Supporting Material, File S2 Text

Frequency switching between oscillatory homeostats and the regulation of p53

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Determination of set-point and period length of the ATM$^*$ controller

Fig S1 shows the p53-ATM$^*$ negative feedback loop when ATM$^*$ is upregulated by DNA damage. With respect to p53 as the controlled variable we have a motif 1 negative feedback loop (1). The active (phosphorylated) form of ATM (ATM$^*$) activates p53 via CHK2 (checkpoint kinase 2) (2, 3), while p53 dephosphorylates ATM$^*$ via the activation of the phosphatase WIP1 (3–5).

\[
\text{DNA damage} \\
\begin{array}{c}
\text{s} \cdot K_{as} \\
\oplus \\
\downarrow \\
\text{CHK2} \\
\downarrow \\
\oplus \\
\text{ATM}$^*$ \quad k_{27}, k_{28} \\
\rightarrow \\
\oplus \\
\text{WIP1} \\
\rightarrow \\
\text{p53} \quad k_2, K_M \\
\rightarrow \\
\text{k}_{29}
\end{array}
\]

Figure S1. The feedback loop between p53 and ATM$^*$. Symbol s represents the stress level and $K_{as}$ is an activation constant.

When the stress level $s$ is between 0.2 and 1.0 ATM$^*$ is the dominating regulator of p53 (Fig 9) and the rate equations for ATM$^*$ and p53 can be written as:

\[
\dot{ATM}^* = \frac{k_{26} \cdot s}{K_{as} + s} - \left( \frac{k_{27} \cdot p53 \cdot ATM^*}{k_{28} + ATM^*} \right) \cdot p53 \quad (S1)
\]

\[
p53 = k_{29} \cdot ATM^* - \frac{k_2 \cdot p53}{K_M + p53} \quad (S2)
\]

By setting Eq S1 to zero, the set-point for p53 ($p53_{set}^{ATM^*}$) is calculated to
(see also Eq 24):

\[
p^{53\text{ATM}}_{\text{set}} = \left(\frac{k_{26}}{k_{27}}\right) \cdot \left(\frac{s}{K_{as} + s}\right) \tag{S3}\]

The dependence/change of \(p^{53\text{ATM}}_{\text{set}}\) as a function of the stress level \(s\) is an example of rheostatic regulation (6) where the set-point changes with the stress level and is defended towards increasing degradation rates \(k_2\) (Fig 11).

When the ubiquitin-independent proteasomal degradation of p53 (via NQO1,(7–9)) is considered to be zero-order (low \(K_M\), Fig S1) the system is described as a harmonic oscillator and the period can be calculated by the double time derivative of p53, \(\ddot{p}53\), i.e.,

\[
p53 = k_{29} A^{\text{ATM}*} = k_{29} \left(\frac{k_{26} \cdot s}{K_{as} + s}\right) - k_{27} k_{29} p53 \tag{S4}\]

Eq S4 can be written in form of the following equation:

\[
\frac{\ddot{p}53}{\omega^2} + p53 = \left(\frac{k_{26}}{k_{27}}\right) \cdot \left(\frac{s}{K_{as} + s}\right) = p^{53\text{ATM}*}_{\text{set}} \tag{S5}\]

with \(\omega^2 = k_{27} k_{29}\).

The solution of Eq S5 is

\[
p53(t) = p^{53\text{ATM}*}_{\text{set}} + A_{\text{ampl}} \sin(\omega \cdot t + \phi) \tag{S6}\]

Thus, \(p53(t)\) oscillates with period

\[
P_{p53}^{\text{ATM}*} = \frac{2\pi}{\omega} = \frac{2\pi}{\sqrt{k_{27} k_{29}}} \tag{S7}\]

and amplitude \(A_{\text{ampl}}\) around its set-point \(p^{53\text{ATM}*}_{\text{set}}\).

References


