The “PAI-1 game”: towards modelling the Plasminogen Activation system (PAs) dependent migration of cancer cells with the game network theory

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The « PAI-1 game »: towards modelling the Plasminoge Activation system (Pas) dependent migration of cancer cells with the game network theory
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An original theory based on the Game theory was applied within an interdisciplinary work to better understand cellular migration, one of the major challenges in cancerology. The “Game Network” theory extends strategic game theory by providing the ability to model modular interactions. The Games Network extension offers the possibility to analyse the modular dynamics of molecular networks.

The process of cell migration requires a repeated sequence of adhesion/anchorage/de-adhesion together with cell translocation. This complex process involves membrane-matrix interactions, reorganization of the cytoskeleton and molecular motors. The plasminogen activation system is a proteolytic system involved in the migration of all kinds of cells and specially cancer cells. Three different molecules constitute the PA system: **urokinase Plasminogen Activator (uPA)**, which is the enzyme capable of transforming plasminogen into plasmin, a wide spectrum enzyme involved in fibrinolysis and cell migration. This enzyme binds to a cell membrane receptor, the **urokinase Plasminogen Activator Receptor (uPAR).** The third molecule of the PA system considered here is **Plasminogen Activator Inhibitor type 1 (PAI-1)**, and in particular matrix bound PAI-1. When uPA binding uPAR is inhibited by PAI-1, a tripartite complex (uPAR-uPA-PAI-1) is formed. This complex, independently of any proteolytic function, has been shown to participate in the process of cell migration, i.e. adhesion, anchorage, de-adhesion and to be associated with cell translocation. Cells adhering on matrix-bound PAI-1, exhibit no stress fibers or adhesion plaques as they do on collagen for example. Moreover, on PAI-1, the cell cytoskeleton is reorganized in an unforeseen way, as shown hereafter. Finally, using matrix bound PAI-1 we have been able to modify the migration of three cancer cell lines; the more they were invasive, the more their motility was increased. As PAI-1 appears as a “promigratory” molecule, it might be pivotal in the metastasis potentiality.

Understanding the regulation of the tripartite complex (uPAR-uPA-PAI-1) formation appears thus to be central. It is probably due to several cascades of molecular interactions providing a relatively large complex network. The modelling aims at: describing the network, analysing the regulatory

interplays and explaining some experimental results concerning the effect of the expression rate of the different enzymes and complexes involved in the migratory process. The Game Network theory offers a suitable framework for these requirements.

And indeed, using the game theory to model biological interactions we hit different goals and considerations: each biological agent selects its strategy to maximize its adaptation according to its environment. The latter is also composed of other biological agents who also maximize their adaptation. Adaptation and evolutionary stability may thus explain the strategies of the agents in the game. The Game Network theory offers a suitable framework to express complex biological interplays.The theory can be imaged by the following metaphor: each player has several strategies and is able to play at different games tables. However each player must use the same strategy for every game played. This is modelled by a bipartite graph where the two categories of vertices denote games and players. By modelling the interactions with Games Networks, we here show interactions between the complex and PAI-1 which seems to be at the core of the complex formation and of the subsequent cell migration.

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