REVIEW ARTICLE

RUNX- Role in Development and Tumourogenesis

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ABSTRACT

RUNX (Runt-related transcription factors) are crucial and important transcriptional factors that regulate vital biological pathways required for proper cellular processing and functioning. They play a pivotal role in maintain a balance in the cellular activities in the body. The role of these factors has been implicated in many signaling pathways in normal as well as in disturbed environment of our body. There are other signaling pathways which work in conjugation with RUNX and improve the cellular interactions. The role of the RUNX factors are so important that any aberration can lead to severe developmental anomalies, role of these factors are also highlighted tumourogenesis. Role of RUNX in physiology as well as in pathology is reviewed briefly.

KEYWORDS: Transcription, Biological Pathways, Ductal Morphogenesis, Tumourogenesis

INTRODUCTION

Runx belongs to a family of transcriptional factors that is known as Runt. It consists of three DNA binding subunits that are RUNX1, RUNX 2 and RUNX 3 each of which is capable of forming a heterodimers. These heterodimers are relatively weak in regulating the transcription. The activity of these transcription factors can be activated by joining these to various regulators like MYB, ETS, and CBP.[1]

RUNX family plays a very important role in determining the cell fate and its differentiation. It has been also found that this transcriptional factor leads to dimerization of the DNA and also DNA binding in the drosophila species. The RUNX 3 ablation models were even tried in the knockout models of the rats, and it was found that the rats which were stillborn. This leads to a conclusion that RUNX also plays an very important role in the formation and organization of the body systems.[2,3]

The TGF-beta pathway plays a significant role in maintaining homeostasis by maintaining a balance between various cell functions like proliferation, differentiation, adhesion and apoptosis. It exerts a strong tumour suppressive action. The signaling of this pathway is governed by numerous factors and also plays an important role in the malignant tumour progression when this particular pathway is altered by external stimuli. The RUNX family along with the Tgf- beta pathway have a role in the epithelial Mesenchymal interaction and hence gets involved in the formation of various tissue organization as well as cancer progression[4,5]. The RUNX-2 factor also interacts with the SMAD pathway i.e. SMAD2 and 3 along with Tgf-Beta receptors and significantly help in the formation of hard tissues like bone[6]. It was also noticed that that the interaction of SMAD 3 along with RUNX2 repressed the osteoblastic-specific genes and decreased their ability to transcript bone forming matrix[7,8]. RUNX3 acts an important tumour suppressor factor along with other tumour suppressor gene and also found to be in association with the pro-apoptotic genes and the apoptotic genes. Any dysregulation or mutation in the RUNX led to the pathogenesis of neoplasia or a tissue derangement[7].

RUNX proteins are important factors which play an important role in determining the cell cycle. They are DNA binding proteins and forms heterodimeric core binding factor (transcription complex).RUNX proteins have also been identified in the primitive organisms which mainly helps in the developmental process, and it indicates the evolutionary and differentiation process. In mammals, three families of RUNX is identified, and they are RUNX1, RUNX2,RUNX3 [9,10].

RUNX1 is mainly associated with hematopoiesis; RUNX2 is associated with osteogenesis whereas RUNX3 is associated to T cell development, thrombopoiesis and mural development. It was observed that a particular gene knockout has led to various defects and abnormalities related to the functioning of this proteins[9,10].

RUNX genes were identified on human chromosomes 6p21, 21q22.12, and 1p36.1. The RUNX proteins bind to the same DNA motif and have a role in the transcription of targeted genes by modulating the transcription factors. Each of the three genes is regulated by distantly located promoter 1 (P1-distal) and promoter 2 (P2- proximal) .P1

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do not have a CpG rich area compared to P2 and this area play an important role in the transcriptional process[11].

RUNX1 and 3 are expressed in the neuronal tissues that are dorsal and the cranial root ganglia. RUNX1 expression starts at the embryonal stage 12.5 while RUNX3 starts at the 10.5 in a larger diameter.RUNX1 are the first to be expressed in the hematopoietic stem cells. It was also seen to be expressed in the endothelial cells, umbilical arteries, and other blood-rich areas. Disruption or knockout mechanisms of RUNX1 showed an absence of fetal liver hematopoiesis as well as the death of embryos[12]. In the adult hematopoietic system RUNX1 were largely expressed in several stem cell lineages like B lymphocytes and T lymphocytes. RUNX1 and RUNX3 are closely related to the development of thymus and its cortication. Initially, these proteins were expressed in the cortex development, but in the later stages, RUNX1 was seen more defined to cortex and RUNX3 were found to be expressed in both cortex and medulla.RUNX3 expression was found to be higher in CD8/CD4 T cells in the medulla and mature CD8 T cells.RUNX2 was also seen to be expressed in the development of thymus and any dysregulation in the protein has shown lethal effects in the development of the T cell development[12,13].

RUNX IN OSTEOGENIC TRANSCRIPTION

All the three RUNX are expressed during the phases of cartilage development. RUNX1 is expressed in the initial stages but in the later pre and hypertrophic chondrocytes, the expression of RUNX2 predominates. In the osteoblasts and mesenchymal portions of the early suture development , expression of the RUNX 2 predominates[14] . The role of RUNX2 was found to be crucial in the epithelial-mesenchymal interactions.RUNX2 is essential for osteogenesis, and it was evidenced that there was a complete lack of ossified structures in RUNX2 deficient mice[15,16].

The vertebrates are divided in to jawless (cyclostomes) and jawed vertebrates (gnathostomes). The gnathostomes are represented by cartilaginous fishes, and they constitute a monophyletic group.Full-length coding sequences of two Runx genes that is MgRunxA and MgRunxB have been cloned in a cyclostome, the Atlantic hagfish (Myxine glutinosa). These Runx genes were found to be expressed in cartilaginous tissues, suggestive of their role in early skeletogenesis. RUNX2 works along with PPAR-gamma for determination of determining adipogenic stem cell differentiation[16,17].

RUNX ROLE IN DUCTAL MORPHOGENESIS

Glandular morphogenesis is governed by both intrinsic (transcription factors) and extrinsic factors (signaling factors). A series of studies were conducted through polymerase chain reaction, immunoblotting and microarray and the RUNX expression was found in the ductal and centroacinar cells of the lacrimal gland[18]. On down-regulation of the RUNX1 and RUNX3 , the development of the lacrimal gland was abolished. The branching of the ductal elements was reduced in such state and hence it overall affected the glandular development. RUNX1 is also found to be involved in stem cell specification, differentiation, proliferation, and homeostasis. It was found that these proteins were expressed in the secretory epithelium lineage. During the embryogenesis, RUNX 1 was expressed in the glandular epithelium of the developing lacrimal gland, parotid gland, submandibular gland[18,19]. The expression was also seen in the centroacinar cells as well as myoepithelial cells signifying their role as the progenitor cells of the ductal epithelium. The epithelial Mesenchymal interaction plays an important role in the ductal and glandular morphogenesis, RUNX3 mRNA was found to be expressed in both the epithelium and connective tissue. On an attempt to regenerate lacrimal gland levels of expression of RUNX 1 and3 both were found to be upregulated, and it was hypothesized that RUNX is expressed in epithelial progenitor cells. RUNX were found to be having a relationship with the levels of e-cadherin molecules and MMP. The down-regulation of e-cadherin and upregulation of MMP are essential molecular pathways in the epithelial Mesenchymal interaction[18,19,20].

RUNX ROLE IN CANCERS

RUNX gene mutation has been reported in human cancers. Any genetic abnormities including point mutations have led to myeloproliferative disorders. Recurrent mutations and inactivation of this gene have even led to alteration of the epithelial cell differentiation which has caused adenocarcinomas, breast carcinomas , carcinoma of esophagus[20,21]. RUNX3 gene mutation was less found compared to RUNX1 and 2. There has been reported a loss of chromosome 1p36 associated with RUNX3 loss. There are few studies which showed the hypermethylation and silencing of RUNX3 gene expression in solid tumors of various origins[21,22,23]. The increase in the age and smoking is reported to cause hypermethylation of RUNX3. It is caused due to elevated levels of DNA methyl transferase which is found to have a correlation with oxidative damage at RUNX3 promoter region. The lifestyle factors do play a role in the causation of reduced cellular activity. Somatic mutations of RUNX3 is rare and hence the inactivation of the cancer cells is brought about by DNA methylation, histone modification, and breakdown of cytoplasm[23,24].

RUNX IN THE SIGNALING PATHWAYS

TGF-Beta is one of the most important signaling pathways involved in growth and development. It is constantly involved in the maintenance of proliferation, differentiation, apoptosis and adhesion[4,5]. It indirectly

takes part in tumour progression and evasion. There is a strong cooperation of the RUNX with the TGF-beta super family (TGF-beta and Bone morphogenetic pathway). The interaction of the RUNX3 with TGF-beta receptor regulated SMAD signaling pathways also induces activation of cancer promoters. SMAD on interaction with with RUNX2 leads to an inhibitory action on the osteoblastic differentiation reflecting the inhibitory action of TGF-Beta on osteoblastic differentiation[6,7]. TGF-beta acts as a tumor suppressor along with RUNX3. RUNX3 gene upregulates CD21, claudin , and Bim in the gastric cells which are required for maintaining homeostasis. Loss of RUNX3 induces the TGF-Beta to start Epithelial-Mesenchymal transition rather than apoptosis[22].

RUNX3 forms a complex with WNT and Beta Catenin pathway resulting in a reduced affinity for TCF and hence attenuates WNT signaling. Increased Wnt signaling helps in showing alterations in an epithelial phenotype of the mucosa while RUNX3 caters to the changes which are occurring in the mucosa[22]. The MST2 signaling pathway has been associated to carcinogenesis[6]. The Yes-associated protein (YAP) linked to MST2 pathway interacts with RUNX protein to enhance transcription. YAP- RUNX is modulated by the cellular environment. The retinoblastoma protein is responsible for the cell cycle progression from G1 to S phase[25]; RUNX2 interacts with hypophosphorylated RB protein resulting in exit from cell cycle and induction of terminal osteoblastic differentiation.

Hence the role of RUNX is in multidirectional and is governed by many signaling factors.

CONCLUSION

The discussion about RUNX is very interesting with numerous factors pro and against the factors already put forward. It has a broad range of roles. The ability of the RUNX proteins to interact with different signaling pathways is a field of research. The role of these proteins in the morphodifferentiation and histodifferentiation of complex organisms need to explored. Along with the developmental aspects , it does play an important role in the creation of disturbances due to aberrancy in its constitution. Exploring the molecular behavior and the activities of RUNX may help the scientist to estimate the role of RUNX in early diagnosis of cancer and treatment of those cancers.

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