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Induced pluripotent stem cells as an innovative model to study drug induced pancreatitis

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Abstract

Drug-induced pancreatitis is a gastrointestinal adverse effect concerning about 2% of drugs. The majority of cases are mild to moderate but severe episodes can also occur, leading to hospitalization or even death. Unfortunately, the mechanisms of this adverse reaction are still not clear, hindering its prevention, and the majority of data available of this potentially life-threatening adverse effect are limited to case reports leading to a probable underestimation of this event. In particular, in this editorial, special attention is given to thiopurine-induced pancreatitis (TIP), an idiosyncratic adverse reaction affecting around 5% of inflammatory bowel disease (IBD) patients taking thiopurines as immunosuppressants, with a higher incidence in the pediatric population. Validated biomarkers are not available to assist clinicians in the prevention of TIP, also because of the inaccessibility of the pancreatic tissue, which limits the possibility to perform dedicated cellular and molecular studies. In this regard, induced pluripotent stem cells (iPSCs) and the exocrine pancreatic differentiated counterpart could be a great tool to investigate the cellular and molecular mechanisms underlying the development of this undesirable event. This particular type of stem cells is obtained by reprogramming adult cells, including fibroblasts and leukocytes, with a set of transcription factors known as the Yamanaka's factors. Maintaining unaltered the donors' genetic heritage, iPSCs represent an innovative model to study the mechanisms of adverse drug reactions in individual patients' tissues not easily obtainable from human probands. Indeed, iPSCs can differentiate under adequate stimuli into almost any somatic lineage, opening a new world of opportunities for researchers. Several works are already available in the literature studying liver, central nervous system and cardiac cells derived from iPSCs and adverse drug effects. However, to our knowledge no studies have been performed on exocrine pancreas differentiated from iPSCs and drug-induced pancreatitis, so far. Hence, in

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this editorial we focus specifically on the description of the study of the mechanisms of TIP by using IBD patient-specific iPSCs and exocrine pancreatic differentiated cells as innovative *in vitro* models.

Key Words: Induced pluripotent stem cells; Therapy personalization; Patient-specific cells; Drug-induced pancreatitis; Thiopurines; Inflammatory bowel disease

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Core Tip: About 5% of inflammatory bowel disease patients develop pancreatitis after thiopurine administration. The mechanism of this adverse effect is still not clear making it difficult to prevent. By differentiating induced pluripotent stem cells into their pancreatic exocrine counterpart, it is possible to set up innovative personalized *in vitro* models to study this adverse effect in a more effective way.

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INTRODUCTION

Gastrointestinal adverse effects are common especially with orally absorbed drugs and may result in undesirable consequences leading to the reduction of treatment efficacy and, in the most serious cases, to therapy interruption with associated healthcare costs. To better study and prevent these adverse events there is the need for dedicated clinical investigation[1]. Over the past years, adverse drug reactions (ADRs) have been widely studied also for their negative effect on the development of new drugs[2,3].

Among the different ADRs, drug-induced pancreatitis has become increasingly recognized as an important cause of acute pancreatitis with a wide range of drug classes involved in its development[4]. Unfortunately, the majority of data available of this potentially life-threatening ADR are principally limited to case reports, leading to a probably underestimated incidence, reported to be around 2%[4]. Furthermore, the mechanisms of drug-induced pancreatitis of many drugs are still not clear, making it difficult to determine a definitive association of causality between specific medications and acute pancreatitis, and in only less than 10% of cases the real cause has been determined. Drugs known to induce pancreatitis have been classified considering the number of case reports, the recurrence of pancreatitis with a re-challenge with the drug, consistent latency between the drug assumption and the onset of acute pancreatitis and the exclusion of alternative causes such as alcohol assumption or gallstones [4,5] (Table 1).

Interestingly, certain types of ADRs are reported to be more frequent in patients affected by specific diseases. An important example is thiopurine-induced pancreatitis (TIP), an idiosyncratic ADR affecting more frequently inflammatory bowel disease (IBD) patients taking thiopurines, such as azathioprine and mercaptopurine[6]. In the vast majority of cases, TIP is manageable, however patients have to stop the treatment and to be sometimes hospitalized until the symptoms are resolved[7]. The higher incidence of this adverse event in IBD patients, especially in the pediatric population, suggests that molecular mechanisms involved in the disease may contribute to TIP predisposition[6]. However, mechanisms determining TIP predisposition are still unknown and only hypotheses have been postulated. In particular, the mechanisms proposed can be divided into three different groups: genetic predisposition[8,9], alteration in thiopurine biotransformation[7] and abnormalities in innate or adaptive immunity[10].

The thiopurines azathioprine, mercaptopurine and thioguanine undergo an extensive biotransformation catalyzed by several enzymes[11]. Regarding genetic predisposition, TIP seems unrelated to candidate variants on important genes of the thiopurine biotransformation pathway, such as *TPMT*, *ITPA* and *NUDT15*, well-known to induce severe ADRs, including myelosuppression and hematologic toxicity[12,13].

Table 1 Classification system of drugs related to pancreatitis development[4,5]

Class	
Class Ia	At least one case report with positive rechallenge, excluding other possible causes such as alcohol, gallstones and other drugs
Class Ib	At least one case report with positive rechallenge but not excluding other possible causes
Class II	At least four cases in the literature without rechallenge but with consistent latency in greater than 75% of cases
Class III	At least two cases in the literature without rechallenge and consistent latency
Class IV	Single case reported in the literature not fitting the previous described classes without rechallenge

Recently, two different research groups have found a strong association between the Class II *HLA* gene region polymorphism rs2647087 and TIP[8,9], but more efforts are needed to translate these variants into clinical practice. TIP development may be also related to direct damage to the exocrine pancreatic cells or to an accumulation of toxic metabolites (biotransformation hypothesis). However, pancreatitis frequently occurs early after thiopurine administration, making the accumulation of toxic metabolites unlikely, while more probably immunological reactions are involved. However, direct toxicity of thiopurines or their metabolites on patients' pancreatic cells cannot be completely excluded[7,10].

To study and discover TIP mechanisms and predisposition, innovative patient-specific *in vitro* models could be helpful and decisive. In this regard, induced pluripotent stem cells (iPSCs) and their differentiated counterpart are widely used to set up groundbreaking personalized *in vitro* models representative of patients' genetic background. The peculiar characteristics of these cells allow to set up *in vitro* models to study disease mechanisms and ADRs with the purpose to personalize patients' therapy, improving the disease outcome. The iPSC model can be a great tool to better understand, and thus prevent, ADRs in particular in comparison to animal models and immortalized cells. Indeed, the predisposition to a specific ADR may be related to the individual genetic patients' background, leading to a wide range of toxicities of different severity[14]. Therefore, the iPSC technology, matching the donor's genetic background, can be extremely helpful for developing patient-specific assays. Indeed, by using iPSCs, it seems reasonable to precisely mimic the patients' susceptibility to an abnormal response to a specific drug, setting up powerful assays useful to identify predictive biomarkers. In the last years, many different models[15] have been developed using the iPSC technology, including the differentiation into pancreatic exocrine cells[16].

PATIENT-SPECIFIC IPSCS AS AN IN VITRO MODEL TO STUDY DRUG-INDUCED PANCREATITIS

Patient-specific iPSCs can be obtained by reprogramming patients' fibroblasts or peripheral blood mononuclear cells using the four Yamanaka's factors OCT4, SOX2, KLF4 and MYC, forcing somatic cells to an embryonic-like state[17,18]. Differentiation of iPSCs allows to generate almost any kind of somatic cells using appropriate protocols. In the literature it is possible to find a wide range of differentiation possibilities including neural-like cells, hepatocytes, enterocytes, pancreatic endocrine cells and many others as recently reviewed by our group[15]. These cells, being patient-specific, have been frequently used to model and study individual susceptibility to develop ADRs. For example, regarding gastrointestinal toxicity, some groups have already tried to model hepatocytes[19-21] and enterocytes[22,23] to study drug-induced liver injury and intestinal toxicity, respectively. However, in comparison to other ADRs, drug-induced pancreatitis has not been deeply studied yet. A limited number of protocols[16,24-26] are available in the literature to generate pancreatic exocrine cells starting from iPSCs in comparison to the endocrine counterpart[15]. To the best of our knowledge, our group recently evaluated for the first time the mechanisms behind TIP predisposition using iPSCs and pancreatic differentiated cells of pediatric patients affected by IBD that developed or not TIP. Differentiation of iPSCs in pancreatic exocrine cells was performed using the protocol developed by Takizawa-Shirasawa *et al*[16]. Briefly, different stimuli were added to the culture medium in 4 different steps (Figure 1). To characterize cells obtained during each differentiation step, genetic expression of specific genetic markers was analyzed and confirmed:

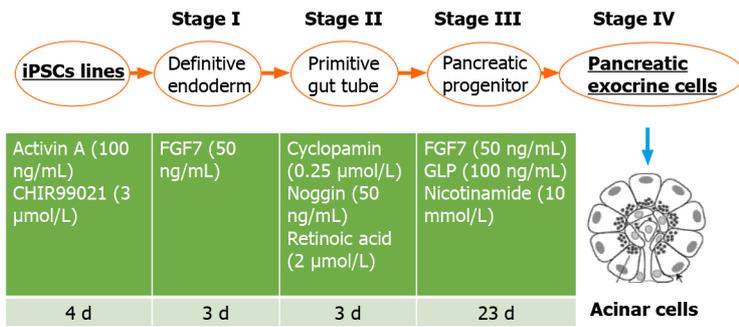


Figure 1 Differentiation of induced pluripotent stem cells into pancreatic cells towards a 4 steps protocol. iPSCs: Induced pluripotent stem cells; d: Days of culture.

OCT4 for undifferentiated cells (iPSCs), *FOXA2* and *SOX17* for definitive endoderm (stage I), *PDX1* for pancreatic progenitors (stage III) and amylase, in particular its pancreatic isoforms *AMY2A* and *AMY2B* for pancreatic exocrine cells (stage IV).

The gold standard of cytotoxicity assay showed an almost double *in vitro* sensitivity of TIP cases cells to thiopurines, more marked in iPSCs rather than in the differentiated counterpart, after mercaptopurine and thioguanine exposure. *TPMT* variants (rs1142345, rs1800460 and rs1800462) were excluded as a possible cause of this different sensitivity because all patients resulted wild-type.

The results obtained are encouraging, however some limitations have to be overcome in the next future. For instance, the differentiation protocol to obtain exocrine pancreatic cells could be further improved in terms of efficiency based on the more recent studies performed by Hohwieler *et al*[24] and Ito *et al*[25] which used 3D culture methods and the distinction between acinar and ductal cell type, by analyzing the expression of different genetic and protein markers such as amylase and chymotrypsin C for acinar cells, and *SOX9* and cytokeratin 19 for ductal cells[24,25]. An important point to consider is if the amylase markers are sufficient to reflect terminal differentiation. Beside studies considering the mRNA levels of these markers[24,25], more functional studies, evaluating the amylase protein concentrations and enzyme activity, should be implemented. These comparisons would allow to ensure that terminal differentiation is as representative as possible of the *in vivo* models. Another important point to focus, linked to pancreatic cell generation, is the time necessary that is too long for a clinical application of this *in vitro* model for TIP predisposition screening. Studies are now ongoing to partially resolve this limitation trying to develop more efficient and faster ready-to-use patient-specific pancreatic exocrine differentiated cells. The cost of hospitalization after a pancreatitis event has been recently calculated, resulting in around 8000 € per patient[27]. Considering an incidence of pancreatitis of 5%, we can estimate that every 20 patients treated with azathioprine one will be at risk of pancreatitis. Therefore, to be cost-effective, the analysis should amount to 400 €, considering only the cost of the analysis, without evaluating the health benefit[28]. Current costs are still higher but there is a trend toward reduction; indeed, the iPSC technology is still expensive and costs have to be reduced before they can be introduced into clinical practice. In particular, characterization costs are high, but several suggestions to address this limitation have been already proposed such as SNP microarray technology for the routine karyotyping and cost-effective methods such as innovative flow cytometry analyses to assess cell surface expression of pluripotent markers[29].

Beyond technical limitations, it is conceivable that thiopurines do not directly reach the pancreatic tissue unmodified, but rather as metabolites. Therefore, to improve the clinical relevance of the *in vitro* model, patient-specific pancreatic cells would need to be exposed to a representative mixture of thiopurine metabolites or to conditioned media of other thiopurine metabolizing cells such as hepatocytes[30]. Moreover, it is important to keep in mind that TIP predisposition could be influenced by the contribution of the immune system that, in predisposed patients, could be activated for unknown reasons after thiopurine administration attacking the pancreatic tissue. This aspect has to be considered, modeled and studied as well[7,31]. Finally, data obtained have to be confirmed in a larger cohort of patients that now includes 3 cases and 3 controls already analyzed while 2 cases and 2 controls still have to be analyzed.

CLINICAL IMPLICATIONS

Drug-induced pancreatitis represents an important clinical issue for different reasons including therapy interruption, reduction of treatment efficacy, the need for unnecessary diagnostic procedures and treatment for the adverse effect resolution[1] with associated healthcare costs. Moreover, in recent years an increasing number of drugs have been associated with pancreatitis development although its recognition by clinicians is still limited because of the lack of biomarkers useful to prevent this ADR.

CONCLUSION

Drug-induced pancreatitis is a growing problem related to several drugs and TIP recapitulates well all complications related to the development of this ADR. The possibility of studying TIP by an iPSC-based model seems a great opportunity to investigate TIP mechanisms that still remain not clear. The *in vitro* model established in our laboratory has proven to be suitable for studying and investigating TIP predisposition in a personalized way in pediatric IBD patients. Alongside thiopurines, several other drugs such as asparaginase, nilotinib and pazopanib can cause pancreatitis. Therefore, the *in vitro* model developed in this study could be applied also to study the sensitivity of other drugs with the purpose of pancreatitis prevention.

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