

BIOMEDIACAL SCIENCES RESEARCH CENTER
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BACKGROUND

During the development of complex multicellular organisms, cells acquire specialized functions in a spatial and temporal manner. The genetic program that directs cells to specific pathways of differentiation involves sequential and selective activation of certain genes in a cell type specific fashion. Understanding how the genetic information is selectively retrieved during the cellular differentiation processes of normal development or by external and internal signals and how this process becomes uncontrolled in various diseases is a major challenge of current and future research in the post-genomic era.

Hepatocytes are derived from the endoderm germ layer, which arises from the epiblast during gastrulation. At around embryonic day 7 (E7), definitive endoderm emerges from the primitive streak to displace the extraembryonic endoderm of the yolk sac. Shortly after this the endoderm invaginates to form a portal at the anterior region of the developing embryo that will ultimately define the foregut of the embryo. Around E8, the ventral wall of the foregut is positioned adjacent to the developing heart. Inductive signals from the cardiac mesoderm induce the underlining endodermal cells to initiate its development toward hepatic fate. The endoderm responds to these signals by generating the primary liver bud that can be defined as an anatomical outgrowth from the ventral wall of the foregut. By E9.5, the nascent hepatoblasts delaminate from the endoderm and cords of hepatoblasts invade the septum transversum mesenchyme. The cells within this environment organize to generate a complex hepatic architecture, which is important for the subsequent differentiation of hepatoblasts to functional hepatocytes. As soon as the mammalian liver is formed, haematopoietic cells invade it and reside there until birth. After birth the liver shifts from a haematopoietic role to being the primary site of known hepatic functions, such as control of metabolite homeostasis and detoxification.

A network of tissue-restricted transcription factors specifies the genetic program that regulates endoderm differentiation and morphogenesis. Previous studies have established that transcription factors LRH-1, HNF-3b, HNF-4, HNF-1b, HNF-6 and HNF-1a, form a transcriptional network via cross-regulatory and autoregulatory loops, which is crucial not only for the specification and maintenance of the hepatic phenotype, as originally thought, but also for the proper development and functioning of other cell types, including cholangiocytes, pancreatic β -cells, intestinal and renal cells. Research aimed at the understanding the mechanisms of how this small set of transcription factors play role in the developmental decisions of progenitor cells to differentiate into so many cellular phenotypes, promises important new insights into the basic principles employed by living organisms that control cellular diversification.

Apart from the above basic scientific reasons, the topic has also a high medical importance. This comes from the recent discovery that in humans heterozygous mutations in HNF-1 β , HNF-1 α and HNF-4, lead to Maturity Onset Diabetes of the Young (MODY), an autosomal dominant form of early onset diabetes mellitus. In addition, loss or malfunctioning of specific HNFs has been linked to various metabolic diseases, such as defects in cholesterol and lipid homeostasis, atherosclerosis and a variety of developmental disorders, including cystic kidneys, defective nephrogenesis, abnormal genital tract and pancreas hypoplasia.

RESEARCH

Our research is broadly centered around the analysis of the function of hepatic regulators and the general transcription machinery. We use biochemical, genetic and cell biology approaches to study the chromatin organization and the regulated assembly of the transcription machinery on hepatic genes involved in the regulation of various metabolic pathways and hepatocyte differentiation. In addition we study epigenetic mechanisms with an ultimate goal to describe the complete Epigenomes matching the hepatocyte cell type at different stages of liver development as well as in disease, such as cancer. The main directions are as follows:

1. Studies on the HNF network and target genes in early steps of hepatocyte specification. Studies in animals towards these questions are hampered by the difficulty to obtain homogenous population of endodermal cells from early embryonic ventral endoderm that have been primed for differentiation to hepatoblasts. Based on knowledge of the key signals required for patterning of the endoderm and subsequent steps for acquiring cell fate competence, reproducible protocols for directed differentiation of Embryonic Stem (ES) cells into functional hepatocytes have been worked out. This experimental system mimics *in vivo* hepatocyte differentiation and allows the analysis of most intermediate steps involved in liver organogenesis during development from the stages of competence through lineage specification and growth to functional hepatocytes. In the above ES cell differentiation system we are studying the targets and the function of the major hepatic regulators using global approaches aiming at the systems level description of the regulatory pathways involved in hepatocyte specification and differentiation.

2. Role of HNF network in controlling hepatic metabolic pathways. The second focus is on studying the mechanistic aspects of transcriptional activation with major emphasis placed on getting insights into the interplay between the recruitment of the preinitiation complex components and changes in chromatin structure upon exposure to various metabolic signals. Here, we are studying the genes involved in the regulation of hepatic cholesterol-bile acid metabolism, fatty acid metabolism and glucose homeostasis using transgenic and knock-out animal models.

3. Analysis of chromatin modifying and transcription complexes implicated in cancer pathogenesis.

Carcinogenesis is a progression of events resulting from alterations in the processing of genetic information. These alterations result from stable genetic changes (mutations) involving tumor suppressor genes, or oncogenes and also from epigenetic changes, which are modifications in gene function without a change in DNA sequence. Epigenetic mechanisms often altered in cancer cells are histone modifications (acetylation, methylation, phosphorylation) and DNA methylation. These aberrant epigenetic mechanisms are manifested in both global changes in chromatin packaging and in localized changes in the binding of regulatory proteins to promoters that influence the transcription of genes important to the cancer process.

Our studies are focused on Set-9 and the Smyd family of histone methyltransferases, both of which have been implicated in the pathogenesis in hepatocellular carcinoma. We aim at the deeper understanding of the biological mechanisms responsible for cancer-specific expression patterns by the description of complete “regulomes” for the epigenetic modifiers. Our work combines three types of global search data (factor occupancy, expression and chromatin modification map) in the same human normal and cancer tissues, and in a variety of relevant mouse models and cell culture systems. Analysis of these data sets is pursued by bioinformatics approaches in order to obtain systems level description of the regulatory network modules deregulated in different cancer cells.

The unique feature of our approach is that the studies also involve analysis of the interplay of epigenetic modifiers with the general transcription machinery. The significance of the latter issue comes from the fact that most of the enzymes responsible for the epigenetic modifications play important functions in the transcriptional regulation of genes during normal mammalian development and during various signal transduction pathways. Importantly many of them are integral components of the transcription machinery required for proper temporal and spatial activation of genes in different cell types. Therefore we argue that studies towards the specific regulatory environment of a protein are essential in order to understand the complexity and disease-related alterations operating in a biological system.

REPRESENTATIVE PUBLICATIONS

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