Interview with Prof. Ralf Weiskirchen: challenges and opportunities in gastroenterology and hepatology

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Received: 15 September 2022; Accepted: 26 September 2022; Published: 30 September 2022.

doi: 10.21037/dmr-22-68

View this article at: https://dx.doi.org/10.21037/dmr-22-68

Editor's note

As an emerging journal in the field of digestive diseases, *Digestive Medicine Research* (*DMR*) has published a number of special series in recent years, receiving overwhelming responses from academic readers around the world. Our success could not have been achieved without the contribution of our distinguished guest editors. Taking this opportunity, this year *DMR* launched a new series, "Interviews with Outstanding Guest Editors", to highlight our active contributors. We hope to express our heartfelt gratitude for their tremendous effort and further uncover the stories behind the special series.

The special series "The Pathogenesis of Hepatic Fibrosis: Basic Facts and Clinical Challenges" (1) led by Prof. Ralf Weiskirchen (*Figure 1*) from RWTH University Hospital Aachen has attracted numerous readers since its release. The main purposes of this series are to summarize and present novel data on the pathogenesis of hepatic disease, to bridge the gap between new research findings and clinical practice, and to present novel hypotheses and ideas that foster the debate on new innovative concepts in basic and clinical hepatology. At this moment, we are honored to have an interview with Prof. Weiskirchen to share his scientific career experience and insights on this special series.

Figure 1 Prof. Ralf Weiskirchen.

Expert introduction

Professor Ralf Weiskirchen was born on February 2, 1964 in Bergisch Gladbach, North Rhine Westphalia (Germany). After his school education, he studied Biology and made his PhD with distinction at the University of Cologne (Germany). Thereafter, he worked several years as a Research Associate in the Institute of Biochemistry at the University of Innsbruck (Austria). Back in Germany, he habilitated at the RWTH University Hospital Aachen and became a Professor assignment that he took in 2007. Currently, he is head of the Institute of Molecular Pathobiochemistry, Experimental Gene Therapy and Clinical Chemistry (IFMPEGKC) at the RWTH University Hospital Aachen. His major research focus is the analysis of transforming growth factor-β (TGF-β)/bone morphogenic protein (BMP) and platelet-derived growth factor (PDGF) signalling pathway in the pathogenesis of fibrogenic liver diseases. Professor Weiskirchen maintains a variety of national and international cooperations aiming to

understand molecular mechanisms of disease formation and translate these findings into the clinic. In addition, he has a strong interest in identification of novel biomarkers that are suitable as measurable indicators of the severity or presence of a specific hepatic disease.

Interview

***DMR**: As a reputable expert in liver and fibrosis, what drove you into this field in the first place?*

Prof. Weiskirchen: At the beginning of my scientific career, I was interested in mechanisms by which proto-oncogenes can promote transformation of primary avian embryo fibroblasts in culture. In this context, I identified a novel gene whose expression was suppressed in all transformed avian cells tested. This gene encoding the cysteine-rich protein 2 (CRP2) turned out to be a member of a specialized protein family, which is implicated in diverse processes linked to cellular differentiation and growth control. By chance, I could then show several years later that CRP2 expression is significantly increased during early activation of hepatic stellate cells, which is the key cellular event in hepatic fibrogenesis. More detailed studies then showed that there is a close link between CRP2 expression and TGF-β signaling, representing the central soluble mediator participating in all stages of hepatic diseases, from initial liver injury through inflammation and fibrosis, to cirrhosis and cancer. Since then, I have been interested in the molecular processes involved in liver disease with a special focus on TGF-β signaling and pathways driven by other pro-fibrogenic-acting cytokines or chemokines.

***DMR**: In 2021, the World Health Organization (WHO) reported that there are 354 million people infected with hepatitis B or C virus worldwide, 78% of whom lack effective testing and treatment. What are your recommendations for the global diagnosis of liver disease?*

Prof. Weiskirchen: Yes, these numbers are frightening and are of course associated with human suffering and large rising economic burdens. Noteworthy, a large number of these persons are unaware of their health status because the viral infection can have different characteristics, ranging in severity from a mild illness to a serious, lifelong illness ending in liver cirrhosis and cancer. In many cases, the disease is even undiagnosed because it can remain asymptomatic for decades. Hence, the early diagnosis of hepatitis virus infections is highly crucial to prevent transmission in high-risk groups and to allow clinicians to make a rapid decision about possible therapies. Nowadays, antiviral medicines can cure more than 95% of persons suffering from hepatitis C infection and further competent vaccines exist for hepatitis B. Disease awareness campaigns, reducing the risk of exposure to the virus, regular health check-ups and screening for liver diseases in individuals at risk of infection with a viral hepatitis are means to reduce the number of patients suffering from hepatitis. Finally, the continuous development of improved tests to assess liver function, screen for infections, or monitor disease progression will help to prevent the spread of the disease. Consequently, the WHO estimates that 4.5 million premature deaths will be prevented by 2030 through vaccination, diagnostic tests, medicines and education campaigns.

***DMR**: What do you think is the biggest challenge in hepatic fibrosis research today?*

Prof. Weiskirchen: Hepatic fibrosis can result from chronic hepatitis infection, nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease, autoimmune disorders, cholestasis, drug abuse, genetic disorders (e.g., Wilson disease, hereditary hemochromatosis), and many other etiologies. Consequently, many general practice guidelines and recommendations for etiology-specific interventions have been established. However, there are no general "anti-fibrotic" drugs or therapies available, most likely because disease progression and outcome is influenced by many factors, including genetics, gender, sex, and life style factors. Therefore, the pathogenesis of each patient is unique and must be treated as such. It is therefore the biggest challenge in hepatic fibrosis research to develop precision therapeutics allowing individualized treatment for each patient.

***DMR**: There are no fully defined and approved drugs for the treatment of liver fibrosis. What is the current progress of new drug development and exploration of new treatment options, and what are the future research priorities and trends?*

Prof. Weiskirchen: Hepatic fibrosis is a progressive but reversible process that is mainly driven by chronic inflammation and an altered biological activity of a

multitude of different molecular and cellular mediators, resulting in an imbalanced extracellular matrix deposition in the liver. The plurality of factors triggering initiation, progression and resolution of hepatic fibrogenesis offers an infinite number of potential therapeutic possibilities. Most strategies aim to arrest chronic liver damage by clearing pathogenic mediators or by shifting the hepatic micro-environment from inflammation to resolution, which is associated with deactivation of profibrogenic cells, degrading of excess extracellular matrix, and reduction of inflammatory cells that infiltrate the diseased liver tissue. There are also large efforts to achieve therapeutic benefits by targeting the intestinal microbiota or restoring intestinal barrier function that are both altered during chronic hepatic disease. In other studies, bile acid derivatives that enable digestion and absorbance of lipids in the small intestine are investigated for their potential to restore central metabolic functions of the liver. Unfortunately, despite the great advances, there are currently no approved antifibrotic acting drugs that have been ultimately shown efficacious in patients. Consequently, the withdrawal of injurious stimuli and lifestyle interventions are still the best option to interfere with disease progression. Nevertheless, there is great hope that ongoing basic studies and clinical trials will identify novel drugs and targets suitable to interfere with or reverse the fibrogenic process.

***DMR**: What kind of projects are you recently working on? How is the topic of this special series associated with some of them?*

Prof. Weiskirchen: As said, the major interest of my research group is the unraveling of cytokine and chemokine signaling pathways underlying hepatic fibrogenesis with the aim to identify suitable therapeutic targets. Moreover, we are currently trying to improve the diagnostic of Wilson disease, which is an inherited disorder associated with heavy copper overload, inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma. These and other research topics are investigated in close cooperation with other basic scientists and clinicians, providing the chance to translate basic science into human research. The articles published in the Special Series "The Pathogenesis of Hepatic Fibrosis: Basic Facts and Clinical Challenges" highlight interesting aspects of liver disease biology and provide insight in novel concepts on basic and clinical hepatology research. As such, this article collection is helpful for both laymen and experts to know about initial studies and latest discoveries in the field of hepatic fibrosis.

***DMR**: If there is a chance to update this special series, what would you like to moderate, add or emphasize more?*

Prof. Weiskirchen: The field of hepatic fibrosis research is very versatile ranging from basic studies to specialized knowledge related to the treatment, diagnosis, and prevention of disease. Therefore, it is difficult to keep track of everything. For example, there is a wealth of information available reporting on substances showing highly beneficial effects in therapy of experimentally-induced hepatic fibrosis. However, there is only limited success in translating these encouraging findings to the clinic because costs and organizational efforts to design advanced clinical trials are extremely high. I am greatly looking for more concerted actions, in which basic scientists, clinicians, patients, government institutions, industrial partners, health insurance companies, and other decision-makers, compile viable concepts that lead to truly improved personalized anti-fibrotic therapies.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Digestive Medicine Research* for the series "Interviews with Outstanding Guest Editors". The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-68/coif). The series "Interviews with Outstanding Guest Editors" was commissioned by the editorial office without any funding or sponsorship. RW serves as an unpaid editorial board member of *Digestive Medicine Research*. AL and LMG report that they are full-time employees of AME Publishing Company. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

doi: 10.21037/dmr-22-68
Cite this article as: Weiskirchen R, Liao A, Gao LM. Interview with Prof. Ralf Weiskirchen: challenges and opportunities in gastroenterology and hepatology. Dig Med Res 2022;5:50.

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