Mission:Cure

Relevant Preclinical Models in Recurrent Acute and Chronic Pancreatitis

William Salerno, Chloe Nelson, Lola Rahib

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Introduction

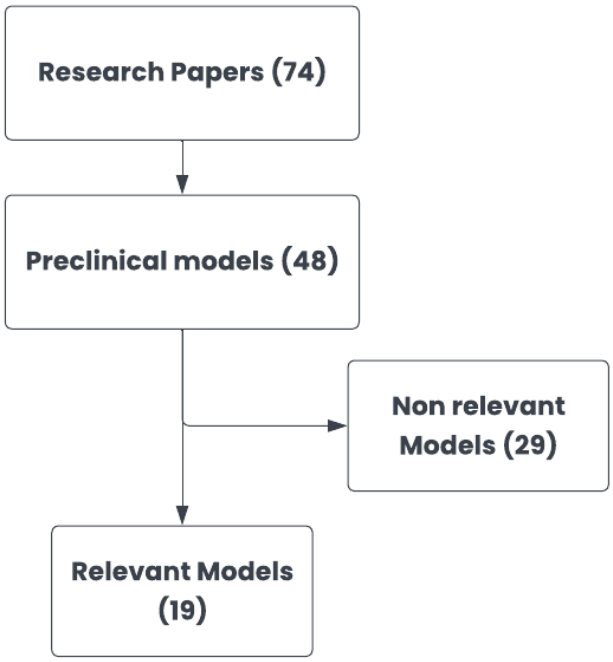
Recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) lack effective disease-modifying therapies; thus, symptom management remains the primary treatment for patients. The complex etiologies and pathophysiological mechanisms of RAP and CP pose challenges in developing therapies, necessitating suitable animal models for preclinical drug screening to successfully translate into clinical trials. The goal of this review is to provide information on relevant preclinical models that can be used for drug screening.

Methodology

Publications reporting on animal models in pancreatitis research were sourced from medical and academic journals. While there were many possible models for pancreatitis research identified, many lacked clinical relevance and/or feasibility. As such, we determined that it was necessary to develop a set of criteria to determine a model's relevance to preclinical drug screening. The overarching criteria we used were based on whether the model produced a phenotype that recapitulates RAP or CP in humans and on whether the model was toxic or had negative side effects in the animals. We also considered the model's feasibility and relevance to researchers. Models were classified into either the 'relevant' or 'non-relevant' categories. Models

published prior to 2013 that were referenced in at least one other publication in the past 10 years and models published prior to 2018 that were referenced in at least one other publication in the past five years were considered "relevant". Models published after 2018 were categorized based on the model's feasibility and replicability through the results of its respective study. Conversely, models with limited evidence, severe adverse effects, limited feasibility due to ethical and financial concerns, and those with limited clinical relevance were considered "non-relevant". Models that have been previously used in preclinical drug screening research were also classified as "relevant".

Figure 1: Evaluation of Preclinical models



Results

74 articles were analyzed for preclinical models used for pancreatitis, there were a total of 48 different preclinical models identified. Of these, 19 were classified as 'relevant' and 29 were classified as 'non-relevant' for preclinical drug screening (Figure 1). Relevant models according to the established criteria are listed in Table 1. A full list of all models reviewed is available on our website. Drugs that have been tested in specific models are also listed (Table 1). Dabigatran, a type of blood thinner, was tested in trypsin dependent GEMM models. Pirfenidone, an antifibrotic drug, was tested in two different models, L-arginine, a type of amino acid model, and in the cerulein model. Proglumide, a cholecystokinin (CCK) antagonist drug, and Baicalin, a flavonoid glycoside, were only tested in the cerulein model. Adipose stem cell therapy[1] and FGF21[2] therapy were tested in the ETOH and cerulein model. The Orai inhibitor, CM5480 was tested in the cerulein model.

Discussion

We have compiled a comprehensive list of preclinical models which may be used for pancreatitis research and listed those that are more relevant based on use and feasibility. While not all the relevant models have been utilized for preclinical drug screening, each holds the potential for such applications. The relevance of these models varies depending on the specific use. Several of the preclinical models have already been used in drug testing for pancreatitis including dabigatran, pirfenidone, proglumide, baicalin, adipose stems cells, FGF21 therapy, and CM5480, an Orai1 inhibitor.

We provide this information to expedite drug screening studies in relevant preclinical models, thereby accelerating the development of therapies for this therapy this disease.

Table 1: List of Relevant Preclinical Models (chronic pancreatitis)

Model	Drug Testing*
GEMM Models	
PRSS1 R122H[3]	Dabigatran
transgenic PRSS1R122H[4]	Dabigatran
The T7D23A mouse model[5]	Dabigatran
T7K24R mouse model[6]	Dabigatran
hPRSS1 R122H /N291[7]	
PRRS2 and PRSS1 R122H[8]	
Atg5-knockout /deletion[9-12 13]	
Atg7-knockout /deletion [14,15]	
IKKa knockout /deletion[15-17]	
PNLIPP p.T122M[18]	
Chemical Models (bile)	
TNBS (intraductal)[17,19,20]	
Amino Acid Models	
L-arginine[15,17,21-26]	Pirfenidone
Nongenic Mouse Models	
Pancreatic duct ligation[27,28]	
Secretagogue Models	
Cerulein[15 1,2,17]	Proglumide, Pirfenidone, Baicalin, adipose stem cell, FGF21

Mechanical	
Ligation/Obstruction[15,17,22,28-42]	
Alcohol induced environmental modulators	
ETOH +HFD chronic (10 week) [2,15,17,43]	Adipose stem cell, FGF21

*not complete list.

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