Supplementary Information

In silico exploration of osteoclast precursor inhibition for preventing rapid bone loss after denosumab discontinuation

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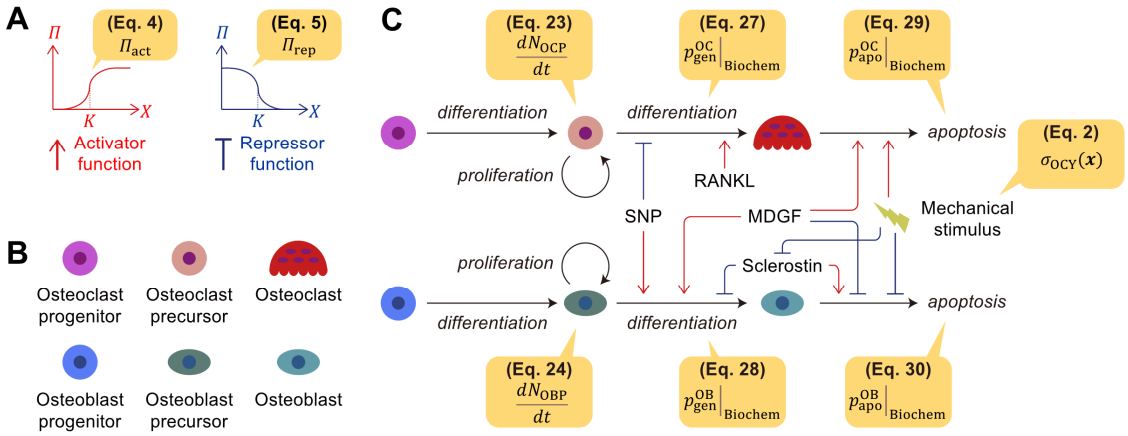

Figure S1. Overview of the mathematical model of bone metabolism.
(A) Activator and repressor functions based on Hill functions. Π: Hill function. Π_{act}: activator function. Π_{rep}: repressor function. X: the mechanical signal or concentration of a signaling molecule. K: the activation/inhibition constant. Eq.: equation. (B) Cell populations considered in our model. (C) Overview of the cell dynamics by mechanobiochemical regulation. RANKL: receptor activator of nuclear factor-κB ligand. SNP: Semaphorin/Neuropilin/Plexin complex. MDGF: matrix-derived growth factor. N_{OCP}: the number density of osteoclast precursors. N_{OBP}: the number density of osteoblast precursors. $p_{\mathrm{gen}}^{\mathrm{OC}}\big|_{\mathrm{Biochem}}$: the probability of osteoclastogenesis considering only the biochemical factors. $p_{\mathrm{apo}}^{\mathrm{OC}}\big|_{\mathrm{Biochem}}$: the probability of osteoclast apoptosis considering only the biochemical factors. $p_{\mathrm{apo}}^{\mathrm{OB}}\big|_{\mathrm{Biochem}}$: the probability of osteoblast apoptosis considering only the biochemical factors. $\sigma_{\mathrm{OCY}}(\boldsymbol{x})$: the stress sensed by osteocytes.

Supplementary Tables

Table S1. Parameters associated with osteocyte mechanosensing and bone resorption/formation.

Symbol	Description	Value	Unit	Ref.
ρ_{OCY}	Number density of osteocytes	25000	mm^{-3}	[1]
$\sigma_{\max}$	Maximum von Mises equivalent stress	20	MPa	
$\sigma_{\min}$	Minimum von Mises equivalent stress	1.0	MPa	
l_{L}	Maximum distance for intercellular communication	50	mm	[2]
T_{lag}	Mineralization lag time	14	day	[3]
T_{act}	Active formation period	140	day	[3]
$\dot{M}_{\mathrm{r}}$	Bone resorption rate	-1.4	$mm \cdot day^{-1}$	[3]
$\dot{M}_{\mathrm{f}}$	Bone formation rate	0.56	$mm \cdot day^{-1}$	[3]

Table S2. Parameters associated with intercellular signaling.

Symbol	Description		Value	Unit	Ref.
β_{SCL}	Maximum production rate of sclerostin		0.24	pM·s^{-1}	
β_{RANKL}	Maximum production rate of RANKL		0.24	pM·s^{-1}	
β_{Nrp1}	Maximum production rate of Nrp1		0.05	pM·s^{-1}	
P_{OPG}	Production rate of OPG		0.24	pM·s^{-1}	
P_{Sema3A}	Production rate of Sema3A		0.24	pM·s^{-1}	
P_{PlxnA}	Production rate of PlxnA		0.05	pM·s^{-1}	
P_{MDGF}	Production rate of MDGF		0.24	pM·s^{-1}	
k_{deg}	Degradation rate constant		0.005	s^{-1}	
D_{SCL}	Diffusion coefficient of sclerostin		5.58	mm^2·s^{-1}	4
D_{RANKL}	Diffusion coefficient of RANKL		5.32	mm^2·s^{-1}	4
D_{OPG}	Diffusion coefficient of OPG		4.49	mm^2·s^{-1}	4
D_{Sema3A}	Diffusion coefficient of Sema3A		3.62	mm^2·s^{-1}	4
D_{MDGF}	Diffusion coefficient of MDGF		4.56	mm^2·s^{-1}	4
$k_{\mathrm{on}}^{\mathrm{RO}}$	Association constant of RANKL-OPG binding		0.001	pM^{-1}·s^{-1}	
$k_{\mathrm{on}}^{\mathrm{NP}}$	Association constant of Nrpl-PlxnA binding		0.01	pM^{-1}·s^{-1}	
$k_{\mathrm{off}}^{\mathrm{RO}}$	Disassociation constant of Nrpl-PlxnA binding		0.1	s^{-1}	
$k_{\mathrm{on}}^{\mathrm{SNP}}$	Association constant of SNP complex binding		0.1	pM^{-1}·s^{-1}	
$k_{\mathrm{off}}^{\mathrm{SNP}}$	Disassociation constant of SNP complex binding		0.1	s^{-1}	
K_{SCL}	Activation/inhibition constant of sclerostin	- on RANKL	9.0	pM	
		- on osteoclastogenesis	3.0	pM	
		- on osteoblastogenesis	3.0	pM	
K_{RANKL}	Activation/inhibition constant of RANKL		18	pM	
K_{SNP}	Activation/inhibition constant of SNP complex		200	pM	
K_{MDGF}	Activation/inhibition constant of MDGF	- on osteoblastogenesis	20	pM	
		- on osteoclast apoptosis	3.0	pM	
		- on osteoblast apoptosis	5.0	pM	
n	Hill coefficient		3.0	-	
γ_{couple}	Threshold of MDGF contribution to osteoblastogenesis		0.3	-	

Table S3. Parameters associated with precursor dynamics.

Symbol	Description	Value	Unit	Ref.
$r_{\mathrm{OC}}^{\mathrm{diff}}$	Differentiation rate of osteoclast	0.02	$mm^{-3}\cdot day^{-1}$	
$r_{\mathrm{OB}}^{\mathrm{diff}}$	Differentiation rate of osteoblast	0.015	$mm^{-3}\cdot day^{-1}$	
$r_{\mathrm{OCP}}^{\mathrm{prolif}}$	Proliferation rate of osteoclast precursor	0.009	$mm^{-3}\cdot day^{-1}$	
$r_{\mathrm{OBP}}^{\mathrm{prolif}}$	Proliferation rate of osteoblast precursor	0.03	$mm^{-3}\cdot day^{-1}$	
$\dot{N}_{\mathrm{OCP}}^{\mathrm{diff}}$	Differentiation rate of osteoclast precursor	1.0	$mm^{-3}\cdot day^{-1}$	
$\dot{N}_{\mathrm{OBP}}^{\mathrm{diff}}$	Differentiation rate of osteoblast precursor	5.0	$mm^{-3}\cdot day^{-1}$	
$N_{\mathrm{OCP}}^{\mathrm{init}}$	Initial number density of osteoclast precursor	100	mm^{-3}	
$N_{\mathrm{OBP}}^{\mathrm{init}}$	Initial number density of osteoclast precursor	1000	mm^{-3}	
$N_{\mathrm{OCP}}^{\mathrm{max}}$	Maximum number density of osteoclast precursor	300	mm^{-3}	
$N_{\mathrm{OBP}}^{\mathrm{max}}$	Maximum number density of osteoblast precursor	1500	mm^{-3}	
K_{OCP}	Activation constant of osteoclast precursor	150	mm^{-3}	
K_{OBP}	Activation constant of osteoblast precursor	500	mm^{-3}	
n	Hill coefficient	3.0	-	

Table S4. Parameters associated with drug administration.

Symbol	Description		Value	Unit	Ref.
$C_{\max}^{\mathrm{Dmab}}$	Maximum serum concentration of denosumab		459000	pM	5,6
$k_{\mathrm{deg}}^{\mathrm{Dmab}}$	Degradation rate constant of denosumab		0.008	day^{-1}	5,6
$T_{\mathrm{delay}}^{\mathrm{Dmab}}$	Time delay constant of denosumab		5.0	day	5,6
$k_{\mathrm{on}}^{\mathrm{R-Dmab}}$	Association constant of RANKL and denosumab binding		0.0000007	$pM^{-1}s^{-1}$	
$C_{\max}^{\mathrm{ALN}}$	Maximum serum concentration of alendronate		154000	pM	7-9
$k_{\mathrm{deg}}^{\mathrm{ALN}}$	Degradation rate constant of alendronate		5.0	day^{-1}	7-9
$T_{\mathrm{delay}}^{\mathrm{ALN}}$	Time delay constant of alendronate		200	day	7-9
α_{ALN}	Maximum effect of alendronate	- on osteoclasts	0.7	-	
		- on osteoclast precursors	0.8	-	
		- on osteoblasts	0.9	-	
K_{ALN}	Inhibition constant of alendronate		700	pM	
α_{OCPI}	Intensity of OCPI effect		0.2, 0.5, 0.8	-	
n	Hill coefficient		3.0	-	

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