Association of mesenchymal cells and immunoglobulins with differentiating epithelial cells

ABSTRACT

These data suggest that the phylogenetically and ontogenetically developed hierarchy of mesenchymal cells (MDC, pericytes, T cells) and immunoglobulins (IgM, IgG) accompanies differentiation of epithelial cells from immature into the mature and aged phenotype. Further studies of an involvement of mesenchymal cells in the regulation of tissue homeostasis may bring novel approaches to the prevention and therapy of tissue dysfunctions characterized by permanent tissue immaturity (muscular dystrophy) or accelerated aging (degenerative diseases).

INTRODUCTION

Background During last two decades, the contribution of specialized mesenchymal cells, i.e., fibroblast-derived vascular pericytes, monocyte-derived cells (MDC), and lymphocytes, to the proliferation, differentiation, and aging of tissue-specific cells in various epithelial, parenchymal, and muscle tissues has gained increasing interest. Recent developments in the understanding of the role of mesenchymal cells and their products in regulation of proliferation and differentiation of tissue cells were initiated more than seventy years ago, when Alexis Carrel demonstrated that leukocyte extracts, like embryonic tissue extracts, stimulate multiplication of fibroblasts in vitro, and suggested that leukocytes can bring growth- activating substances to tissue-specific cells. Later, in the 1960s and 1970s, lymphocytes were shown to promote tissue growth and regeneration (reviewed in Ref.). In spite of these achievements, our understanding of the interactions between mesenchymal and tissue-specific cells is still in its beginning. While a lot of work has been done on the role of various growth factors and cytokines produced by mesenchymal cells on the cell cycle and death in vitro, little is known about interactions between mesenchymal and tissue-specific cells in vivo. The role of mesenchymal cells in homeostasis of normal tissues (and cancer) is still poorly understood. Our studies, and those of others, demonstrate that the interaction between mesenchymal cells and tissue-specific cells is complex. The nature of the interactions may depend on the tissue type, e.g., liver, brain and muscle with very long lived differentiated cells, vs. epidermis, ectocervix and vagina, where cells growth and die at a relatively rapid rate. Alternatively, it may depend on the prevention ("stop effect") or allowance/stimulation of differentiation of cells into the suicidal state (apoptosis) by mesenchymal cells in a given epithelium. The relationship of mesenchymal and epithelial cells appears to be tissue-specific and established during the critical period of development, which coincides with the end of the immune adaptation. Specialized mesenchymal cells, such as pericytes, MDC and T lymphocytes, may significantly influence the differentiation and aging of epithelial cells. The extent to which epithelial cells are stimulated to differentiate by mesenchymal cells is dependent on the extent to which the particular tissue differentiates during the critical period of development. We have also suggested that advanced differentiation of epithelial cells may require certain cytokines released from T cells and DC undergoing suicide. The terminal stage of cell differentiation is apoptosis, during which cells undergo DNA fragmentation and die. Apoptosis is an active process, and it is induced by p53, which inhibits cell growth and activates and represses gene transcription. Proapoptotic function of p53 appears to be regulated by ras proto-oncogene. Cells transformed with mutated ras exhibit a defect in the signal transduction

pathway regulating p53 function and alteration in the expression of apoptotic (bax) or anti-apoptotic proteins (bcl-2). In human ectocervix, the interactions between cells of mesenchymal origin and these of epithelial origin change when examined in a cross section from the basal (immature) layer, where stem cells reside, to the outermost layers, where the epithelial cells are oldest and highest differentiated. Hence the ectocervix represents a suitable model for the investigation of mesenchymal cell association with the differentiating and aging epithelial cells in vivo. The data presented here indicate that phylogenetically and ontogenetically developed hierarchy of mesenchymal cells (MDC, pericytes, T cells) and immunoglobulins (IgM, IgG) accompanies differentiation of epithelial cells from immature into the mature and aged phenotype. Intraepithelial T lymphocytes and mature DC exhibit suicide, and immunoglobulins are associated with aging and apoptosis of epithelial cells.

CONCLUSION

Conclusions Our observations indicate that the phylogenetically and ontogenetically developed hierarchy of mesenchymal cells (MDC, pericytes, T cells) and immunoglobulins (IgM, IgG) accompanies differentiation of epithelial cells from immature into the mature and aged phenotype. In agreement with views of others, we propose that the complex of interactions involved (Fig. 6) is not uniquely concerned with immunity, but it includes basic interactions which stimulate differentiation of mesenchymal and epithelial cells. Involvement of immune system-related elements (MDC, T cells and B cells) in regulation of epithelium differentiation represents a basic mechanism of immune physiology toward self, from which the immune surveillance toward nonself has evolved. Accordingly, when required, the intraepithelial mesenchymal cells regulating tissue differentiation may be converted into effectors of immunity against infected epithelial cells. Further studies of the mesenchymal-epithelial network may bring novel approaches to the prevention and therapy of tissue dysfunctions characterized by permanent tissue immaturity (muscular dystrophy) or accelerated aging (degenerative diseases).