground substance that can contribute considerably through its influence on all cellular elements to the development of chronic diseases, even to that of tumors (Heine).

H. Heine, Herdecke 1989;012:56