Logical Modeling of Cellular Senescense Induced by DNA Damage and TGFβ signaling

Veronica Venturini Rossato, José Carlos Merino Mombach

Departamento de Física - Universidade Federal de Santa Maria, RS, Brasil

Upon DNA damage or by external stimuli (like TGFβ) a cell can activate cell cycle checkpoints (mechanisms that arrest the cell cycle to ensure that the required steps are satisfied prior to a phase transition) which promote DNA repair, senescence or apoptosis. Senescent cells release factors that induce permanent senescence as a bystander effect in the cellular environment. These factors are known as SMS (Senescense-messaging secretome), and among them, TGFβ is an important component involved in the 'bystander senescence'. In this work we present an expanded version of the logical model proposed by Mombach *et al.* in 2015 by including an input representing the influence of TGFβ. The model contemplates the crosstalk between TGFb and DNA damage pathways that are important in inducing cellular senescence. In a logical model the variables representing proteins are discrete and the interactions among them are represented by logical operators (And, Or and Not). The model inputs are: TGFβ level of stimulation, repairable or irrepairable SSB (DNA single Strand Breaks) and DSB (DNA double Strand Breaks). The outputs of the model are the following phenotypes: senescence, apoptosis, cell cycle arrest and proliferation. Mutations representing gain of function or loss of function of proteins were produced using the tool GINsim 2.9 and the simulations have demonstrated consistency with the experimental literature on cell growth phenotypes obtained from mutant cells. We also observe the crosstalk effect enhancing senescence and apoptosis upon the combined stimulation of TGFβ and irreparable DNA damage.

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