Supporting Material, File S1 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 up-regulated 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).

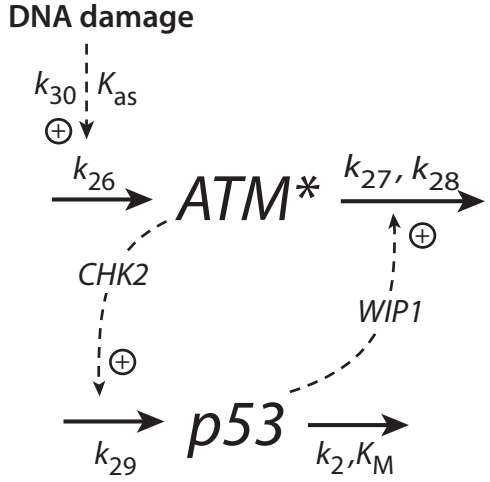

Figure S1. The feedback loop between p53 and ATM*. k_{30} represents the stress level and K_{as} is an activation constant.

When the stress level k_{30} is between 0.2 and 1.0 ATM* is the dominating regulator of p53 (Fig 8) and the rate equations for ATM* and p53 can be written as:

$$\dot{ATM^*} = \frac{k_{26}k_{30}}{K_{as}+k_{30}} - \left(\frac{k_{27}\cdot ATM^*}{k_{28}+ATM^*}\right)\cdot p53 \tag{S1}$$

$$\dot{p53} = k_{29}\cdot ATM^* - \frac{k_2\cdot p53}{K_M+p53} \tag{S2}$$

By setting Eq S1 to zero, the set-point for p53 ($p53^{ATM^*}_{set}$) is calculated to (see also Eq 21):

$$p53^{ATM^*}_{set} = \left(\frac{k_{26}}{k_{27}}\right) \cdot \left(\frac{k_{30}}{K_{as} + k_{30}}\right) \tag{S3}$$

The dependence/change of $p53^{ATM^*}_{set}$ as a function of the stress level k_{30} 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 10).

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, $\ddot{p53}$, i.e.,

$$\ddot{p53} = k_{29}\dot{ATM^*} = k_{29}\left(\frac{k_{26}k_{30}}{K_{as}+k_{30}}\right) - k_{27}k_{29}p53 \tag{S4}$$

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

$$\frac{\ddot{p53}}{\omega^2} + p53 = \left(\frac{k_{26}}{k_{27}}\right) \cdot \left(\frac{k_{30}}{K_{as} + k_{30}}\right) = p53^{ATM^*}_{set} \tag{S5}$$

with ω^2=$k_{27}k_{29}$.

The solution of Eq S5 is

$$p53(t) = p53^{ATM^*}_{set} + A_{ampl}\sin(\omega{\cdot}t + \phi) \tag{S6}$$

Thus, $p53(t)$ oscillates with period

$$P^{ATM^*}_{p53} = \frac{2\pi}{\omega} = \frac{2\pi}{\sqrt{k_{27}k_{29}}} \tag{S7}$$

and amplitude A_{ampl} around its set-point $p53^{ATM^*}_{set}$.

References

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