

Met signaling in adult liver

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TABLE OF CONTENTS

1	INTRODUCTION	6
1.1	Met, the tyrosine kinase receptor	6
1.2	The structure of HGF/SF and its receptor, Met	6
1.3	Met signal transduction	7
1.4	Met signaling in development	9
1.5	Met function in the adult	10
1.6	Liver regeneration	11
1.6.1	Experimental models of liver regeneration	12
1.6.2	Hepatocyte proliferative capacity	13
1.6.3	Liver regeneration is a multi-step process	13
1.6.4	Factors that regulate hepatocyte growth	15
1.7	Cell cycle progression: entry into S-phase	16
1.7.1	Positive and negative regulation and degradation of cdks	18
1.8	The aim of this study	20
2	MATERIALS AND METHODS	21
2.1	Abbreviations	21
2.2	Materials	23
2.2.1	Bacterial strains	23
2.2.2	Vectors/plasmids	23
2.2.3	ES cell line	23
2.2.4	Antibodies	24
2.2.5	Mouse strains:	25
2.2.6	Cell Culture Media	25
2.3	Methods	27
2.3.1	Extraction and Purification of DNA	27
2.3.2	Polymerase chain reaction (PCR)	28
2.3.3	DNA sequencing	30
2.3.4	Southern blotting	31
2.3.5	Cell culture	32
2.3.6	Generation of conditional knockout mice	35
2.3.7	Partial hepatectomy	35
2.3.8	Histology and staining procedures	36
2.3.9	Protein biochemistry	39

3	RESULTS	45
3.1	Generation of conditional <i>Met</i> mutant mice	45
3.2	Elimination of <i>Met</i> function in an adult liver	48
3.3	<i>Met</i> function in the normal liver	49
3.4	Met is essential for liver regeneration	51
3.4.1	Exit from quiescence in the <i>Met</i> -deficient regenerating livers	58
3.4.2	Entry into S-phase during liver regeneration in conditional <i>Met</i> mutant mice	59
3.4.3	Negative regulators of cell cycle progression during liver regeneration in conditional <i>Met</i> mutant mice	61
3.4.4	Changes in the regulation of growth factors and cytokines in <i>Met</i> mutant mice after partial hepatectomy	62
3.4.5	Signaling pathways activated during liver regeneration in control and conditional <i>Met</i> mutant mice.	64
4	DISCUSSION	66
4.1	Analysis of <i>Met</i> function in the adult liver	67
4.2	Cell cycle progression in conditional <i>Met</i> mutant mice	69
4.3	Cytokines and growth factors are increased in the blood during liver regeneration	72
4.4	Signaling of cytokines and growth factor during liver regeneration	74
4.5	Outlook	76
5.0	Summary	71
	Zusammenfassung	72
6.0	References	80

5 Summary

The Met tyrosine kinase receptor and its ligand, HGF/SF, play important roles in embryonic development of the liver, placenta and muscle. The placenta defects are responsible for lethality of *Met*^{-/-} and *HGF/SF*^{-/-} mutants in uterus. This embryonic lethality had precluded a genetic analysis of Met functions in the adult. I used here conditional gene targeting in mice to examine the function of Met receptor in the adult liver. The *Mx-cre* transgenic strain was used to introduce a Met mutation in the adult liver, after growth of the organ had ceased. The ablation of the Met receptor had little effect on the adult liver and only the long-term loss of the receptor caused a stress and led to abnormal lipid accumulation in the liver. In contrast, Met signaling played a crucial role in the liver that was challenged by partial hepatectomy. Liver regeneration was severely impaired in mice carrying the *Mx*-induced *Met* mutation, and was accompanied by a decrease in hepatocyte proliferation. Analysis of cell cycle progression in conditional *Met* mutant mice revealed an impaired exit from quiescence, i.e. a reduced cyclin D expression. In addition, the expression or the activity of several S-phase molecules was reduced, indicating impaired entry into S-phase. Moreover, conditional *Met* mutant mice showed an abnormal up-regulation of cdk-inhibitor p21Cip1/Waf1 in the regenerating liver. Impaired liver regeneration was accompanied by compensatory physiological responses, for instance a prolonged up-regulation of HGF/SF and IL-6 in the blood. A biochemical analysis enabled me to determine the contribution of HGF/SF/Met to the activation of various of signaling pathways in the regenerating liver. Activation of Erk/MAP kinases depended exclusively on HGF/SF/Met signaling. In contrast, Met cooperated to activate other signaling pathways, for instance the Akt kinase. Thus, interplay between different signaling systems plays an important role during liver regeneration. The mutation of Met receptors in the adult liver allowed me to demonstrate that the HGF/SF/Met signaling system is not only important for liver development, but also for regeneration and homeostasis of this organ.

Zusammenfassung

Der Tyrosinkinase Rezeptor Met und sein Ligand Hepatocyte Growth Factor/Scatter Factor (HGF/SF) besitzen essentielle Funktionen in der Embryonalentwicklung der Leber, der Skelettmuskulatur, sowie der Plazentaentwicklung. Mäuse mit homozygoten Mutationen des Met- bzw. des HGF/SF-Gens sterben während der Embryogenese an den Folgen einer gestörten Plazentaentwicklung. Es war daher bisher nicht möglich, adulte Funktionen des HGF/SF/Met Signalsystems genetisch in Mäusen zu untersuchen. Ich habe *Konditionelles Gene Targeting* in Mäusen eingesetzt, um Funktionen des Met-Rezeptors in der adulten Leber zu untersuchen. Mit Hilfe eines induzierbaren Cre des transgenen Mausstamms *Mx-Cre*, wurde Met in der adulten Leber, d.h. nach Abschluß des Organwachstums mutiert. Nach Deletion von Met wurden keine unmittelbaren Organveränderungen in der adulten Leber beobachtet. Mutante Mäuse entwickelten jedoch während eines längeren Beobachtungszeitraums eine ausgeprägte Fetteinlagerung (Steatose) der Leber. Ich konnte außerdem zeigen, daß Met essentiell ist für die Leberregeneration. Nach partieller Hepatektomie war die Regeneration des Lebergewebes in Met mutanten Mäusen hochgradig gestört. Dies war begleitet von einer reduzierten Hepatozytenproliferation. Eine Zellzyklusanalyse ergab, daß die Cyclin D Expression reduziert, also der Wiedereintritt in den Zellzyklus in Met Mutanten gestört ist. Es konnte außerdem anhand der reduzierten Expression mehrerer S-Phase Marker eine gestörte Progression in die S-Phase beobachtet werden. Mäuse mit konditioneller Mutation von Met zeigten darüber hinaus eine abnorm gesteigerte Expression des Cdk-Inhibitors p21Cip1/Waf1 im regenerierenden Lebergewebe. Die gestörte Leberregeneration war ebenfalls begleitet von prolongiert erhöhten Blutkonzentrationen für HGF/SF und IL-6. Ich konnte biochemisch den relativen Beitrag des HGF/SF/Met Signalsystems zur Aktivierung unterschiedlicher, intrazellulärer Signalwege in der regenerierenden Leber bestimmen. So ist die Aktivierung von Erk/MAP Kinasen ausschließlich Met-abhängig. Demgegenüber kooperiert Met mit anderen Signalsystemen z. B. bei der Aktivierung von Akt Kinasen. Das Zusammenwirken mehrerer Signalwege spielt damit eine bedeutsame Rolle bei der Leberregeneration.

Durch die konditionelle Mutation des Tyrosinkinase Rezeptors Met in der adulten Leber konnte ich zeigen, daß das HGF/SF/Met Signalsystem neben der Embryogenese der Leber auch für die adulte Biologie und Regeneration dieses Organs essentiell ist.