A mathematical model of chronic pancreatitis

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Supporting Information (SI)

Parameter estimation

A summary of all the model parameters is given in tables 1 and 2.

In the sequel, in an expression of the form $\frac{X}{K_X+X}$ in the context of activation, the half-saturation parameter K_X is taken to be the steady state of the species X provided X tends to a steady state. Hence in steady state equations this factor is equal to $\frac{1}{2}$.

It is technically hard to assess the level of cytokines in acutal pancreatic tissue. We shall assume that the concentrations in the tissue may be anywhere from 2-fold to 10-fold greater in tissue compared to serum.

Eqn. (1)

- P_0**:** The ratio of cells volume to ECM volume varies from less than 1:10 to more than 10:1 [7]. Based on [36], we estimate the ratio between cells volume and ECM in the pancreatic islets to be close to 1:1. However, taken over the entire organ, the ratio of cells volume to ECM volume is smaller, and we take it to be 1:10. The mass of PSC is 4-7% of the total cells mass in the pancreas [4]; we take it to be 5%. Assuming average density of 1 g/ml in the pancreas, we get P_0 = density of PSC=5×10^{-3} g/ml.

- K_{T_α}**:** There are several reports on the level of TNF-α in serum of patients with chronic pancreatitis (CP) and in healthy control case (C). In [18], the level is 9.88 pg/ml in CP and 10.09 in C; in [24] it is 23 pg/ml in CP and 13 pg/ml, in [36] it is 8.52 pg/ml in C, and in our own clinical tests (see Supplementary Material (SM)) it was 8.54 pg/ml in PC and 4.58 pg/ml in C. We assume that the concentration of TNF-α in tissue is larger than in serum and take T_α steady state in blood of heathy individuals to be 9 pg/ml, and $T_\alpha = K_{T_\alpha} = 30\ pg/ml$=$3 \times 10^{-11}$ g/ml in tissue.

- K_G**:** The level of serum concentration of healthy individual was reported in [5] to be 17.5 pg/ml. Our clinical data (in SM) show concentrations of

0.102 ng/ml in CP and 0.363 ng/ml in C. We take larger tissue concentration in healthy steady state, namely, $G = K_G = 60$ ng/ml=6×10^{-8} g/ml in tissue.

- K_{T_β}**:** In our clinical tests we found that the level of TGF-β in blood was 6.602 ng/ml for CP and 7.736 ng/ml for C. On the other hand, a larger concentration of 36.75 ng/ml was reported for C in [36]. We assume that concentration of TGF-β in tissue of healthy individuals is larger than in blood, and take $T_\beta = K_{T_\beta} = 8 \times 10^{-7}$ g/ml.

- K_{I_6}**:** There are several report on the level of IL-6 in CP and C. In [24] it was reported to be 7.3 pg/ml in CP and 3.3 pg/ml in C; in [36] it was reported to be 0.58 pg/ml in C, while our clinical tests give 9.16 pg/ml in CP and 7.14 pg/ml in C. We take the level of IL-6 in healthy tissue to be $I_6 = K_{I_6} = 8\ pg/ml = 8 \times 10^{-12}\ g/ml$.

- λ_{PT_α} **and** λ_{PI_6}**:**

  Experiments in vivo in [2, 23] reported on the activation of PSC by cytokines TGF-β, TNF-α and IL-6. We assume that TGF-β activates PSC more effectively than TNF-α, but less effectively than IL-6, and take $\lambda_{PT_\beta} = 2.2 \times 10^{-2}$/day, $\lambda_{PT_\alpha} = 1.82 \times 10^{-2}$/day and $\lambda_{PI_6} = 3.67 \times 10^{-2}$/day.

- λ_P **and** λ_{PG}**:** Experiments in [3] show that PDGF, and to lesser extend TNF-α, increase the proliferation of APSC. We take $\lambda_P = 4 \times 10^{-3}$/day, and $\lambda_{PG} = 2.7 \times 10^{-3}$/day.

Eqn. (2)

- A_{P_0}**:** From the steady state of PSC for a healthy pancreas, we have $A_{P_0} = d_{P_0} P_0$. Taking $P_0 = 5 \times 10^{-3}$ g/ml and using the value $d_{P_0} = 1.66 \times 10^{-2}$ day^{-1} [33], we get $A_{P_0} = 8.3 \times 10^{-5}\ g/cm^3$ day^{-1}.

Eqn. (3)

- d_{CM}**:** The degradation rate of MCP-1 is $d_C = 1.73$ day^{-1} [6]. MCP-1 chemoattracts macrophages, so some of the cytokines get internalized by macrophage [21, 27]. We assume that the rate of internalization is the same as the rate of degradation when C is at half-saturation

$$d_C K_C = d_{CM} \frac{K_C}{K_C + K_C} M_0.$$

  and $M_0 = 5 \times 10^{-5}$ [10], we get $d_{CM} = \frac{2 d_C K_C}{M_0} = 2.08 \times 10^{-5}$ day^{-1}.

- K_C**:** In our clinical tests (SM) we found that the serum concentration of MCP-1 in CP is 54.66 pg/ml and in C is 58.89 pg/ml. We assume a larger concentration of MCP-1 in tissue of healthy individuals and, accordingly, take $K_C = 300$pg/ml=3×10^{-10} g/ml.

- λ_{CP}**:** According to the experiments of MCP-1 production by TNF-α in [30], we have the following linear relation

$$\lambda_{CP}P - d_C C = 0.$$

More precisely, the concentration of MCP-1 is 1.8 ng/ml when TNF-α is 100 ng/ml. Assuming that in this experiment the density of P exceeded its half-saturation K_P, we take $\lambda_{CP} = 2 \times 10^{-7}$ day^{-1}.

Eqn. (6)

- $\lambda_{\rho T_\beta}$**:** We take $\lambda_{\rho P} = 0.0432$ day^{-1}. It was reported in [3] that collagen synthesis with TGF-β = 1 ng/ml, was increased to three fold.

We assume that with such a small amount of T_β (compared to K_{T_β}) the production would increase only 5% the collagen in the pancreas, so that

$$\lambda_{\rho T_\beta}\frac{1}{20} = 3\lambda_{\rho P}, \tag{1}$$

or $\lambda_{\rho T_\beta} = 3\lambda_{\rho P} = 2.673$ day^{-1}.

- ρ^***:** The steady states of ρ^*, Q^* and Q_r^* of ρ, Q and Q_r are determined by solving the following steady state equations in healthy pancreas

$$\begin{cases} \lambda_{\rho P}P_0\big(1 - \dfrac{\rho}{\rho_0}\big) - d_{\rho Q}Q\rho - d_\rho \rho = 0, \\ \lambda_{QP_0}P_0 - d_{QQ_r}Q_rQ - d_Q Q = 0, \\ \lambda_{Q_rP_0}P_0 - d_{Q_rQ}QQ_r - d_{Q_r}Q_r = 0. \end{cases},$$

where all the parameters are given in Table 1 and 2. By direct computation, we find that $\rho^* = 3.22 \times 10^{-4}$ g/cm^3, $Q^* = 4.18 \times 10^{-6}$ g/cm^3 and $Q_r^* = 4.24 \times 10^{-11}$ g/cm^3.

Eqn. (7)

In steady state in health, $\lambda_{T_\beta} = \frac{d_{T_\beta}T_\beta}{P}$, where $d_{T_\beta} = 3.33 \times 10^2$/day [31], $T_\beta = 8 \times 10^{-7}$ g/ml and $P = P_0 = 5 \times 10^{-3}$ g/ml, so that $\frac{d_{T_\beta}T_\beta}{P} = 5.328 \times 10^{-1}$/day. P is proliferating, so in steady state P is larger than P_0 and hence λ_{T_β} should be smaller; we take $\lambda_{T_\beta} = 6.7 \times 10^{-2}$/day.

Eqn. (8)

In steady state in health

$$\lambda_{T_\alpha} = \frac{d_{T_\alpha}T_\alpha}{M},$$

where $d_{T_\alpha} = 55.45$/day [25], $T_\alpha = 3 \times 10^{-11}$g/ml, and $M = M_0 = 5 \times 10^{-5}$g/ml [10], so that $\frac{d_{T_\alpha}T_\alpha}{M} = 3.3 \times 10^{-5}$/day. In chronic pancreatic case the concentration of T_α is higher, so we take $\lambda_{T_\alpha} = 9.98 \times 10^{-5}$/day.

Eqn. (9)

- λ_{I_6}**:** In steady state in health, $\lambda_{I_6} = \frac{d_{I_6} I_6}{P}$ where $d_{I_6} = 0.173$/day [19], $I_6 = 4\times10^{-12}$g/ml and $P = P_0 = 5\times10^{-3}$ so that $\frac{d_{I_6} I_6}{P} = 1.4\times10^{-10}$/day. In chronic pancreatic case P is larger than P_0, so we take the smaller value $\lambda_{I_6} = 7 \times 10^{-11}$/day.

Eqn. (10)

- λ_G**:** In steady state in health, $\lambda_G = \frac{d_G G}{P}$ where $d_G = 2.84$/day [34], $G = 6 \times 10^{-8}$g/ml and $P = P_0 = 5 \times 10^{-3}$ g/ml. Hence $\frac{d_G G}{P} = 4 \times 10^{-5}$/day. For the chronic pancreatitis case P is larger than P_0, so we take $\lambda_G = 2 \times 10^{-7}$ day^{-1}.

Eqn. (11)

- λ_{QP_0} **and** λ_{QP}**:** We take $\lambda_{QP_0} = 3.025 \times 10^{-5}$ day^{-1} as in [16]. In [26], it was reported that the amount of MMP activated by P is 30% more than that by P_0. Accordingly, we have

$$\lambda_{QP} = 1.3\lambda_{QP_0} = 3.93 \times 10^{-5} \text{ day}^{-1}.$$

- λ_{QT_β} **and** λ_{QI_6}**:** According to [26], T_β increases the production of Q by P more than I_6 does, we assume that T_β increases this production by approximately 1-fold and I_6 increases it by approximately $\frac{1}{2}$-fold, and take $\lambda_{QT_\beta} = 7.6 \times 10^{-5}$ day^{-1}. and $\lambda_{QI_6} = 3.72 \times 10^{-5}$ day^{-1}.

Clinical data

Peripheral venous blood was collected into sodium heparin tubes by venipuncture from human patients. All studies were conducted under an IRB-approved protocol from patients with clinically confirmed chronic calcific pancreatitis (17 patients), non-calcific pancreatitis (9), a family history of pancreatic disease (non-pancreatitis) (12), and no disease(7). Blood samples were centrifuged at 1200 x g for 10 minutes to obtain plasma, and was stored at -80 ^oC . Plasma samples were batch analyzed using a custom Luminex Multiplex Cytokine Kits (Procarta Cytokine Assay Kit, Affymetrix). Analyte concentrations were calculated based on a standard curve for each analyte and represent the average of two batched duplicates. Additional single-plex ELISA kits were used to analyze the concentration of additional factors, including TGF-β and IL-6 (R&D Systems, Inc.), as per manufacturer instructions.

Table 1: Parameters' description and value

Parameter	Description	Value
D_P	diffusion coefficient of activated PSC	1.47×10^{-4} cm^2 day^{-1} [10]
D_{P_0}	diffusion coefficient of quiescent PSC	1.47×10^{-4} cm^2 day^{-1} [10]
D_{M_1}	diffusion coefficient of M1 macrophage	8.64×10^{-7} cm^2 day^{-1}[10]
D_{M_2}	diffusion coefficient of M2 macrophage	8.64×10^{-7} cm^2 day^{-1}[10]
D_C	diffusion coefficient of MCP-1	17.28 cm^2 day^{-1}[10]
D_{I_6}	diffusion coefficient for IL-6	1.08×10^{-2} cm^2 day^{-1}[10]
D_{T_α}	diffusion coefficient for TNF-α	1.29×10^{-2} cm^2 day^{-1}[10]
D_{T_β}	diffusion coefficient for TGF-β	4.32×10^{-2} cm^2 day^{-1} [12]
D_G	diffusion coefficient for PDGF	8.64×10^{-2} cm^2 day^{-1}[10, 34]
D_Q	diffusion coefficient of MMP	4.32×10^{-2} cm^2 day^{-1}[10, 22]
D_{Q_r}	diffusion coefficient for TIMPs	4.32×10^{-2} cm^2 day^{-1} [10, 22]
λ_{PT_β}	activation rate of PSC by TGF-β	2.2×10^{-2} day^{-1} [3] & estimated
λ_{PT_α}	activation rate of PSC by TNF-α	1.82×10^{-2}day^{-1} [3, 23] & estimated
λ_{PI_6}	activation rate of PSC by IL-6	3.67×10^{-2} day^{-1} [3, 23] & estimated
λ_P	proliferation rate of PSC by TNF-α	4×10^{-3} day^{-1} [23] & estimated
λ_{PG}	proliferation rate of PSC by PDGF	2.7×10^{-3} day^{-1} [3] & estimated
$\lambda_{\rho P}$	production rate of ECM due to PSC	0.0432 day^{-1} [15]
$\lambda_{\rho T_\beta}$	activation rate of ECM due to TGF-β	2.673 day^{-1} [15, 3] & estimated
λ_{CP}	activation rate of MCP-1 due to PSC	2×10^{-7} day^{-1} [30] & estimated
λ_{I_6}	activation rate of IL-6 due to PSC	7×10^{-11} day^{-1} [2, 20] & estimated
$\lambda_{I_6T_\beta}$	activation rate of IL-6 due to TGF-β	7×10^{-11} day^{-1} [2] & estimated
λ_{T_α}	activation rate of TNF-α due to macrophage	9.98×10^{-5} day^{-1} [1] & estimated
$\lambda_{T_\beta P}$	activation rate of TGF-β due to PSC	6.7×10^{-3} day^{-1} [25, 28] & estimated
$\lambda_{T_\beta M_2}$	activation rate of TGF-β due to M2 macrophages	1.5×10^{-2}/day [11]
λ_{GP}	activation rate of PDGF due to PSC	2×10^{-6} day^{-1} [32]
λ_{GM_2}	activation rate of PDGF due to M2 macrophages	4.8×10^{-4}/day [13]
λ_{QP_0}	activation rate of MMP due to quiescent PSC	3.025×10^{-5} day^{-1} [16]
λ_{QP}	activation rate of MMP due to activated PSC	3.93×10^{-5} day^{-1} [26, 16] & estimated
λ_{QT_β}	activation rate of MMP by TGF-β	7.6 day^{-5} [26, 10] & estimated
λ_{QI_6}	activation rate of MMP by IL-6	3.72×10^{-5} day^{-1} [26, 10] & estimated
$\lambda_{Q_rP_0}$	activation rate of TIMP due to quiescent PSC	6×10^{-5} day^{-1} [10, 17]
λ_{Q_rP}	activation rate of TIMP due to activated PSC	6×10^{-5} day^{-1} [10, 17] & estimated
λ_S	production rate of Scar	1 estimated
λ_{SQ}	production rate of Scar due to MMP	1 estimated

1 Tables

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Table 2: Parameters' description and value

Parameter	Description	Value
d_P	degradation rate of activated PSC	4.15×10^{-2} day^{-1} [33]
d_{P_0}	degradation rate of quiescent PSC	1.66×10^{-2} day^{-1} [33]
d_{M_1}	death rate of M1 macrophage	0.02 day^{-1} [8]
d_{M_2}	death rate of M2 macrophage	0.015 day^{-1} [9]
d_C	degradation rate of MCP-1	1.73 day^{-1} [6]
d_{CM_1}	degradation rate of MCP-1 due to macrophage	2.08×10^{-5} day^{-1} [6, 21, 27] & estimated
d_{I_6}	degradation rate of IL-6	0.173 day^{-1} [19]
d_{T_β}	degradation rate of TGF-β	3.33×10^2 day^{-1} [31]
d_{T_α}	degradation rate of TNF-α	55.45 day^{-1} [25]
d_ρ	degradation rate of ECM	0.37 day^{-1} [34]
d_G	degradation rate of PDGF	3.84 day^{-1} [34]
d_{QQ_r}	binding rate of MMP to TIMP	4.98×10^8 cm^3g^{-1} day^{-1} [10]
d_{Q_rQ}	binding rate of TIMP to MMP	1.04×10^9 cm^3g^{-1} day^{-1} [10]
d_Q	degradation rate of MMP	4.32 day^{-1}[10, 15]
d_{Q_r}	degradation rate of TIMP	21.6 day^{-1} [10, 35]
$d_{\rho Q}$	degradation rate of ECM due to MMP	2.59×10^7 cm^3g^{-1} day^{-1} [10, 16]
χ_G	chemotactic sensitivity parameter	10 cm^5g^{-1} day^{-1}[15, 16]
χ_C	chemotactic sensitivity parameter	10 cm^5g^{-1} day^{-1}[15, 16]
A_{P_0}	PSC source	8.3×10^{-5} g/cm^3 day^{-1} estimated
K_{I_6}	IL-6 half saturation	8×10^{-12} g/cm^3 [29, 24, 36], SM* & estimated
K_{T_α}	TNF-α half saturation	3×10^{-11} g/cm^3 [18, 36], SM* & estimated
K_{T_β}	TGF-β half saturation	8×10^{-7} g/cm^3 [36], SM* & estimated
K_G	PDGF half saturation	6×10^{-8} g/cm^3 [5], SM* & estimated
K_C	MCP-1 half saturation	3×10^{-10} g/cm^3 SM* & estimated
K_P	PSC half saturation	3×10^{-3} g/cm^3 [14] & estimated
P_0	inactive PSC density	5×10^{-3} g/cm^3
M_0	source of macrophages	5×10^{-5} g/cm^3
ρ_0	ECM density	10^{-3} gcm^{-3} [17]
ρ^*	ECM density	3.22×10^{-4} gcm^{-3} estimated
Q^*	MMP density	4.18×10^{-6} gcm^{-3} estimated
Q_r^*	TIMP density	4.24×10^{-11} gcm^{-3} estimated
β	influx rate	1

SM*: data from supplementary material.

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