DIFFERENTIATION AND TRANSDIFFERENTIATION OF NORMAL AND NEOPLASTIC CELLS

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Differentiation can be defined as a process leading to differential expression of genes in cells forming specific tissues and/or their precursors and primordia. In most instances cellular differentiation is a step-wise gradual process beginning with undifferentiated, developmentally committed or uncommitted embryonic cells or organ and tissue specific stem cells, which give rise to more differentiated cells at intermediate levels of maturation. Ultimately the differentiation of cells results in the formation of anatomically and functionally fully established cells, typical of specific tissues or organs.

Transdifferentation is a process in which mature cells of one phenotype change into another cell type. This process involves differentiated cells, and is typically found only in adult tissues.

Differentiation has been extensively studied in embryonic cells. Embryonal carcinoma (EC) cells, the malignant immortalized equivalents of early embryonic cells have been used as an adequate surrogate for normal embryonic cells. Numerous experiments performed in different laboratories worldwide have not been able to establish significant differences between the EC cells and their normal counterparts indicating that the basic processes governing gene activation or suppression are identical in malignant and non-malignant normal cells. Like the normal embryonic cells EC cells respond to morphogens ,such as retinoic acid, and differentiate into either somatic tissues, or extraembryonic tissues such as yolk sac epithelium. This process can be monitored by means of molecular biology techniques, demonstrating activation of specific genes; biochemically and immunochemically by demonstrating the appearance of new cell surface and cytoplasmic marker proteins, and new secretory products; morphologically, by showing the evolving cytoplasmic complexity and changes in cell morphology.

Using EC cells isolated from murine and human teratocarcinomas we have been able to show that EC cell of these two species share some common features, but also that they express species specific features. We have also been able to show that not all EC cells are identical with regards to their developmental potential and that not all EC cells are at the same level of differentiation. A spectrum of phenotypic features has been identified in various EC cells, which apparently resemble normal embryonic cells at different stages of development. In the mouse EC cells correspond to normal cells found in the inner cell mass of the blastocyst or ectodermal cells in the 5 to 7 days old egg cylinder. The phenotype and the developmental potential of these EC cells depends on which stage of development they have been fixated. The phenotype and the developmental potential of established EC stem cells remains stable over years. New stem cells may however evolve during propagation of the original stem cell lines. These new stem cells usually have a distinct phenotype and are usually equivalent to yolk sac carcinoma cells. Somatic forms of malignant stem cells, such as those corresponding to osteosarcoma have been also cloned. These data indicate that the phenotype of EC is stable in most instances, and that the pattern of differentiation of these cells remains comparable to that of equivalent normal cells.

Transdifferentiation has been studied in the model of murine vagina. Adult mouse vagina is lined with squamous epithelium which changes cyclically in response to sex hormones secreted during the normal estrous cycle. The superficial layers of the stratified squamous epithelium undergo transdifferentiation into cuboidal mucinous cells during the proestrus phase of the cycle. The change in the cell phenotype can be detected morphologically. It is associated with the appearance of glycoproteins that are packaged into secretory granules and extruded into the lumen of the vagina. At the same time the basic ultrastructure of these cells changes. The cytoskeletal protein pattern changes, characterized by the reappearance of low molecular weight keratin polypeptides , typically found in simple non-keratinized epithelia. Transdifferentiation of superficial squamous epithelium of the vagina can be induced hormonally. It also occur during pregnancy indicating that this form of transdifferentiation has functional significance.

Comparative studies of differentiation of embryonic cells and transdifferentiation of squamous epithelium of adult sexually mature animals point to certain common pathways in these structurally distinct processes.

References

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