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REVIEW ARTICLE

Role of epithelial–mesenchymal transition in orofacial development - An insight

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Abstract

Epithelial–mesenchymal transition, commonly known as EMT, plays the dominant role in the developmental process, wound repair and tissue regeneration, and metastasis. EMT is classified into Type I, Type II, and Type III based on the molecular pathway it affects. Various molecular players such as transcription factors, growth factors, and cytokines play a significant role in the transition from epithelial cell type to mesenchymal cell type by change in the cell surface markers as well as the physiological changes such as increased mobility and invasiveness of the altered cell. In orofacial development, EMT plays a crucial role in organogenesis such as salivary gland development and tooth development. It is also contributory to palatogenesis.

Introduction

Gary Greenburg and Elizabeth Hay first coined the term "epithelial–mesenchymal transition" (EMT) to describe the fundamental embryological processes of cell shape changes during animal development process.[1,2] Epithelium and mesenchyme are two basic tissue phenotypes in vertebrates. EMT permits a polarized epithelial cell to undergo multiple biochemical changes and finally assuming a mesenchymal cell property both morphologically and functionally.[3] This results in physiological changes in the epithelial cells such as enhanced migratory capacity, invasiveness, elevated resistance to apoptosis, and overall increased production of extracellular matrix components.[4] Besides, there is a change from the apical-basolateral polarity of the epithelial cells to the front-rear polarity of the mesenchymal cells. This change is accompanied by a reduction in the expression of epithelial cell markers, the acquisition of a spindle cell shape, and the increased expression of mesenchymal markers such as fibroblast-specific protein-1 (FSP1), vimentin, N-cadherin, and a-smooth muscle actin (a-SMA).[5] The process of EMT is completed by the degradation of underlying basement membrane and the formation of a mesenchymal cell that migrates away from the epithelial layer in which it originated. EMT is crucial for organized embryonic development. This process has a contributory role in adult life during wound healing, tissue regeneration, organ fibrosis, and cancer progression.[6] Based on functional consequences and expressed biomarkers, EMT can be classified into three subtypes: Type I, Type II, and Type III. Type I is dedicated to embryonic development where primitive epithelial cells give rise to their mesenchymal offspring and vice versa where mesenchymal cells obtain epithelial morphology harmonizing to an organized organogenesis. Type II is attributed to the differentiation of epithelial cells into new fibroblast-like cells in the interstitium; those are involved in wound repair, tissue regeneration, or organ fibrosis. Type III is associated with epithelial carcinoma and metastasis.[5]

Molecular Markers Confirming EMT

During EMT, cells have an altered epithelial structure and more fibroblast-like phenotype. The cells attain increased motility and migratory capacity and increased resistance to apoptosis. The cells maintain this altered phenotype even after removal of stimuli.[7] There are several proteins undergoing decreased expression such as E-cadherin, ZO-1, mucin1, cytokeratin, occludin, desmoplakin, collagen IV, laminin 1, and MiR-200

family. These groups of proteins are mainly epithelial or basement membrane markers confirming the total dissolution of epithelial characteristics. During EMT, some proteins have increased expression levels such as Snail (Snai1/Snail1), Slug (Snai2/Snail2), ZEB1 (TCF8/dEF1), ZEB2 (SIP1), E47 (TCF3), E2-2 (TCF4), Twist1, and FOXC2. These proteins are transcription factors which trigger the cells for increased expression of mesenchymal characteristics. Besides, increase in the matrix metalloproteinases such as MMP2, MMP3, and MMP9 is also noted, facilitating the mesenchymal cell growth.[7] Expression of cell surface proteins characteristics of mesenchymal cells such as N-cadherin, OB-cadherin, a5b1 integrin, αVb6 integrin, and DDR2 is increased. Few other markers distinct for mesenchymal cytoskeleton such as vimentin, fibronectin, a-SMA, and FSP1 have raised expression levels during EMT.[8] The growth factors and cytokines promoting EMT are tumor growth factor β (TGFβ), epidermal growth factor, hepatocyte growth factor, and fibroblast growth factor (FGF). Among them, TGFβ plays the most significant role. The central cascade for the promotion of EMT is mediated by Wnt proteins and Notch. The external factors contributing to the pathologic stimulus for EMT are hypoxic condition and generation of reactive oxygen species.[9]

Role of EMT in Orofacial Development

Development of palate

The secondary palate also known as the definitive palate develops between the 6th and 8th week of intrauterine life of human fetus. Lack of palatal shelf adhesion contributes to the most common craniofacial deformity, i.e. cleft palate.[10] Palatal shelves grow out bilaterally from the internal surfaces of the maxillary processes, elongating on each side of the tongue, and become horizontal above the tongue as it descends. As the opposing shelves reach each other, the lateral surfaces of the underlying basal medial edge epithelial (MEE) cells contact with the opposite palatal shelves and subsequently form a medial epithelial seam.[11] Complete disintegration of the MEE is essential to form a single confluent palate craniofacial structure and EMT has a significant role in disintegration of this MES.[6] The stages of palatal development are coordinated and controlled by various proteins and specifically increased expression of TGFβ3 in the MEE facilitating MEE disintegration.[12] TGFβ3 signaling causes transformation of midline epithelial cells into mesenchymal cells along with further downregulation of E-cadherin, desmosomes, keratin, and syndecan along with simultaneous upregulation of vimentin, confirming the mesenchymal transition that results in a confluent palate.[13,14]

Development of salivary gland

During the glandular development, the epithelial cells usually originate as ectodermal thickenings which subsequently form buds, and during the further development underlying mesenchymal cells, condensation occurs around it. The salivary gland development involves complex processes such as branching and/or folding of epithelia which denotes advancing morphogenesis. The interactions between epithelial and mesenchymal tissues were crucial for glandular tissue to form. There are sequential epithelial-mesenchymal interactions and the advancing development front results due to a series of cross talk between these two tissues and finally results in the formation of salivary acini. The development of salivary gland includes different stages such as prebud, initial bud, pseudoglandular, canalicular, and terminal bud.[15] During the developmental stages of salivary gland, branching precede the acinar cytodifferentiation. Different experimental studies have revealed that mesenchymal tissue from the anatomical location of the salivary gland has a key role controlling the glandular pattern formation, and it specifically controls the branching of the glands.[16] After the branching has occurred, the salivary gland epithelium has its indigenous potential for cytodifferentiation. In summary, differentiation of salivary gland acini is not dependent on signals from the mesenchyme, and the secretory granules formation is totally dependent on acinar function without having any mesenchymal interaction. On the other hand, temporal and spatial relations also contributes in the development of salivary gland tissue.[17]

Development of tooth

The process of tooth development begins with the development of dental lamina. There is an ectomesenchymal condensation in relation to area of tooth development and epithelial cells from the primary epithelial band that invaginates inside the ectomesenchymal condensation resulting in the formation of tooth bud. During this stage, there is an expression of Shh helping in the formation of tooth germ by interacting with the underlying mesenchyme.[18] Formation of this ectomesenchymal condensation is guided by FGF10.[19] Altogether, TGF β signaling promotes cell proliferation for matrix formation. After the formation of the bud stage, bone morphogenetic protein promotes the transmission of tooth development from the dental lamina stage to bud stage.[20] Positioning of the tooth germ is guided by Pax-9, which is a mesenchymal responding gene. Loss of Pax-9 causes arrest of tooth development at bud stage. Pax-9 mutation may lead to oligodontia or hypodontia. Wnt/β-catenin signal is essential at the lamina-early bud stage. This factor is also associated with molar cusps development. Large, shapeless tooth buds and ectopic teeth can be formed as a result of the mutation of β-catenin.[21] During further tooth development, Shh is expressed in the enamel knot area playing an important role in ameloblast formation.[22] Wnt/β-catenin signal also has an important role in differentiation of ameloblast and odontoblast. TGFβ2 is found to have a significant role in tooth crown development and expression of TGFβ2 is found in the basement membrane, the epithelial cells in the basal layer, the enamel knot, the mature odontoblast, and ameloblast.[23] Role of EMT is also found in dentinoenamel junction formation. The process of root dentin formation is almost similar like crown dentin formation except for the expression of Osterix which is specifically found in

root dentin.[24] Besides morphodifferentiation, EMT has a role to play in dental mineralization process and several molecules controlling the dental mineralization are Pitx2, Msx2, Lef1, Lhx6, Lhx7, Dix1, Dix2, Paz9, Gli1, Gli2, Gli3, Barx1, and Runx2.[25]

Conclusion

Epithelial-mesenchymal interactions appear to play an important role in the development and maintenance of normal tissue architecture. Any abnormality or dysregulation in their function contribute to developmental anomalies. A detailed knowledge about the molecular cascade of orofacial development enables us to reason out the causes of developmental malfunctions. The role of EMT can be best explained in oral tissues, due to the higher epithelial contribution and to the development of oral anatomical structures. In modern era of molecular biology, we need genetic research and molecular level of contemplation to highlight the significance of biological processes, thus helping us planning for overall management protocols.

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