Protein-protein interaction map is a key gateway into liver regeneration

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INTRODUCTION

Liver has the capacity to regenerate by a process of compensatory growth following injury and various molecular and cellular pathways are involved in this process[3,4]. It is still difficult to understand precisely how the process of liver regeneration is regulated. Previous studies of liver regeneration have been made at the functional, cellular, molecular or gene level[5]. It is generally believed that most cellular processes are determined by protein-protein interactions (PPIs)[6,7] and, therefore, PPIs maps provide a valuable framework for a better understanding of the functional organization of the proteome during liver regeneration[8,9]. Various methods have been used to study the functions of specific proteins during liver regeneration. In this review, we describe the use of high-throughput experimental methods and algorithmic predictions to unravel the complex processes of liver regeneration through the use of PPI maps.

LIVER REGENERATION

Source of liver cells and genes analysis in liver regeneration processes

Liver regeneration can be seen as a timely sequence of...
Liver regeneration can be divided into four phases: G0: Corresponds to approximately the first 4 h; G1: Quiescent cells enter the cell cycle during production of hepatocyte growth factor (HGF), epidermal growth factor (EGF), tumor necrosis factor (TNF), etc.; S: Chromosomal DNA is replicated and peak DNA production occurs at approximately 24 h; then, after 48 h or more, the process of regeneration is terminated. The curves following the gene products and the dashed line represent the changes in gene expressions measured in our lab using Gene Chip® mouse 430 2.0 during liver regeneration following CCl₄-induced liver injury. Changes on the level of gene expression were log2-transformed using signal value at 0 h time-point as baseline. Genes with their expression levels varying at least 2-fold between any two time-points were subjected to hierarchical clustering analysis. TGF: Transforming growth factor; MMP9: Matrix metalloproteinase 9.

### Table 1  Liver cell types and their functions during liver regeneration

| Cell types       | Functions                                                                 |
|------------------|---------------------------------------------------------------------------|
| Hepatocytes      | Organized in single cell plates; perform metabolic and detoxification function; can secrete HGF, IL-6, proteases and protease inhibitors |
| Sinusoidal       | Involved in endocytosis and metabolism of molecules; can produce TGFβ, HGF, IL-6 and nitric oxide | endothelial cells |
| Biliary          | Can promote fibrogenesis by attraction of hepatic epithelial cells and can secrete cytokines such as MCP-1 and IL-6 |
| Kupffer cells    | Major producers of cytokines such as TNF and IL-6 |
| Hepatic          | Store vitamin A and secrete laminins, collagens and growth factor: HGF, EGF, TGFβ and cytokines IL-6; also produce MMPs |
| Oval cells       | Can differentiate to biliary and hepatocytes lineage |

HGF: Hepatocyte growth factor; IL-6: Interleukin-6; EGF: Epidermal growth factor; TGF: Transforming growth factor; MCP: Monocyte chemotactic protein; MMP: Matrix metalloproteinase; TNF: Tumor necrosis factor.

Termination response during liver regeneration

Many research studies have focused on the regulation of the initiation and proliferation phases of liver regeneration. Although the molecular mechanisms for termination of liver regeneration are still not completely understood, TGFβ and activins, which belong to the TGFβ superfam-
ility, appear to be important\(^{14}\). TGFβ and activin A may bind to their high-affinity cell surface type II receptor (TGFβR II) and ActR II or ActR II b, respectively and TGFβ inhibits G1 to S phase transition in hepatocytes. TGFβ levels rise rapidly after CCl\(_4\)-induced injury and, therefore, TGFβ is known to have growth inhibitory effects on liver regeneration. So, at its simplest, the basic TGFβ signals through its Type I and Type II receptors (TGFβR I and TGFβR II) cause phosphorylation of Smad proteins and activate the Smads complex that controls transcription (Figure 2). Diersse \(\text{et al}^{[15]}\) demonstrated that gp130-dependent Stat3 activation and concomitant suppressor of cytokine signaling 3 (Socs3) is involved in timing of DNA synthesis during liver regeneration. Also, Riehle \(\text{et al}^{[16]}\) showed that Socs3 modulates several signaling pathways and involved in physiological proliferative processes and protects hepatocyte proliferation in liver regeneration. Therefore, there is more to be understood about the TGFβ signaling pathway and its effects in termination of regeneration, but this still should underscore the complexity of other related pathways and their contribution to the process of termination of liver regeneration\(^{[17]}\). Further studies need to be conducted on understanding the mechanism of liver regeneration.

**PEELING THE PPI MAPS DURING LIVER REGENERATION**

During liver regeneration, cytokine, growth factors and metabolic pathways were both active after PH or CCl\(_4\)-induced liver injury, and the pathways interacted with each other\(^{[18]}\); although, there is indeed a flow of information via interactions between DNA, RNA and proteins on which this review will mainly focus. More research about PPI maps is on the level of proteome (Table 2), and these PPI maps will reveal the connectivity of the proteome. If we construct a PPI map during liver regeneration, it will reflect the particular cellular or unique signaling pathway status. As to the PPI map analysis, the so called small-world and scale-free behavior are considered, which indicates that in the maps only few nodes (stand for proteins) are highly connected with others (hub protein) and most of the nodes are connected with only a few nodes (low degree)\(^{[19]}\). In this processes, to capture the changes in protein connectivity and find the key signaling pathways, especially those that interact, is most attractive. For the mechanisms of liver regeneration to be completely understood, a multitude of PPI maps must be coordinated\(^{[20]}\).
Understanding the processes and mechanisms of liver regeneration involves recognizing components in liver regeneration system, the dynamic change of these components and their interactions.

In this review, it is pointed out that PPI maps (or PPI data) are closely correlated with TGFβ regulated Smad signaling pathways during liver regeneration. Collard et al. have used Y2H technique identified 755 interactions, mainly in a focused analysis of TGFβ signaling pathways and have constructed the PPI maps. They used this method to analyse LMO4, HYP, KIAA1196 and LAPTm5 proteins, which are additional proteins involved in regulation of TGFβ signaling pathways. Also, they present an integrated approach for the identification of new factors implicated in TGFβ signaling pathway involved in several human pathologies and in the termination of liver regeneration. From this point of view, we can apply this strategy to study liver regeneration.

This review focuses on PPI maps and liver regeneration, and pays attention to the TGFβ signaling pathway. The PPI maps were constructed containing proteins related to the TGFβ signaling pathway and some of these proteins may have potential functions on the termination of liver regeneration (Figure 3). It can be easily used to find the key proteins in this process and additional experiments should be done to validate this hypothesis. Regardless, it is confirmed that the PPI map is an effective tool to study liver regeneration.

**A PPI maps acting during liver cell proliferation**
Gao et al. constructed a PPI map of transcription factors acting during liver regeneration which contains 32 regulatory proteins. Among them, 27 transcription factor genes that might have roles in the control of liver regeneration and five other genes that encode signal transducers might modulate transcription. After using a matrix mating Y2H technique, a PPI map in which all the components are related with liver cell proliferation was constructed (Figure 4) and some of the interactions were validated by α-glutathione S-transferase pull-down and CoIP assays. From this PPI map, Gao et al. pointed out that ATF3, a member of the mammalian activation transcription factor/cAMP responsive element-binding protein family of transcription factors, interacts with FHL2 which may be an important interaction during liver regeneration, especially for liver cell proliferation. When it comes to the termination response during liver regeneration, FHL2 and ATF3 may form a complex which abolishes its function on DNA synthesis and might terminate the liver regeneration. Also, it is possible that FHL2 may interact with Stat3 to inhibit its function in activating downstream gene expression that is necessary to terminate the liver regeneration. Nearl all the interactions in this map are growth repressors during liver regeneration and this is one of the ways in which the termination of hepatocyte proliferation and liver regeneration is regulated. Although this is one hypothesis for termination of liver regeneration, there is still growing evidence which shows that it is feasible to understand liver regeneration.

This PPI map is only a small-scale map and already can make sense of termination of liver regeneration. It would be no exaggeration to say that if large-scale, more complicated PPI maps are constructed it will greatly help us to know more about mechanism of liver regeneration.

**FUTURE PROSPECTS**

During the last decade, several efforts had been made to demonstrate the mechanism of liver regeneration. But unfortunately, an important gap is the lack of understanding of liver regeneration and therefore, some difficulties appear in liver cancer treatments or liver transplantation and drug development, which remain to be
Figure 3  A protein-protein interaction comprising the transforming growth factor β signaling pathway. This figure just lists the protein-protein interactions which correlated with transforming growth factor β type I receptor (TGFβ R I), TGFβ R II and Smads and all the proteins that directly interact with these three proteins which indicate that additional partners are not represented in this figure.

Figure 4  Protein-protein interaction maps comprising the transforming growth factor β signaling pathway of transcription factors associated with liver cell proliferation. The protein-protein interaction maps consist of different stages of liver regeneration (0 d, 0.5 d, 1.5 d, 4.5 d and 7 d after CCl4-induced liver injury).
solved. Constructing PPI maps is a powerful step toward addressing these challenges. The most important profiles shall be discussed.

**Integration of PPI data during liver regeneration**

Different high-throughput PPI data are difficult to cover even if in the same species, also, it has a higher rate of false positives than that of small-scale data\[44\]. However, it may be useful to increase the capacity of false positive identification in order to find out the real PPI from the noise data. The first step is to collect the correct and reliable PPI data and find several criteria which can be used to evaluate the PPI data sets. By integrating small-scale and large-scale PPI data, PPI databases have emerged and it is generally believed that a PPI database is a symbol of the level of PPIs. Although a series of PPI databases such as BIND (http://bind.ca), MIPS (http://mips.gsf.de) and DIP (http://dip.doe-mbi.ucla.edu) are popular and helpful, there are still no PPI databases for liver cells, liver regeneration or specific liver diseases, such as liver cancer. PPI data should be collected, evaluated, retrieved and systemically stored (including the detailed information for PPIs).

With liver regeneration PPI data which is integrated into the databases and is made readily accessible through the internet, researchers will be able to quickly locate the PPIs for their proteins of interest during liver regeneration, also, they will get the interpretation of PPIs in detail, which means any type of available information on proteins or protein domains can be verified. Meanwhile, we should also explore a tool that allows easy navigation in this complex of PPI databases especially for liver regeneration.

Already, the Y2H system has increasingly been applied in high-throughput applications intended to map genome-scale PPI for liver regeneration and is definitely believed to be an effective way to construct large-scale PPI maps during liver regeneration. Also, the low coverage and experimental bias call for development of computational methods to predict PPIs\[45\], and mining of existing inter-

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**Figure 5** A protein-protein interaction map of transcription factors associated with liver cell proliferation. Node stands for protein and the edge means the two proteins are interactive; the node size symbolizes the degree of this protein (the more highly connected with others, the bigger node); the edge target arrow shape and color: delta and blue, interactions are only validated by yeast two-hybrid (Y2H); diamond and green means validated by Y2H and α-glutathione S-transferase pull-down; T and black means validated by Y2H and co-immunoprecipitation.
action data to infer additional interactions is also a trend to enlarge the PPI database. Nowadays, lots of PPI data are obtained from different organisms and we can get PPI from interacting proteins to exhibit similar phylogenetic trees[46]. As to PPIs during liver regeneration, much more computational methods and algorithms must be fixed in order to predict PPIs during liver regeneration, and it may be obtained from signaling pathways level or proteome level.

**Static and dynamic architecture of PPI maps during liver regeneration**

Static PPI maps during liver regeneration, especially the PPI maps on signaling pathways, will help us to understand the different phases and different gene changes of liver regeneration. In order to understand the mechanism of liver regeneration, the PPI map furthered the understanding of the architecture of cellular machinery and revealed fundamental properties[47]. The large-scale and static PPI maps show us some information and they are quite important to understand the spatiotemporal existence of PPIs. Obviously, PPI maps are dynamic and not static, but unfortunately nearly all the PPI maps are static and do not consider the PPI strength and spatiotemporal existence let alone the types of PPI maps and do not reflect the actual situation in liver cells. Therefore, dynamic PPI maps are of more importance for cell signaling and dictate timing and intensity of map outputs. Our lab has also tried to construct dynamic PPI maps during mouse liver regeneration.

We picked up 5 major time points (0 d, 0.5 d, 1.5 d, 4.5 d and 7 d) during the mouse liver regeneration process after CCl4-induced liver injury, in which all the proteins are transcription factors associated with TGFβ signaling pathway and constructed 5 PPI maps (Figure 5). It is easy to identify the PPIs change in the whole process of liver regeneration including numbers and the protein category. The numbers of PPIs increased at the beginning and then decreased. A detailed analysis of these PPI maps are in progress, which is a mark of the beginning of dynamic PPI maps construction.

Though no large-scale data sets are yet available on liver PPI map dynamics, the time dimension can be added by projecting time series of liver regeneration mRNA expression data onto transcription factors, allowing one method to interpret dynamic PPI maps. Researchers also need to consider addressing where and when interactions take place in different phases of liver regeneration and how they regulate the process. It will be a great help for us to know about liver regeneration if we know the full range of PPIs, from static to dynamic, and this is a useful method for studying liver regeneration over the next few years which will hopefully improve our ability to understand the PPI maps during liver regeneration.

Liver regeneration remains a fascinating project and the exact cellular and molecular mechanisms are still a mystery to us. In order to understand this phenomenon, many methods must integrate and we are just beginning to appreciate the relationship between PPIs and liver regeneration. We strongly believe that PPI maps from systems biology is a key gateway for deciphering liver regeneration. Certainly, like the sequencing of the human genome, the construction of a PPI map during liver regeneration will represent a major step along the path towards understanding the mechanisms of liver regeneration.

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