Role of miRNA in drug-induced hepatic injury

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Abstract:

Acute liver disease is characterized by loss of liver function within days or weeks however, in the patient who is not previously diagnosed, its less common compared with chronic liver failure, which developed slowly and irreversible process. It's caused by drug-induced liver damage (DILI) therefore identifying liver injury is challenging for clinical treatment and diagnosis. The major causes of liver failure involve toxic metabolites of some medications that consumed Adenosine Tri Phosphate (ATP) compared with normal conditions and increased oxidative stress due to overexpression of MicroRNAs, it is necessary to do complete diagnosis of patients. Biomarker parameters can be utilized to validate liver damage like microRNAs (miRNAs) analysis, it is a more receptive marker because increased earlier than the transaminases enzymes allowing for a more accurate diagnosis. we summarized recent signs of progress disease concerning the role of miRNA as a novel DILI biomarker, the miRNA levels can be measured in plasma, saliva, urine, fetal fluid (amniotic), as well as other materials either in human or animals like mice, rats which significantly elevate during illness, therefore, provide e specific biomarker of hepatoinjury.

Key words: miRNA, hepatic injuries, Drug induce liver injuries.

دور الحامض النووي(miRNA) فس اصابة الكبد الناتجة عن الادوية

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الخلاصة:

فشل الكبد الحاد هو فقدان وظائف الكبد الذي يحدث بسرعة خلال أيام أو أسابيع على الرغم من ان المريض الذي لم يشخص مسبقا . وهو أقل شيوعًا مقارنة بالفشل الكبدي المزمن الذي يتطور ببطء وبعملية غير عكسية والذي ينتج من الادوية المحفزة للاصابة الكبدية (DILI)، وبالتالي فإن تحديد إصابة الكبد يمثل تحديًا للعلاج السريري والتشخيصي. الأسباب الرئيسية لفشل الكبد تنتج من نواتج الأيض السامة لبعض الأدوية التي تستهلك الأدينوزين ثلاثي الفوسفات (ATP) مقارنة بالظروف الطبيعية وزيادة الإجهاد التأكسدي بسبب الإفراط في تكوين MicroRNAs ، وهو أمر ضروري لإجراء التشخيص الكامل للمرضى. يمكن استخدام البارامترات الكيموحيوية للتحقق من الاصابة بالتلف الكبدي مثل تحليل microRNAs (miRNAs) ، وهي أكثر تقبلاً لأنها تزداد في وقت مبكر مقارنة بإنزيمات الترانساميناز مما يسمح بتشخيص أكثر دقة. تم تلخيص العلامات الحديثة لتقدم المرض فيما يتعلق بدور (miRNA) كمؤشر حيوي جديد لـ DILI ، يمكن قياس مستويات miRNA في البلازما واللعاب والادرار والسائل الجنيني (الذي يحيط بالجنين) ،

وغير ذلك سواء في الإنسان أو الحيوان مثل الفئران والجرذان ، ووالتي ترتفع بشكل ملحوظ أثناء المرض ، وبالتالي توفر علامة بيولوجية نوعية للاصابة الكبدية..

الكلمات المفتاحية: miRNA , اصابة الكبد, الدواء المحفز لاصابة الكبد

Introduction

MicroRNA (miRNA) is a tiny non-coding RNA with a length around 22 bp that regulates post-transcriptional gene expression by binding to and blocking miRNA targeting. Currently, more than 1800 MiRNAs have also been discovered, and it looks that miRNA regulates over 60 percent of the human protein-coding genes. During the past decades, the process of miRNA synthesis and participation is normal for all functions. However, recently, revealed that dysregulation of miRNA has been linked to human diseases. Numerous studies have been conducted to investigate miRNA as a high sensitivity and specificity biomarker of toxicities. [1], because it is increased in the early phase of disease more than transaminase enzymes.

The Metabolic Pathway of Detoxifications

Phase 1 Metabolism Enzyme

The effect of cytochrome P450 (CYP) mediates metabolisms and its detoxification's ability based on a study of idiosyncratic DILI. As a result, cytochrome P450 plays an important role in the pathophysiology of DILI. Several research has been conducted on many cytochrome variations have a strong correlation been shown with detoxifications. [3]

Phase 2 Detoxification Enzymes

The detoxification enzyme must be acetylated by various factors, such as the N-acetylation of the enzymes involved in DILI. Reduced acetylation capacities are implicated in the development of hepatotoxicity and oxidative stress from sulfa drugs. Antioxidant enzyme-like Superoxide dismutase and Glutathione S-transferase are cytoplasmic enzymes that maintain the tissue from reactive oxygen species while antimicrobial agents and NSAIDs, for example, are linked to an increased risk of hepatotoxicity when it drops. [4,5]

Classes of drug-induced liver injury (DILI)

Drug-induced liver injury (DILI) is classified as either non-idiosyncratic (predictable) or idiosyncratic (unpredictable) types. The most prevalent cause of non-idiosyncratic DILI is acetaminophen, which is a widely used drug with an excellent safety if used appropriately while Idiosyncratic DILI like amoxicillin plus clavulanic acid and NSAID drugs is not a single disease entity, but rather a group of uncommon disorders with different clinical, histologic, and laboratory aspects. [6]

MicroRNA: biogenesis and functions

Recent research has shown different biogenesis processes and regulation mechanisms. [7] miRNA is a short strand of about (20–25 nucleotides), its regular gene expression. The pathway of miRNA biosynthesis is depicted schematically in Figure 1. miRNA biogenesis is a multistage process and the regulation of gene expression by miRNA is through an inhibitor effect on proteins translations via interacting with the mRNA of its target

gene. Throughout the last ten years, miRNA has been demonstrated to involve in physiological systems and activities such as the development and differentiation of organs, cell growth, and carcinogenesis. In contrast to mRNA, miRNA has been found for long period in biological fluids, for this property makes miRNAs an ideal translational marker of illness and injuries. For this reason, it was employed as a screening tool for the early detection of several liver diseases, including DILI, using miRNA analysis in numerous fluids, notably plasma or serum, urine, saliva swab, and cerebral spinal fluids. [8]

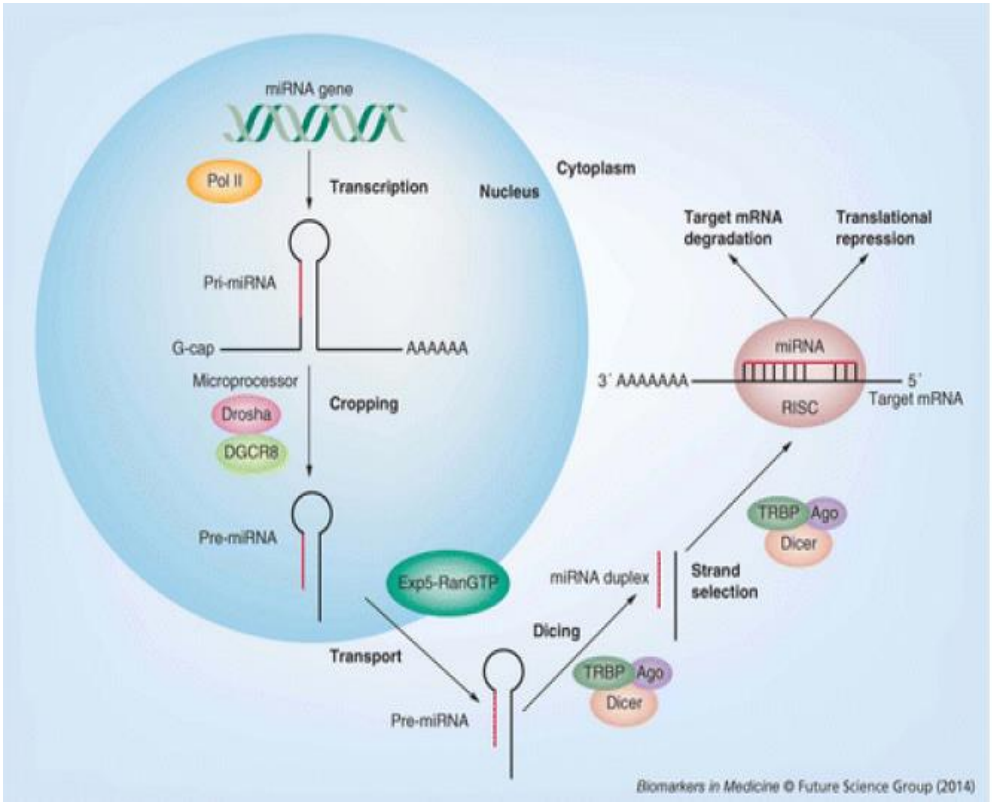

Figure (1): General pathway of miRNA biosynthesis[8]

MicroRNA and pathogenesis of DILI

The major causes of liver failure involve toxic metabolites of some medications that consumed Adenosine Tri Phosphate (ATP) compared with normal conditions and increased oxidative stress due to overexpression of microRNAs, the mechanism involved mitochondrial uncoupling and hepatic apoptosis since no ATP is consumed. The active metabolite increases mitochondrial permeability, resulting in a rise in cytoplasmic Ca and cell apoptosis. Each of these processes can influence miRNA expression, and a deregulating of miRNAs may occur. [9] Moreover, several studies have found that drug-metabolizing enzymes, such as cytochrome P450 1B1, which is abundant in the human liver, are targeted by specific miRNA. [10,11] Therefore, many studies showed miRNAs play an important role in the pharmacologic and toxicological progressions for hepatotoxicity. As shown in Figure 2, MiRNAs can play an important role in several DILI development processes by regulating their target genes. [12]

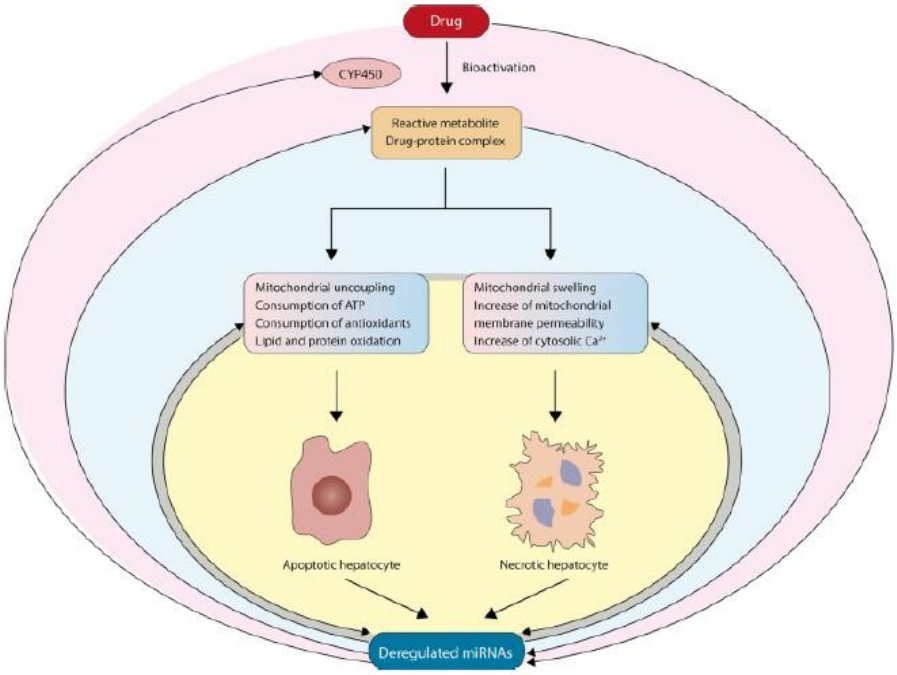

Figure (2): Schematic presentation for the process of miRNA pathogenesis [12]

The technical challenge of miRNA isolations and detections

The technical challenge of miRNA isolations and detections measured by different methodologies, like microarray and real-time reverse transcription PCR and (qRT-PCR) and the comparison between advantage and disadvantage of current technology for miRNA expressions profiling as described below in Table (1). [8]

Table: The benefits and drawbacks of existing technology for miRNA expression profiling [8]

Items	Reverse-transcriptase qPCR	Microarray	RNA-seq
Preferential field of application	Relative and absolute quantification; validation of other miRNA profiling approaches	Relative and absolute quantification of miRNA regulation; miRNA biomarker identification; routine application and higher throughput with respect to sample number compared with small RNA sequencing	*De novo* identification of small RNAs; simultaneous relative quantification of different small RNA species; holistic picture of the small RNA transcriptome
Advantages	Well-established method; sensitive and specific; can be used for absolute quantification of miRNAs	Well established; fairly low cost and high throughput	High accuracy in distinguishing miRNAs that is very similar in sequence, as well as isomiRs. Can detect novel miRNAs
Disadvantages	Only medium throughput with respect to the number of samples processed per day; cannot identify novel miRNAs	Lower specificity than reverse-transcriptase qPCR or RNA sequencing. Cannot identify novel miRNAs; difficult to use for absolute quantification	Substantial computational support needed for data analysis. Cannot be used for absolute quantification

Traditional biomarkers of liver functions

level of alanine aminotransferase ALT, aspartate aminotransferase AST, alkaline phosphatase ALP, and gamma-glutamyl transferase biomarkers GGT are signs of drug-drug-induced injury monitor or diagnosis depending on altering in the liver functions and change in tissues and cells integrities. [13,14] As shown with Gilbert disease, the level of bilirubin based on conjugated bilirubin can be confused with the level of unconjugated bilirubin. Conjugated bilirubin is a specific biomarker of liver injury; however, traditional biomarkers may reflect hepatic toxicity but are useless in the diagnosis of drug-induced liver injury. Moreover, ALT and AST are commonly used to diagnose hepatic injury, however, they can also be elevated in muscle and heart damage, hence liver enzymes exhibited weak associations in DILI. [15] For these reasons, diagnosis of DILI depends on the specific criteria. [16,17] In another hand, increased levels of antibodies like anticytochrome 1A2, antimitochondrial antibodies, anti-cytochrome 3A can measure the hepatotoxicity of some medications. [17] While Anti-epoxide hydrolase antibodies are employed as sensitive indicators for antipyretic and analgesic medication that cause hepatotoxicity. Finally, hepatotoxicity medications should be banned from pharmacies, and new safety drugs should be detected. [18,19], It can also be utilized as an antioxidant supplement to protect cells from free radical and oxidative stress. [20,21]

Conclusion

Drug induce hepatic injury are the main causes of liver failure, through their toxic metabolite includes increased consumptions of ATP with increased oxidative stress due to expressions of miRNA therefore it is particular in this situation to use microRNA for diagnosis which increased in the early stage of disease compared with transaminase enzymes.

Recommendation

The hepatotoxicity drugs should be prevented from the pharmacy and detect new safety drugs.

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