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Targeted therapy of liver fibrosis/cirrhosis and its complications

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Introduction

Do we need targeting to specific liver cells? Uptake of drugs in the liver is usually high. While most existing drugs are not cell-specific at all, they are effective. However, uptake by fibrogenic cells in the fibrotic liver is usually low and off-target effects can be high, e.g., due to compromised hepatic metabolism and excretion. Therefore, most experimental drugs are not effective at the preclinical level when they are administered in animals with advanced and established fibrosis (i.e. a situation similar to the clinical practice). To date, no antifibrotic drug has reached the clinic.

Some drugs are intrinsically targeted to the fibrogenic process due to their (receptor) specificity. Examples are PDGFRβ or integrin αVβ6 antagonists/blocking antibodies, or liposomal aptamers or siRNA against procollagen I, but even here delivery to their target cells in advanced fibrotic livers may be limited.

Rationale for drug targeting

- The hepatic uptake of (xenobiotic) drugs largely occurs via hepatocytes and/or macrophages, not by myofibroblast-like cells which are the key effector cells in fibrogenesis.
- Biologicals like chemokines, cytokines or prostaglandins have a short plasma half life and the ubiquitous expression of their receptors can induce unwanted side effects.
- Interference with normal matrix turnover and wound healing may restrict the use of untargeted antifibrogenic drugs for prolonged periods of time.
- Inhibition of inflammation may lead to inhibition of ECM turnover and thus to enhanced fibrogenesis (skewing of the immune system towards alternative macrophages, a Th2 T cell response, or production of TGFβ).
- Chronic viral infection and/or an enhanced risk of bacterial translocation from the intestine combined with a compromised immune system in cirrhotic patients prevent the chronic administration of generally active immunosuppressive drugs.
- An enhanced risk of tumorgenesis or metastasis in the fibrotic (virus infected) liver precludes the use of anti-apoptotic drugs or drugs that enhance MMP activity due to an increased perceived risk of tumorgenesis and metastasis.
- Induction of splanchnic and peripheral hypotension restricts the systemic use of drugs that reduce portal hypertension.

How to reach the target cells (Fig. 1)

Activated hepatic stellate cells/myofibroblasts (Table 1)

- Proteins/peptides/sugars:
  RGD-modified proteins targeted at the collagen type VI receptor,
  proteins modified with peptides that bind to the platelet derived growth factor β (PDGFβ)-receptor,
  mannose-6-phosphate (M6P) substituted proteins targeted at the M6P-insulin-like growth factor II (IGFII) receptor.
- Viruses modified with PDGF-β-binding peptides or adenoviral transfection targeted at HSC-specific promotors and genes.
- Antibodies: human single chain antibodies against Synaptophysin, (C1–3 ScAb).
- Vitamin A containing liposomes.

Kupffer cells (KC) and sinusoidal endothelial cells (SEC)

Carriers modified with:

- mannose targeted at CD206 (M2 macrophages),
- fucose moieties targeted at the fucose receptor (KC),
- succinylated/aconylated proteins targeted at scavenger receptors on SEC and/or KC (CD36, CD68/macrosialin, LOX-1, SREC-1),
- hyaluronic acid targeted at the hyaluronan receptor CD44 (SEC).
- Nanoparticles: adsorptive pinocytosis: non-receptor mediated uptake of high molecular weight particles, e.g., clodronate liposomes (KC).

Keywords: Antifibrotic therapy, Cholangiocyte; Drug; Fibrosis; Hepatocyte; HCC; Kupffer cell; Liver; Macrophage; Myofibroblast; Stellate cell; Targeting.
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Hepatology Snapshot

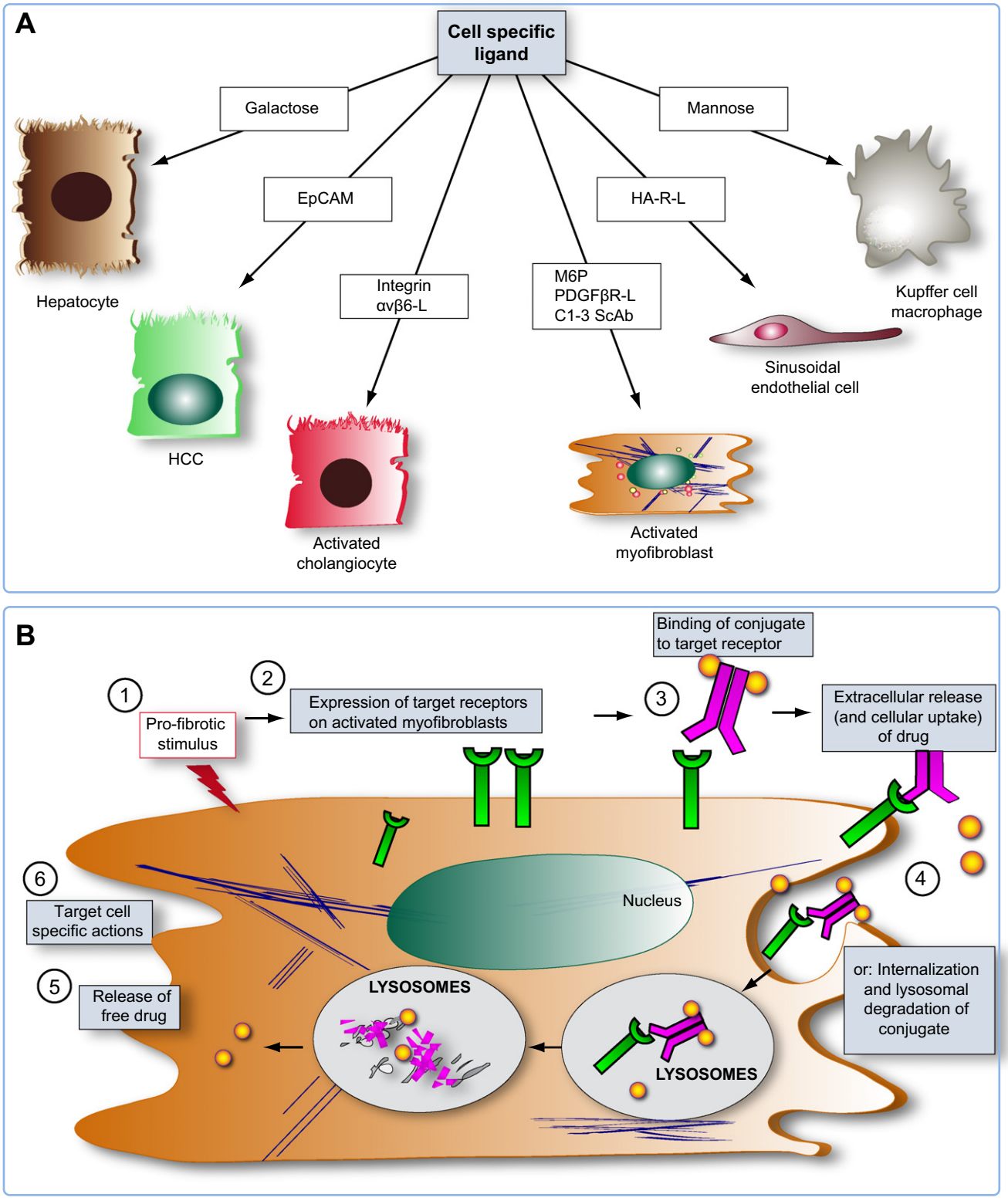

Fig. 1. Drug targeting in the liver. (A) Cell-specific ligands directed at resident hepatic cells that can be used for targeted therapies of liver fibrosis/cirrhosis and HCC. (B) Binding, uptake, internalization, and release of compounds targeted at extracellular receptors resulting in target cell-specific actions.

Table 1. List of drugs targeted to HSC/myofibroblasts and examined *in vivo*.

Mycophenolic acid	antiproliferative drug + immunosuppression
Losartan	AT-II R antagonist, inhibitor of HSC activation, vasoactive drug
Pentoxifylline	inhibitor of collagen synthesis, anti-inflammatory drug
18β-glycyrrhetinic acid	anti-fibrogenic drug
Gleevec derivative: PAP-19	PDGF-kinase inhibitor, anti-inflammatory, anti-fibrogenic agent
Rho-kinase inhibitor (Y27632)	anti-inflammatory, anti-fibrogenic drug
Interleukin-10	anti-inflammatory cytokine
Doxorubicin	cytostatic drug
Gliotoxin	induction of apoptosis
15d-Prostaglandin J_2	induction of apoptosis, inhibition of collagen synthesis

Hepatocytes

- Galactose (lactose) targeted at the asialoglycoprotein receptor (ASGP-R).
- Viruses: adeno and adeno-associated viruses binding to the coxsackie and adenovirus cell adhesion receptor (CAR) or to CD46.

Activated cholangiocytes/hepatic progenitor cells

- RGD-analogs targeting the integrin αvβ6 (e.g., EMD524070).
- Secretin: targeting the secretin receptor.

Hepatocellular carcinoma cells

- Monoclonal antibodies against:
  EpCAM,
  AF-20,
  EGF-R.
- EGF – receptor binding oligopeptide.

Factors that dermine the success of a targeted drug

- Specific target receptor expression: expression on the target cell relative to other key tissues and cells.
- High receptor affinity of the drug carrier.
- High receptor density on target cells.
- Sufficient stability of the construct in serum.
- Intracellular release of active compounds: endocytosis and subsequent intracellular cleavage is required to ensure release of the active compound from the drug carrier, which is facilitated by an appropriate linker between drug and carrier. The drug itself should either be resistant to the endocytotic process or released extracellularly after binding to its target receptor.
- Sufficient amount of drug loaded on the carrier.
- Low immunogenicity of the construct.
- Size big enough to prevent immediate renal clearance, small enough to ensure tissue penetration in the diseased area.
- Possibility of long-term treatment: low toxicity, appropriate administration routes and intermediate-long biological half life.
- Simplified synthesis according to GMP criteria.

Conclusions

Cell-specificity is essential for most antifibrogenic as well as anticancer drugs. All key cells in the fibrogenic process can be reached by cell-specific drug carriers, and future research should address the key factors that determine success. Coupling of a tracer to a drug carrier also opens opportunities for diagnosis, early detection and individualized therapy monitoring, e.g., via quantitative imaging of liver fibrosis, fibrogenesis and cancer. This promises to facilitate a personalized medicine (sending a drug and a tracer to the same cells) which is particular relevant for chronic liver diseases, which subclinically progresses to end-stage liver failure and which may need long-term treatment.

Conflict of interest

KP received funding from Biorion Technologies.