Review Article

Translational medical research and liver transplantation: systematic review

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Abstract: Translational medicine has become a priority, but there is still a big difference between the arrival of new treatments and investment. Basic science should not be neglected because the translation from basic research is not sustained in the absence of basic research. The purpose of this literature review was to analyze the translational medicine in the liver transplant field: liver ischemia-reperfusion injury (IRI), immunosuppression, clinical and surgical complications, small-for-size syndrome (SFSS), rejection, and ongoing innovations (liver machine, liver preservation, artificial livers, and regenerative medicine). We performed a systematic literature review that were updated in October 2016. The searches were performed in the Cochrane Central Register of Controlled Trials and Review, PubMed/Medline, Embase, and LILACS databases. All the selected studies on the management of translational medical research in liver transplantation (LT) were analyzed. Initially the search found 773 articles. Methodological viewing and analysis of the articles, followed by the application of scientific models, including translational medicine in the liver transplant field. In conclusions, this review demonstrates the application of scientific research with translation medical benefits regarding the LT. The literature has a great tendency, improvements and investments in the study of translational medicine in LT. Innovative studies and technologies from basic science help to clarify clinical doubts. Moreover, evidence increases the importance of scientific research in quality of clinical practice care.

Keywords: Liver transplantation (LT); transplantation; systematic review; translational medical research

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Introduction

Translational medicine aims to introduce innovations from basic research to clinical development and has become a priority. Nevertheless, there is still a vast challenge to the arrival of new treatments and their real benefits for practical medicine (1). Indeed, advances are not sustained by the absence of basic research, and therefore strategies and a methodology have been shaped in order to develop new treatment, mainly for complex diseases that demand better resolutions (1).

Liver transplantation (LT) is an efficacy approach and complex therapeutic technique in medicine. Despite of all basic research accomplished for this therapeutic method, this procedure still has many complications that require scientific models in order to improve the results (2). Additionally, promoting the validation of studies in precision medicine, immunological and surgical fields (including genome and epigenome studies), nanotechnology, signaling

pathways, and biobanking could improve the advances of translational research and personalized medicine toward LT, offering potential solutions for further advancement through better integration between health care, academia, and industry (3).

The purpose of this literature systematic review was to analyze the translational process in the specific setting of LT, including liver ischemia-reperfusion injury (IRI), immunosuppression, clinical and surgical complications, small-for-size syndrome (SFSS), rejection, and ongoing innovations (liver machine, liver preservation, artificial livers, and regenerative medicine).

Methods

Identification and selection of the studies

This literature systematic review was performed to up to date the translational medical research in LT. The Medline-PubMed, Embase, Cochrane Databases (Controlled Trials and systematic review) and LILACS databases were electronically searched for articles published from January 2000 to October 2016, and updated in 19 October 2016.

The Mesh-terms utilized in Medline-PubMed database for literature search were developed using the PICO structure: patient, intervention, comparison or control, outcome. The Mesh-terms were used in combination with "OR". The results for the search Mesh-terms used "P" (Patients) were associated with the result that formed with the "I" (Intervention), using the "AND" and "NOT" operators.

The Medline-PubMed search was conducted in PubMed (www.ncbi.nlm.nih.gov/pubmed) and used the Mesh-terms: (((((“Liver Transplantation”[Mesh]) AND “Translational Medical Research”[Mesh]) and (((((“Liver Transplantation”[Mesh]) AND “Translational Medical Research”[Mesh]) OR “Genomics”[Mesh]) OR “Epigenomics”[Mesh]) OR “Molecular Targeted Therapy”[Mesh]) OR “Bioethics”[Mesh]))))). The equal strategy was used the others databases in the Embase (www.embase.com) and LILACS (http://lilacs.bvsalud.org) with the terms: (((((“Liver Transplantation”[Mesh]) AND “Translational Medical Research”[Mesh]). The Cochrane Library Database (http://www.cochrane.org) was searched for registered and published systematic reviews (CDSR) and clinical trials (CCTR) on the management of LT and Translational Medical Research.

Inclusion and exclusion criteria

Selection criteria were performed within the research question with the PICO structure; therefore, randomized controlled trials, non-randomized controlled trials, or comparative clinical studies and others were included. Specific analysis and article selection in the LT surgical approach include the following topics: liver IRI; immunosuppression; complications: clinical and surgical; SFSS; rejection; and miscellaneous (liver machine and liver preservation; artificial liver and regenerative medicine; and experimental LT model).

Data collection, analysis, and critical evaluation

Independently the reviewers were assessed the studies quality and extracted data. The quality and selection of the studies data was evaluated by 2 researchers (LS Nacif and V Kim). In case of discordance, the researchers promoted a consensus to select the final verdict. The study design and quality of the studies, level of evidence, and article choice were based on the article's close relation to the topic of this review.

Results

Study selection and study quality

Initially the search found 773 articles. The entire study selection and description are detailed in *Figure 1*.

The characteristics of all search and databases were demonstrated on *Table 1*. Cochrane Library Database (http://www.cochrane.org) literature was searched for registered and published systematic reviews (CDSR) and clinical trials (CCTR) on the management of LT and Translational Medical Research (*Table 1*).

Articles selection with PICO structure were summarized in Supplementary files.

In the qualitative analysis of the present study we selected 44 studies for further analysis (4-23), the specific analysis was demonstrated on *Figure 1* and *Table 2* (24-47).

Qualitative analysis evaluation of the selected articles was follow below as liver IRI (n=9); immunosuppression (n=16); SFSS (n=3); acute cellular rejection (ACR) (n=11); liver machine and preservation; artificial livers and regenerative medicine (n=5) (4-23). The sensitive analysis shows us the vast presence of prospective original studies in these

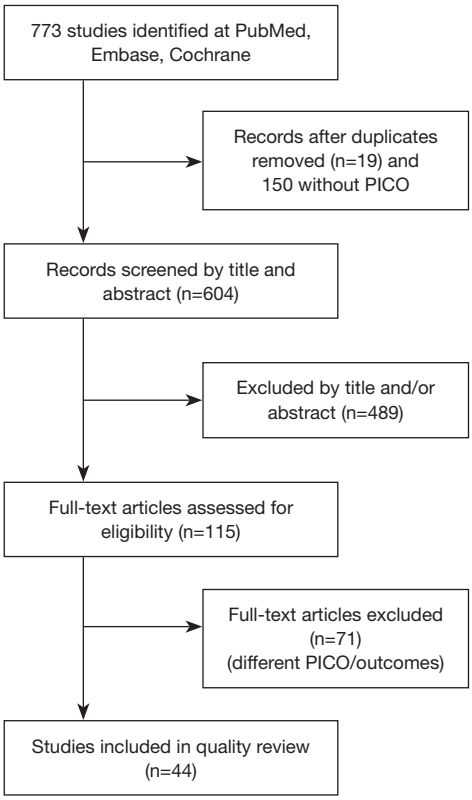

Figure 1 Flowchart of the study selection.

Table 1 Characteristics of all search and databases

Search terms	PubMed	Embase	Cochrane	Total
1	6	222	11	239
2	53	330	1	384
Total	68	693	12	773

Search 1: 'Liver Transplantation' AND 'translational research'; search 2: (Epigenomics OR Genomics OR Molecular Targeted Therapy) AND Liver Transplantation).

fields with more than 33 articles selected, the others was retrospective and reviews. The articles selected in the search were detailed and demonstrated in *Table 2* (24-47). The selected articles were initially tabulated and characterized according to study type and PICO structures (*Table 2*).

Discussion

The present subject of this article shows us the important topic from "bench to bedside" is being re-thought around the world in the scientific and health-care communities. An integrated institutional, multidisciplinary medical and research approach for the application of translational medicine promotes the validation of studies to translate to the clinical and surgical fields regarding LT. Indeed, diverse advances on translational research have been made over the past decades in the field of LT in an attempt to increase organ utilization and improve the health care for these patients.

Liver IRI is an important complication from hemorrhagic shock, large resection, and transplant. IRI in general is a dynamical manner with two stages: the local insult on ischemia phase and reperfusion phase with inflammation mediators (12). Regarding the LT process, these injuries occur at three distinct steps: firstly, the liver is stored at 0 ℃ to 4 ℃ after explanted from the donor (cold ischemia); then followed by the vascular anastomosis (warm ischemia). The ischemia period increases the liver temperature 0.5 ℃/minute. Liver reperfusion configures the third step (8,10,11). Over the last decade, the prevention of early graft failure was performed using some therapeutic approach and donor-recipient well match strategies to prevent and decrease the IRI effects.

Immunosuppressive therapy has been optimized and evolving over the last years following LT (2). The therapeutic options vary from diverse types of agents and depend on the specific patient whether one should use the immunosuppression agent alone or in association. The types of LT immunosuppression drugs include: calcineurin inhibitors (CNIs), cyclosporine (CsA) or TAC; mycophenolate mofetil (MMF), azathioprine (AZA), mTOR inhibitors (rapamycin), and steroids (methylprednisolone or prednisone) (2). Post-transplant acute or chronic rejection and fibrosis are even difficulties to obtaining long-term survival in LT. Some translational studies show us interesting advances in this field, the mostly studies found in this review was regarding the acute cellular rejection (n=11) and immunosuppression (n=16).

Chronic kidney disease (CKD) after liver transplant is one of the biggest clinical problems that arise to be related with genetic and non-genetic determinants. CNI is considered the main guilty in the development of CKD after LT (15). Kidney injury is usual in recipients with cirrhosis and related with decrease of survival rate after LT. This dysfunction perhaps associated to damage or functional alterations and can be better with following the LT.

Another poorly understood complication in LT is the concept of early allograft dysfunction (EAD), which demonstrates post-transplantation with increase serum

Table 2 Characteristic of studies with liver transplantation and translational medical research

Reference year	Type of article	Sample	N	Intervention	Outcomes
Ischemia-reperfusion (IRI)					
Qin 2016 (4)	Original	Animal	–	Short-term starvation	Attenuates liver IRI via the Sirt1-autophagy pathway
Zhuang 2016 (5)	Original	Animal	–	Dichloroacetate diisopropylamine	Recovery of donor liver function after transplantation
Emadali 2006 (6)	Original	Human	–	Proteomic analysis of IRI	Regulation of IRI-induced cytoskeleton remodeling and led to the identification of IQGAP1 as a regulator of bile canaliculi
Jassem 2009 (7)	Original	Human	19/16	IPC (× IRI)	Reduction in the expression of immune response genes and promotion of those involved in protection and repair
Kristo 2011 (8)	Original	Human, RCT	13/13	TAC (× Placebo)	Did not enhance early graft function (AST, ALT) in the donor graft
Raza 2010 (9)	Original	Human, RCT	–	IPC (× standard organ recovery)	Increases expression of transcripts which are likely to increase antioxidant defenses.
Cursio 2010 (10)	Leading	–	–	Caspase inhibitors	Cold ischaemia/normothermic reperfusion injury
Selzner 2012 (11)	Review	–	–	–	Mechanisms of pre-, post-, and remote conditioning of solid organs
Zhai 2013 (12)	Review	–	–	–	Innate-adaptive immune crosstalk and cell activation cascades
Immunosuppression		–	–	–	
Goto 2014 (13)	Abstract	–	–	Anti-nuclear histone H1antibody	Histone H1 was upregulated during liver fibrosis
Nakano 2010 (14)	Abstract (p-194)	Animal (rat)	–	Hepatic mast cells, OLT	Stem cell factor is an important factor for proliferation and maturation of mast cells
Parikh 2014 (15)	Editorial	–	–	–	–
Egawa 2012 (16)	Original	Human	158	TAC, LDLT and non-inflammatory central sinusoidal fibrosis (NICSF)	NICSF might be an indicator of inadequate immunosuppression in pediatric patients under TAC withdrawal
Hsu 2007 (17)	Original	Human	15	Cyclosporin, biliary atresia	Detection of several proteins associated with a drug-free OLT patient
Fukudo 2008 (18)	Original	Human	60	TAC,living-donor liver transplantation (LDLT)	CYP3A5*1 genotype as well as the MDR1 mRNA level in enterocytes contributes to interindividual variation in the CL/F of TAC in adult recipients early after living-donor liver transplantation
Crettol 2008 (19)	Original	Human	64	Cyclosporine, renal, liver or lung transplant	ABCB1 polymorphisms (1199A and 3435T carriers) influence cyclosporine intracellular concentration
Smith 2008 (20)	Original	Human	163	Calcineurin inhibitors (CNIs), LT patients receiving CNIs for at least 3 years	CYP2C8*3 is associated with a higher risk of developing renal toxicity in patients treated chronically with CNIs
Chen 2013 (21)	Original	Human	96	TAC, LT	Combined SNPs of donor CYPA5 rs776746, IL6 rs1800796, and recipient CYP3A5 rs776746 have a greater effect on TAC metabolism than CYP3A5 rs776746
Levitsky 2013 (22)	Original	Human	20	TAC to Sirolimus, LT	CNI to SRL conversion after LT could take advantage of the regulatory properties of SRL

Table 2 *(continued)*

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Reference year	Type of article	Sample	N	Intervention	Outcomes
Chen 2014 (23)	Original	Human	96	TAC, LT	Hb, donor CYP3A5, NR1I3 gene polymorphisms, and recipient CYP3A5 gene SNPs were associated with TAC pharmacokinetics.
Kurian 2015 (24)	Original	Human	40/36	EAD/non-EAD	Relevant pathways (PPARa and NF-kB) and targets (CXCL1, IL1, TRAF6, TIPARP, and TNFRSF1B) are associated with the phenotype of EAD
Béland 2014 (25)	Original	Human	–	Cyclosporine or TAC, OLT pediatric	High prevalence of infection and a high Torque Teno virus load among OLT recipients; Viral load was influenced by immunosuppressive regimen
Elens 2007 (26)	Original, prospective	Human	150	TAC, Liver donors	CYP3A5 SNPs in liver tissue is significantly associated with TAC dose requirement; SLCO1B1 seem to influence early trough blood concentrations, SNPs in ABCB1 seem to influence the TAC hepatic levels and the graft outcome
Tapirdamaz 2014 (27)	Original, retrospective	Human	125	TAC, LT	CYP3A5 and ABCB1 genes were not significant risk factor for the development of CKD after LT
Li 2015 (28)	Review	–	–	–	Roles of CXCL4 and CXCL4L1 in the pathogenesis of chronic liver allograft dysfunction
Small-for-size syndrome					
Hsu 2015 (29)	Original	Animal (rat)	–	Granulocyte colony-stimulating factor (G-CSF), dipeptidyl peptidase IV (DPP-IV) inhibitor	Combined treatment may synergistically induce migration and differentiation of recipient-derived stem cells into the hepatic progenitor cells
Chen 2011 (30)	Original	Animal (rat)	–	miRNA expression profile, partial hepatectomy (PH) LT	Down-regulated miRNAs play a pivotal role in promoting the growth of small size grafts and the remaining liver after PH
Iguchi 2014 (31)	Original	Animal (pig)	–	Olprinone, hepatectomy model	OLP may have the therapeutic potential to overcome PHLF and SFSS
Acute cellular rejection					
Nakano 2012 (32)	Original	Animal (rat)	–	Immunological and regenerative aspects of hepatic mast cells in liver allograft rejection and tolerance, OLT	Early induction of c-Kit, Foxp3+ Tregs, and cd T cells may be indispensable for overcoming acute rejection and that Foxp3+ Tregs, CD T cell
Wei 2015 (33)	Original	Animal (rat)	–	Biomarkers of the chronic rejection, OLT	CLU, Lcn2 and Krt19 were identified and quantified as early and reliable biomarkers
Xu 2014 (34)	Original	Animal (rat)	–	Biomarkers of immune response, OLT	HPX serves as a negative predictor for AR of liver allograft
Cheng 2010 (35)	Original	Animal (rat)	–	Global protein expression changes in liver allograft during AR	Altered protein expressions act coordinately in hepatocyte dysfunction by depressed energy, enhanced oxidative stress-induced molecular damage and restrained biotransformation
Wu 2009 (36)	Original	Animal (rat)	–	Variation of serum metabolites, OLT	Changes in metabonomic profiles reflected in the graft injury are correlated with histological changes instead of classical liver function

Table 2 *(continued)*

Table 2 *(continued)*

Reference year	Type of article	Sample	N	Intervention	Outcomes
Gehrau 2016 (37)	Abstract	Human	22	DNA methylation patterns, post-LT	CpGs methylation identified apoptosis activation signaling, ubiquitin protein degradation, and cell cycle regulation. CpGs hypomethylation increases in liver cell death and G1/S cell cycle check-point
Taubert 2012 (38)	Original, prospective	Human	151	Intrahepatic T cell infiltration pattern in correlation to the severity of ACR	Active role of regulatory T cells (Tregs) in controlling rejection
Joshi 2013 (39)	Original	Human	29	Intragraft miRNA expression profiles, recurrent HCV from ACR post-LT	miRNA-19a and miRNA-20a could represent potential serum biomarkers for fibrosis progression
Uesugi 2014 (40)	Original	Human	412	TAC, ACR post-LT	Graft liver CYP3A5*1 genotype might increase the risk for ACR after living-donor LT
Bonaccorsi-Riani 2016 (41)	Original, prospective	Human	55	Molecular Characterization, ACR post-LT	Potential utility of transcriptional markers in peripheral blood as a predictor for rejection
Ningappa 2016 (42)	Original	Human (pediatric)	62/60	Rabbit antihuman thymocyte globulin and steroid-free TAC, non-rejector/rejector	Association between rs9296068 HLA-DOA gene and LT rejection
Miscellaneous					
Yagi 2013 (43)	Original	Animal (rat)	–	Venous systemic oxygen persufflation (VSOP) with nitric oxide (NO) gas, partial liver preservation and LT	Novel and safe preservation method that improve liver regeneration after transplantation
Zhou 2014 (44)	Original	Animal (rat)	–	Arterialized OLT	Done quickly with a high patency rate
Dong 2016 (45)	Original	Animal (pig)	–	Development of an organ culture system	Liver function can be maintained in ex situ organ culture without the use of erythrocytes
Orlando 2011 (46)	Review	–	–	–	Recent advances in the engineering of several key tissues and organs
Hashmi 2015 (47)	Review	–	–	–	Genomics of liver transplant injury and regeneration

Number and percentages. EAD, Early allograft dysfunction; IPC, Ischemic preconditioning; IRI, ischemia/reperfusion injury; LT, Liver Transplantation; TAC, Tacrolimus; TMR, Translational Medical Research.

transaminases, cholestasis and coagulopathy (28). Chronic liver graft dysfunction is the main morbidity and late graft waste cause after LT.

Small remnant of the liver or a small-for-size liver commonly induces SFSS or post-hepatectomy liver failure (PHLF). An inordinate portal flow for these small livers is primordial factor for SFSS (45). Some of these modalities, as living donor LT or split livers, were solutions to the liver donor shortages and decrease the waiting-list time for the patients to the LT procedure (45). This study shows us some specific papers on raising the mortality rate and require the progress of organ culture system that livers can be cultured and hold ex situ for a long time.

Regenerative medicine has demonstrated feasible for "bench-to-bedside" translational research in cell progress, stem cell biology and tissue engineering (46). We found some papers regarding models of functioning livers that have been engineered application "natural tissue" scaffolds and are in evolution to produce kidneys, pancreas, and small intestines.

The regenerative potential of the liver is unparalleled with its regeneration recover after damage from ischemia, resection, and acute or chronic rejection (47). The signatures of gene expression were characterized for these events and may be possible to precise therapies to decrease damage, improve regeneration and survival rates.

The limitations of this study were that we were unable to perform a meta-analysis due to the diversity and heterogeneity of the papers studied. This study has others limitations; the specific outcomes of interest have been

evaluated separated. In this subject, more randomized clinical trials are needed to focus on translational medicine and LT. The benefit of this systematic review was to evaluate more patients with important positive factors in the liver transplant field. This is an original research that we described a systematic review of articles that shows us an important topic from "bench to bedside" is being re-thought around the world in the scientific and health-care communities. Indeed, diverse advances on translational research have been made over the past decades in the field of LT in an attempt to increase organ utilization and improve the health care for these patients.

Conclusions

Translational medicine was initially conceived as an integrated institutional, multidisciplinary, medical research approach toward the application of "bench-to-bedside" rather than promoting advancement and technologies in LT around the world in the scientific and health-care communities

This systematic review demonstrated due to the increasing number of publications that have been improvements regarding the study of translational medicine in LT. Innovative studies and technologies from basic science help to clarify clinical doubts and basic scientific research has increasingly contributed to the quality of care in clinical practice.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Articles selection with PICO structure

(I) Liver transplantation AND Translational Medical Research
Duplicates: 5
("Liver Transplantation"[Mesh]) AND "Translational Medical Research"[Mesh]
Cochrane: 11
("Liver Transplantation"[Mesh]) AND "Translational Medical Research"[Mesh]
PubMed: 6
'Liver Transplantation' AND 'translational research'
Embase: 222

(II) (Epigenomics OR Genomics OR Molecular Targeted Therapy) AND Liver Transplantation
Duplicates: 14
((("Epigenomics"[Mesh]) OR "Genomics"[Mesh]) OR "Molecular Targeted Therapy"[Mesh]) AND "Liver Transplantation"[Mesh]
PubMed: 53
(Genomics OR Epigenetics OR molecularly targeted therapy) AND Liver Transplantation
Embase: 330
(Genomics OR Epigenomics OR molecularly targeted therapy) AND Liver Transplantation
Cochrane: 1