Supplementary information 5:

Predictive Model of Collagen Homeostasis

Reactions and Equations

$$\mathrm{S} \xrightarrow{k_{4a}} \mathrm{S} + \mathrm{H_{ER}}$$
$$\varnothing \xleftarrow{k_{4b}} \mathrm{H_{ER}}$$
$$\varnothing \xleftarrow{k_{4c}} \mathrm{H_{G}}$$
$$\mathrm{S} \xrightarrow{k_{5a}} \mathrm{S} + \mathrm{K}$$
$$\varnothing \xleftarrow{k_{5b}} \mathrm{K}$$
$$\mathrm{H_{G}} + \mathrm{K} \xrightarrow{k_{16}} \mathrm{H_{ER}} + \mathrm{K}$$

$$\mathrm{S} \xrightarrow{k_{8}} \mathrm{S} + \mathrm{C_{ER}}$$
$$\mathrm{C_{ER}} + \mathrm{T} + \mathrm{H} \underset{k_{-9}}{\overset{k_{9}}{\rightleftharpoons}} \mathrm{C_{H}} + \mathrm{T}$$
$$\mathrm{C_{H}} \xrightarrow{k_{10}} \mathrm{C_{G}}$$
$$\mathrm{C_{G}} + \mathrm{V} \xrightarrow{k_{11}} \mathrm{C_{PG}} + \mathrm{V}$$
$$\mathrm{C_{PG}} \xrightarrow{k_{12}} \mathrm{C_{PM}}$$
$$\mathrm{C_{PM}} + \mathrm{M} \xrightarrow{k_{13}} \mathrm{C_{E}} + \mathrm{M}$$
$$\mathrm{C_{E}} + \mathrm{D} \xrightarrow{k_{14}} \mathrm{D}$$

$$\dot{C}_{ER} = k_8 S - k_9 C_{ER} T H_{ER} + k_{-9} C_H T$$
$$\dot{C}_{H} = k_9 C_{ER} T H_{ER} - k_{-9} C_H T - k_{10} C_H$$
$$\dot{C}_{G} = k_{10} C_H - k_{11} C_G V$$
$$\dot{C}_{PG} = k_{11} C_G V - k_{12} C_{PG}$$
$$\dot{C}_{PM} = k_{12} C_{PG} - k_{13} C_{PM} M$$
$$\dot{C}_{E} = k_{13} C_{PM} M - k_{14} D C_E$$
$$\dot{H}_{ER} = k_{4a} S - k_{4b} H_{ER} - k_9 C_{ER} T H_{ER} + k_{-9} C_H T + k_{16} H_G K$$
$$\dot{H}_{G} = k_{10} C_H - k_{16} H_G K - k_{4c} H_G$$
$$\dot{K} = \frac{k_{5a} S}{1 + k_{5c} P} - k_{5b} K$$
$$F(t; t_0) = \frac{1}{2} \cos\left(\frac{2\pi(t - t_0)}{\bar{t}}\right) + 1$$
$$G(t; t_0) = \bar{G}^{-1} \left[\frac{\cos\left(e^{-1}\right) - \cos\left(e^{\cos\left(\frac{2\pi(t-t_0)}{\bar{t}}\right)}\right)}{\cos\left(e^{-1}\right) - \cos\left(e\right)} \right]^4$$

$$S = k_1 F(t; 3)$$
$$T = k_2 G(t; 9)$$
$$P = k_3 F(t; 19)$$
$$V = k_6 F(t; 19)$$
$$M = k_7 G(t; 3)$$
$$D = k_{15} F(t; 9)$$

$t_0 =$ phase (hours)
$\bar{G} =$ mean pulse function value determined by mean value theorem

Variables

All variables are protein concentrations in units of μM relative to typical fibroblast cell size.

Variable	Description
C_{ER}	ER located collagen
C_H	Collagen-HSP47 complex in ERGIC
C_G	Golgi located collagen
C_{PG}	Post-Golgi compartments located collagen
C_{PM}	Plasma membrane located collagen
C_E	Extracellular collagen
H_{ER}	ER located HSP47
H_G	Golgi located HSP47
K	Pka

Variable	Description
S	SEC61A2
T	TANGO1
P	PDE4D
V	VPS33B
M	MMP14
D	CTSK

Parameters

Parameter values for the model were derived where possible from existing results in the literature (such as [1]). This paper lists protein copy numbers in molecules per cell, translation rates in molecules per mRNA per hour, mRNA copy numbers in molecules per cell, and protein half-life in hours, among others. These, along with a typical fibroblast cell size of 2.04 pL were combined to give translation rates in micro-molar per hour, and concentrations in micro-molar, or time scale rates in per hour. For example, k_1 was calculated by dividing protein copy number by the cell size and Avogadro's number to give concentration. Where values for a particular protein were not available, translation rates were taken as the median values from [1], as detailed below. The values for procollagen transport rates from one intracellular compartment to the next were guided by knowledge of the speed of vesicular transport in the eukaryotic cell.

Parameter	Value	Description	Source
μ_{typ}	0.0342 μM	Median typical protein concentration	Median value calculated from [1]
k_1	0.00822 μM	SEC61A2 mean protein concentration	Calculated directly from [1]
k_2	0.0105 μM	TANGO1 mean protein concentration	Calculated directly from [1]
k_3	0.0342 μM	PDE4D mean protein concentration	Median value calculated from [1]
k_6	0.00335 μM	VPS33B mean protein concentration	Calculated directly from [1]
k_7	0.00457 μM	MMP14 mean protein concentration	Calculated directly from [1]
k_{15}	0.0342 μM	CTSK mean protein concentration	Median value calculated from [1]
$\bar{t}$	24 h	Circadian period	Length of one circadian cycle
k_{4a}	4.84 h^{-1}	HSP47 protein synthesis rate	Adjusted for physicality from values calculated directly from [1]
k_{4b}	0.00413 h^{-1}	ER HSP47 protein degradation rate	Calculated directly from [1]
k_{4c}	0.00413 h^{-1}	Golgi HSP47 protein degradation rate	Calculated directly from [1]
k_{5a}	1.89 h^{-1}	PKA protein synthesis rate	Calculated directly from [1]
k_{5b}	0.00690 h^{-1}	PKA protein degradation rate	Calculated directly from [1]
k_8	0.0693 h^{-1}	Col-I synthesis rate	Adjusted for physicality from values calculated directly from [1]
k_{10}	3600 h^{-1}	ERGIC to Golgi Col-I transition rate	Estimated time scale (~1 second) of ERGIC vesicular transport calculated from typical cellular vesicle speeds and inter-compartmental distances [2]
k_{12}	0.0417 h^{-1}	Post-Golgi compartments to plasma membrane Col-I transition rate	Estimated from dimensionally consistent powers of $\bar{t}$
k_{5c}	29.2 μM^{-1}	Rate constant for repression of PKA by PDE4D	Estimated from dimensionally consistent products of μ_{typ} and $\bar{t}$
k_{-9}	1.22 $\mu M^{-1}h^{-1}$	Col-I-HSP47 complex dissociation rate	Estimated from dimensionally consistent products of μ_{typ} and $\bar{t}$
k_{11}	1.22 $\mu M^{-1}h^{-1}$	Golgi to Post-Golgi compartments Col-I transition rate	Estimated from dimensionally consistent products of μ_{typ} and $\bar{t}$

k_{13}	12.2 μM^{-1}h^{-1}	Plasma membrane to extracellular Col-I transition rate	Estimated from dimensionally consistent products of μ_{typ} and $\bar{t}$
k_{14}	1.22 μM^{-1}h^{-1}	CTSK dependent extracellular Col-I degradation rate	Estimated from dimensionally consistent products of μ_{typ} and $\bar{t}$
k_{16}	1.22 μM^{-1}h^{-1}	Golgi to ER HSP47 transition rate	Estimated from dimensionally consistent products of μ_{typ} and $\bar{t}$
k_9	0.356 μM^{-2}h^{-1}	Col-I-HSP47 complex association rate	Estimated from dimensionally consistent products of μ_{typ} and $\bar{t}$

1 Schwanhausser, B. *et al.* Global quantification of mammalian gene expression control. *Nature* **473**, 337-342, doi:10.1038/nature10098 (2011).

2 Milo, R., Jorgensen, P., Moran, U., Weber, G. & Springer, M. BioNumbers--the database of key numbers in molecular and cell biology. *Nucleic Acids Res* **38**, D750-753, doi:10.1093/nar/gkp889 (2010).