The ordinary differential equations of AA metabolic network

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Construction of the AA metabolic network model in human PMN

Method

On the basis of the AA metabolic network, a set of ODEs were constructed to describe cell behavior of inflammation in human PMN (see details in Supplementary information). The ode 45 s routine of Matlab was used to integrate the ODEs. Michaelis Menten equations (equation (3)) were used to describe enzyme catalytic reactions in the network:

$$\frac{d[S]}{dt} = \frac{K_{cat}[E_t][S]}{K_m + [S]} \tag{1}$$

where $[S]$ is the concentration of the substrate, $[E_t]$ is the total concentration of enzyme, K_{cat} is turnover number, and K_m is the Michaelis-Menten constant.
If competitive reversible inhibitors are involved in the catalysis, the equation is:

$$\frac{d[S]}{dt} = \frac{K_{cat}[E_t][S]}{K_m(1 + \frac{[I]}{K_i}) + [S]} \tag{2}$$

where $[I]$ is the concentration of inhibitor and K_i is the inhibition constant, which is defined as:

$$K_i = \frac{[E][I]}{[EI]} \tag{3}$$

If the inhibitors are irreversible, we assume the enzymes would decay according to the following equation:

$$\frac{d[E]}{dt} = -K[E][I] \tag{4}$$

where K is a constant.
When activators are involved in the catalysis, we use the following equation:

$$\frac{d[S]}{dt} = \frac{K_{cat}(1 + ([A]/KI))[E_t][S]}{K_m + [S]} \tag{5}$$

where $[A]$ is the concentration of activator and KI is a constant.
When up regulation occurred though transcription, we described its effect with the following equation:

$$\frac{d[E]}{dt} = \frac{k[g]^2}{[g]^2 + [k]^2} \tag{6}$$

where $[g]$ is the concentration of the metabolite up regulating the transcription of the enzyme, K and k are constants.

Equations

The ordinary differential equations (ODEs)of the AA metabolic network was developed. A series of ODEs was established to simulate unicellular behavior, which included 24 initial concentrations and 45 reaction constants (as the following equations). The ODEs for PMNs are:

$$(1)\ \frac{d[AA]}{dt} = \frac{K_{cat,PLA2}(1 + \frac{[12-HPETE]}{K_{12HPETE \to PLA2}} + \frac{[15-HPETE]}{K_{15HPETE \to PLA2}} + \frac{[LTB4]}{K_{LTB4 \to PLA2}} + \frac{[5-HETE]}{K_{5HETE \to PLA2}})[PLA2][PL]}{K_{m,PLA2}(1 + \frac{[AA]}{K_i}) + [PL]}$$

$$- \frac{K_{cat,15LOX}[15-LOX][AA]}{K_{m,15LOX}(1 + \frac{[15-HPETE]}{K_i}) + [AA]} - \frac{K_{cat,12LOX}[12-LOX][AA]}{K_{m,12LOX}(1 + \frac{[12-HPETE]}{Ki_{12HPETE \to 12LOX}} + \frac{[15-HETE]}{Ki_{15HPETE \to 12LOX}}) + [AA]}$$

$$- \frac{K_{cat,5LOX}[5-LOX][AA]}{K_{m,5LOX}(1 + \frac{[5-HPETE]}{K_i} + \frac{[12-HETE]}{Ki_{12HETE \to 5LOX}} + \frac{[15-HETE]}{Ki_{15HETE \to 5LOX}} + \frac{[PGE2]}{Ki_{PGE2 \to 5LOX}} + \frac{[5-HETE]}{Ki_{5HETE \to 5LOX}}) + [AA])}$$

$$- \frac{K_{cat,COX2}[COX-2][AA]}{K_{m,COX2}(1 + \frac{[PGH2]}{K_i} + \frac{[PGE2]}{Ki_{PGE2 \to COX2}}) + [AA]} - Kd_{exoAA}[exoAA] - Kd_{AA}[AA]$$

$$(2)\ \frac{d[15-HPETE]}{dt} = \frac{K_{cat,15-LOX}[15-LOX][AA]}{K_{m,15LOX}(1 + \frac{[15-HPETE]}{K_i}) + [AA]} - \frac{K_{cat,PHGPx}[PHGPx][15-HPETE]}{K_{m,PHGPx}(1 + \frac{[15-HETE]}{K_i}) + [15-HPETE]} - Kd_{15HPETE}[15-HPETE]$$

$$(3)\ \frac{d[15-HETE]}{dt} = \frac{K_{cat,PHGPx}[PHGPx][15-HPETE]}{K_{m,PHGPx}(1 + \frac{[15-HETE]}{K_i}) + [15-HPETE]} - Kd_{15-HETE}[15-HETE]$$

$$(4)\ \frac{d[12-HPETE]}{dt} = \frac{K_{cat,12-LOX}[12-LOX][AA]}{K_{m,12LOX}(1 + \frac{[12-HPETE]}{Ki_{12-HPETE \to 12-LOX}} + \frac{[15-HETE]}{Ki_{15-HPETE \to 12-LOX}} + [AA]} - \frac{K_{cat,PHGPx}[PHGPx][12-HPETE]}{K_{m,PHGPx}(1 + \frac{[12-HETE]}{K_i}) + [12-HPETE]}$$

$$(5)\ \frac{d[12-HETE]}{dt} = \frac{K_{cat,PHGPx}[PHGPx][12-HPETE]}{K_{m,PHGPx}(1 + \frac{[12-HETE]}{K_i}) + [12-HPETE]}$$

$$(6)\ \frac{d[PGH2]}{dt} = \frac{K_{cat,COX2}[COX-2][AA]}{K_{m,COX2}(1 + \frac{[PGH2]}{K_i} + \frac{[PGE2]}{Ki_{PGE2 \to COX2}}) + [AA]} - \frac{K_{cat,TXAS}[TXAS][PGH2]}{K_{m,TXAS}(1 + \frac{[TXA2]}{K_i}) + [PGH2]}$$

$$- \frac{K_{cat,PGES}[PGES][PGH2]}{K_{m,PGES}(1 + \frac{[PGE2]}{K_i} + \frac{[AA]}{Ki_{AA \to PGES}} + \frac{[15-HETE]}{Ki_{15-HETE \to PGES}}) + [PGH2]}$$

$$(7)\ \frac{d[PGE2]}{dt} = \frac{K_{cat,PGES}[PGES][PGH2]}{K_{m,PGES}(1 + \frac{[PGE2]}{K_i} + \frac{[AA]}{Ki_{AA \to PGES}} + \frac{[15-HETE]}{Ki_{15-HETE \to PGES}}) + [PGH2]}$$

$$(8)\ \frac{d[TXA2]}{dt} = \frac{K_{cat,TXAS}[TXAS][PGH2]}{K_{m,TXAS}(1 + \frac{[TXA2]}{K_i}) + [PGH2]} - Kd_{TXA2}[TXA2]$$

$$(9)\ \frac{d[TXB2]}{dt} = Kd_{TXA2}[TXA2] - Kd_{TXB2}[TXB2]$$

$$(10)\ \frac{d[5-HPETE]}{dt} = \frac{K_{cat,5-LOX}[5-LOX][AA]}{K_{m,5-LOX}(1 + \frac{[5-HPETE]}{K_i} + \frac{[12-HETE]}{Ki_{12-HETE \to 5-LOX}} + \frac{[15-HETE]}{Ki_{15-HETE \to 5-LOX}} + \frac{[PGE2]}{Ki_{PGE2 \to 5LOX}} + \frac{[5-HETE]}{Ki_{5-HETE \to 5-LOX}}) + [AA]}$$

$$- \frac{K_{cat,5-LOX}[5-LOX][5-HPETE]}{K_{m,5-LOX}(1 + \frac{[LTA4]}{K_i} + \frac{[12-HETE]}{Ki_{12-HETE \to 5-LOX}} + \frac{[15-HETE]}{Ki_{15-HETE \to 5-LOX}} + \frac{[PGE2]}{Ki_{PGE2 \to 5-LOX}} + \frac{[5-HETE]}{Ki_{5-HETE \to 5-LOX}}) + [5-HPETE]}$$

$$- \frac{K_{cat,PHGPx}[PHGPx][5-HPETE]}{K_{m,PHGPx}(1 + \frac{[5-HETE]}{K_i}) + [5-HPETE]}$$

$$(11)\ \frac{d[5-HETE]}{dt} = \frac{K_{cat,PHGPx}[PHGPx][5-HPETE]}{K_{m,PHGPx}(1+\frac{[5-HETE]}{K_i})+[5-HPETE]} - Kd_{5HETE}[5-HETE]$$

$$(12)\ \frac{d[LTA4]}{dt} = \frac{K_{cat,5LOX}[5-LOX][5-HPETE]}{K_{m,5-LOX}(1+\frac{[LTA4]}{K_i}+\frac{[12-HETE]}{Ki_{12-HETE\to 5-LOX}}+\frac{[15-HETE]}{Ki_{15-HETE\to 5-LOX}}+\frac{[PGE2]}{Ki_{PGE2\to 5-LOX}}+\frac{[5-HETE]}{Ki_{5-HETE\to 5-LOX}})+[5-HPETE]}$$

$$-\frac{K_{cat,LTA4H}[LTA4H][LTA4]}{K_{m,LTA4H}(1+\frac{[LTB4]}{K_i})+[LTA4]} - Kd_{LTA4}[LTA4]$$

$$(13)\ \frac{d[LTB4]}{dt} = \frac{K_{cat,LTA4H}[LTA4H][LTA4]}{K_{m,LTA4H}(1+\frac{[LTB4]}{K_i})+[LTA4]} - Kd_{LTB2}[LTB2]$$

$$-\frac{K_{cat,CYP4F3}[CYP4F3][LTB4]}{K_{m,CYP4F3}(1+\frac{[20-OH-LTB4]}{K_i}+\frac{[12-HETE]}{Ki_{12-HETE\to CYP4F3}}+\frac{[5-HETE]}{Ki_{15-HETE\to CYP4F3}})+[LTB4]} - Kd_{LTB4}[LTB4]$$

$$(14)\ \frac{d[20-OH-LTB4]}{dt} = \frac{K_{cat,CYP4F3}[CYP4F3][LTB4]}{K_{m,CYP4F3}(1+\frac{[20-OH-LTB4]}{K_i}+\frac{[12-HETE]}{Ki_{12-HETE\to CYP4F3}}+\frac{[5-HETE]}{Ki_{5-HETE\to CYP4F3}})+[LTB4]}$$

$$(15)\ \frac{d[PLA2]}{dt} = 0$$

$$(16)\ \frac{d[15-LOX]}{dt} = \frac{k_{PGE2\to 15-LOX}[PGE2]^2}{[PGE2]^2+(K_{PGE2\to 15-LOX})^2} - Kd_{15-LOX}[15-LOX]$$

$$(17)\ \frac{[12-LOX]}{dt} = -Ki_{15-HPETE\to 12-LOX}[15-HPETE][12-LOX]$$

$$(18)\ \frac{d[COX-2]}{dt} = 0$$

$$(19)\ \frac{d[PGES]}{dt} = 0$$

$$(20)\ \frac{d[TXAS]}{dt} = -(Ki_{15-HPETE\to TXAS}[15-HPETE]+Ki_{PGH2\to TXAS}[PGH2])[TXAS]$$

$$(21)\ \frac{d[5-LOX]}{dt} = (K_{LTB4\to 5-LOX}[LTB4]-Ki_{LTA4\to 5-LOX}[LTA4]-Ki_{5-HPETE\to 5-LOX}[5-HPETE]$$

$$-Ki_{15-HPETE\to 5-LOX}[15-HPETE])[5-LOX]$$

$$(22)\ \frac{d[LTA4H]}{dt} = -\frac{K_{cat,LTA4H}[LTA4H][LTA4]}{129(K_{m,LTA4H}+[LTA4])}$$

$$(23)\ \frac{d[CYP4F3]}{dt} = 0$$

$$(24)\ \frac{d[PHGPx]}{dt} = 0$$