How cells assemble: A fundamental process in the formation of the body

Dr. Takeichi, Masatoshi

The world of living things can be broadly divided into single-celled and multicellular organisms. The former group includes bacteria, yeast, and protozoa, while the latter consists of nearly every life form visible to the naked eye. Unicellular organisms are individual cells that do not need to associate with other cells in order to live. In contrast, the body of a multicellular organism contains multiple cells, sometimes huge numbers of them. Each of these cells works only as a building block within some greater bodily structure and cannot function as an independent living entity. The different types of cells that make up a multicellular organism each have specific roles to play, which they can realize only by assembling into a larger functional unit.

A number of features distinguish multicellular organisms from single-celled ones. One of the most fundamental of these is the ability of the cells in a multicellular organism to adhere to each other. Although both plants and animals can be referred to as multicellular organisms, these two kingdoms differ greatly in terms of structure, and I will limit my talk today to a discussion of multicellular animals (or metazoans). Metazoan cells are able to adhere to one another. Tissues made up of such cells can be dissociated into individual living cells by various methods, and, when cultured under appropriate conditions, the cells spontaneously adhere to each other and reorganize into multicellular structures. What is perhaps even more surprising is that such cells demonstrate the ability to recognize specific adhesion partners. For example, when a tissue containing cartilage cells and epithelial cells is dissociated and the cells randomly mixed, cells of both types recognize and adhere preferentially to their compatible partners - cartilage to cartilage and epithelium to epithelium - enabling the reconstitution of a multicellular assembly by isolated individual cells. This shows that animal cells have an innate capacity for organizing into complex, tissue-specific structures. The importance of this ability is seen most clearly in wound healing, in which cells in the vicinity of the wound area associate with each other to reconstitute the damaged tissue.

Early in my career, I became interested in identifying molecules involved in cell-cell adhesion and, in particular, working out the means by which cells are able to recognize specific adhesion partners, questions that I continue to explore today. By the 1970s, many outstanding researchers had shown interest in these same questions, proposing a range of hypotheses and engaging in heated debates, but none had been able to solve the mystery of cell-cell adhesion. It struck me that the process must involve a set of complex mechanisms and that the best approach to solving the puzzle might be to break it down into its component parts and attack each question individually, rather than to try to arrive at a single universal explanation.

Cell adhesion takes two main forms: the adhesion of cells with other cells, and adhesion between cells and non-cellular material. In the latter process, cells adhere to a complex substrate known as the extracellular matrix, which fills the spaces between cells. A similar type of cell adhesion is also seen when cells proliferate on a glass or plastic culture dish, using its surface as a kind of scaffold. We refer to the two forms of cell adhesion as "cell-cell" and "cell-matrix" adhesion. I found that these two types of cell adhesion differ from each other in their dependency on divalent cations, and it occurred to me that both might be controlled by

different mechanisms. Calcium and magnesium are the two most important divalent ions present in body fluids, and I noted that each seemed to be necessary for a different form of adhesion to take place, with cell-matrix adhesion requiring magnesium ions and cell-cell adhesion dependent on calcium. My subsequent research has focused mainly on cell-cell adhesion, but it is now clear from others' work that magnesium-dependent cell-matrix adhesion is mediated by integrins.

I next found that cell-cell adhesion can itself be categorized into calcium-dependent and calcium-independent processes. I was sure that by studying these mechanisms separately, I would be able to develop a better understanding of the underlying principles. I began by searching for molecules playing central roles in the two processes and found that, in each case, cell-cell adhesion involved proteins present on the cell surface and that the function of either mechanism was sufficient to produce adhesion between cells. There is, however, a fundamental difference between the two mechanisms in that cellular activity seems to be necessary for calcium-dependent adhesion. At low temperatures, for example, the calcium dependent mechanism does not function at all, while the calcium-independent mechanism works even in the absence of cellular activity, suggesting that calcium-independent cell-cell adhesion is purely a molecular reaction. This led me to think that the calcium-dependent mechanism would be of greater significance in cellular functions and I decided to study the phenomenon in more detail.

Cadherins are transmembrane, cell-surface proteins that mediate cell-cell adhesion in a calcium-dependent manner. These molecules extend through the cell surface membrane, and the binding of extracellular domains of cadherin molecules present on neighboring cells results in cell-cell adhesion. Experiments have shown that cadherins are essential for cell-cell adhesion and, interestingly, that various types of cadherins exist, each of which functions in specific types of cells. For example, a form called E-cadherin is expressed and functions in epithelial cells, while another form, N-cadherin, is found in neural cells. Cells that express cadherins of a certain type adhere only to cells presenting the same type of cadherins. This may help to explain the phenomenon of selective adhesion (adhesion only to cells of a specific type), which has been observed in mixed populations of cells. Since the discovery of this selectivity, dozens of varieties of cadherins and related molecules have been identified. Many different types of cadherins seem to be required for the morphogenesis of complex body structures, and while cadherins were first discovered in vertebrates, they are currently thought to be present in all metazoan organisms.

Subsequent research has made it clear why the calcium-dependent mechanism of cadherin-mediated cell-cell adhesion requires cellular activity. The intracellular domain of the cadherin molecule binds to other proteins, called catenins, which themselves interact with contractile proteins, such as actin. These contractile proteins seem to be important to cadherin function, and since their activity requires biological energy sources, it is little wonder that cell-cell adhesion itself is dependent on the physiological activity of cells. It can be seen from this that cell adhesion is neither static nor a simple gluing together of cells, but is a vital, dynamic process. Cells utilize cell-cell adhesion machinery in different ways, as dictated by

specific functional demands. At times a group of cells might form tight and stable associations, while in a different setting the same cells might form looser junctions or, in extreme cases, detach from each other completely. Ongoing research into these mechanisms suggests that this cell adhesion machinery may be important to understanding the behavior of metastatic cancer cells, as indicated by the finding that metastasis tends to accelerate when aberrancies in cadherin function disrupt intercellular adhesion. A number of abnormalities in cadherin function have already been identified in cancer cells, and further investigations into the role of cadherins in cancer are strongly warranted.

It has also become clear that cadherins play an important role in the regulation of the functions of the specialized form of cell-cell junction known as synapses, which are the central points of communication in neural networks. Multiple defects in neuronal function have been demonstrated in experimental models of cadherin loss-of-function. Afflictions of the nervous system remain one of the great unresolved medical problems confronting mankind, and it is my hope that my work will make a contribution to determining pathological factors underlying neurological and psychiatric disorders.