Results and Problems in Cell Differentiation

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Cell Communication in Nervous and Immune System

With 28 Figures, 8 in Color, and 3 Tables

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Preface

Signal exchange between cells is a key feature of life from humble monads to human beings. Appropriate communication is of particular importance between cells of multi-cellular organisms. Various basic mechanisms of cell–cell communication have evolved during phylogenesis, which were subject to organ, tissue and cell type-specific adaptation. These mechanisms range from long-distance communication via hormones to more and more local processes, e.g. via cytokines, chemokines or neuromodulators/neurotransmitters, and eventually direct physical interactions of molecules anchored at cell surfaces. Accordingly, highly specialized transient or stable cell–cell contact sites have evolved that mediate signaling between cells. With few exceptions (e.g. lipophilic hormones, gases) intercellular communication depends on specific signal detection devices at the cell surface coupled to a signal transduction apparatus that mediates the signal transfer across the cell membrane and activates intracellular effector systems, which generate intracellularly decipherable signals.

Prime examples for tissues of intensely communicating cells are the nervous and the immune systems. Although at the first glance these systems appear very different, both have developed sophisticated mechanisms for the formation of memory, though of quite different quality and significance for the organism. Memory formation in the immune system serves the recognition and tolerance of the organism's own cells and tissues as well as the effective recognition of and defense from invading pathogens. It is based on a complex network of cellular communication and signaling processes between cells of this "dispersed" organ and with target cells. Brain mechanisms of learning and memory, on the other hand, are indispensable for survival of an organism in its natural and social environment. They are based on the function and plasticity of the probably most complex cell junction: the chemical synapse. However, other cell–cell connections, such as gap junctions or specialized neuron-glia interaction sites, play an essential part in brain performance and plasticity.

This collection of reviews, contributed by internationally recognized immunologists and molecular and cellular neurobiologists, juxtaposes cellular communication devices and signaling mechanisms in the immune and the nervous system and discusses mechanisms of interaction between the two systems, the significance of which has only been fully appreciated in recent years.

Thus messengers produced by one of the two systems, such as cytokines or neuropeptides, can modulate cellular communication in the other system as well. Moreover, the central nervous system (CNS) has long been considered an immune-privileged organ lacking the classical immune response. Based on recent studies this view had to be revised and refined, and the particular role of the immune system in neuropathological as well as in neuroprotective and neurorepair processes has been recognized. This implies that the potentially harmful effects of the immune system in the CNS have to be tightly controlled by precise communication between cells of neural and immune systems.

The first four review articles deal with chemical synapses of the CNS. This highly sophisticated asymmetric cell–cell contact is designed for particular communication between neurons via chemical substances, the neurotransmitters. Neurotransmitters are stored in little membranous containers, i.e. synaptic vesicles, and released from the presynaptic cell in response to incoming electrical signals in a regulated manner. Different postsynaptic devises have evolved to detect excitatory (the first chapter) or inhibitory (the second chapter) transmitters and transduce the signals into the postsynaptic cell. Also the site of regulated neurotransmitter release from the presynaptic neuron—the active zone—is a complex molecular machine that organizes the synaptic vesicle cycle (the third chapter). The gap between the pre- and the postsynaptic membranes, the synaptic cleft, is a specialized extracellular compartment arranged by various cell adhesion molecules and components of the extracellular matrix that is thought to contribute importantly to synaptic assembly and plasticity (the fourth chapter).

Though known for more than 50 years, the electrical synapses have had a shadowy existence for a long time and only during recent years have their identity and their physiological relevance been studied in more detail. The fifth chapter discusses the role of gap junctions that form electrical synapses in the CNS. The next chapter discusses another intriguing cell–cell contact site that determines the capacity and efficacy of the vertebrate nervous system is the neuron-glia interaction at the so-called nodes of Ranvier, which facilitates rapid propagation of electrical signals along myelinated axons.

Also within the immune system the term “synapse” has been meanwhile well established. Here, the so-called immunological synapse describes the molecular and biophysical events that occur when immunocompetent cells interact with each other at the beginning of the adaptive immune response. T-cells, the major components of the adaptive immune system are by themselves incapable of detecting complete bacteria or viruses. Rather, the major structure on the T-cell surface that initiates T-cell activation, the T-cell receptor (TCR) only recognizes small, 9 to 12 amino acid-long bacterial or viral (antigenic) peptides. These have to be generated by particular immunocompetent cells, which have collectively been termed antigen presenting cells (APCs). Although it is well known that B-cells, dendritic cells and macrophages rep-

resent the major types of APCs that activate T-cells, it is still unclear whether, for example, endothelial cells, which are spread throughout the whole body, are also capable of presenting antigens to T-cells, at least in particular organs such as the liver, or under particular conditions such as inflammation. These questions are addressed in the seventh chapter, which also discusses the immunological consequences of the interaction between T-cells and endothelial cells.

Importantly, the mere generation of antigenic peptides is not sufficient to activate T-cells. This is due to the fact that the TCR only signals when antigenic peptides are presented to the T-cell by APCs in conjunction with self-molecules, the so-called major histocompatibility complex (MHC) molecules. The detection of antigen/MHC by the TCR occurs at the beginning of the immune response at the interface between the T-cell and the APC and this first physical contact between the two cells induces the formation of the immunological synapse. Consequently, the immunological synapse is a highly dynamic structure that changes its morphology and molecular composition during the initial phase of the immune response. During the past decade numerous groups have begun to dissect the molecular events that either regulate the formation of the immunological synapse or occur after immunological synapse formation by applying sophisticated microscopic and biochemical techniques. As a result, several models of the molecular composition and the function of the immunological synapse have evolved. The eighth and ninth chapters focus on the biophysics and the morphological changes of the immunological synapse under different conditions of stimulation and further discuss the role of the immunological synapse during T-cell activation. While these two articles primarily deal with the dynamics of APC/T-cell interactions and the morphological changes of the immunological synapse on the microscopic level, the following two chapters focus on the signaling events that regulate particular aspects of immunological synapse formation and T-cell activation. The first of these discusses alterations of the cytoskeleton and the second the regulation of intimate membrane contacts via adhesion molecules and integrins.

The final two chapters shed some light on the communication between the immune and the nervous system and the control of immune responses in the nervous system. To gain access to the CNS, immune cells have to cross the blood–brain barrier provided by composed of endothelial cells. How this process is mediated and controlled under physiological and pathological conditions is discussed in the penultimate chapter. Endocannabinoids, the endogenous ligands for the "Marihuana" receptors, seem to be intricately involved in the neural control of the immune system. The current view of how the CNS endocannabinoid system contributes to the immune surveillance is discussed in the final chapter.

This book is dedicated to our colleague Werner Hoch, who intended to contribute an article on the neuromuscular junction, the supposedly best-

studied vertebrate synapse and long-time focus of Werner's scientific work. Werner passed away last summer—unexpectedly and much too early for all of us.

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