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A mathematical model of HiF-1α-mediated response to hypoxia on the G1/S transition

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ABSTRACT

Hypoxia is known to influence the cell cycle by increasing the G1 phase duration or by inducing a quiescent state (arrest of cell proliferation). This entry into quiescence is a mean for the cell to escape from hypoxia-induced apoptosis. It is suggested that some cancer cells have gain the advantage over normal cells to easily enter into quiescence when environmental conditions, such as oxygen pressure, are unfavorable [43,1]. This ability contributes in the appearance of highly resistant and aggressive tumor phenotypes [2].

The HiF-1α factor is the key actor of the intracellular hypoxia pathway. As tumor cells undergo chronic hypoxic conditions, HiF-1α is present in higher level in cancer than in normal cells. Besides, it was shown that genetic mutations promoting overstabilization of HiF-1α are a feature of various types of cancers [7]. Finally, it is suggested that the intracellular level of HiF-1α can be related to the aggressiveness of the tumors [53,24,4,10]. However, up to now, mathematical models describing the G1/S transition under hypoxia, did not take into account the HiF-1α factor in the hypoxia pathway.

Therefore, we propose a mathematical model of the G1/S transition under hypoxia, which explicitly integrates the HiF-1α pathway. The model reproduces the slowing down of G1 phase under moderate hypoxia, and the entry into quiescence of proliferating cells under severe hypoxia. We show how the inhibition of cyclin D by HiF-1α can induce quiescence; this result provides a theoretical explanation to the experimental observations of Wen et al. (2010) [50]. Thus, our model confirms that hypoxia-induced chemoresistance can be linked, for a part, to the negative regulation of cyclin D by HiF-1α.

1. Introduction

The integration of environmental factors influencing cell proliferation is the actual challenge of cell cycle modeling [12]. Indeed, since the 1990's, many models were developed to describe the evolution of protein levels during the cycle [36,11,5,52]. However, few of them take into account external parameters, such as the temperature, the mechanical properties of the substrate, or hypoxia. This last factor is particularly interesting to study. In physiological conditions, hypoxia can occur if the blood does not bring enough oxygen to the cells. If hypoxia is too severe or too long, the cell enters into apoptosis [23]. In pathological conditions, cancer cells undergo a chronic hypoxia [30,31]. This hypoxia induces more aggressive, metastatic and resistant tumors[23,25]. In particular, if hypoxia can induce apoptosis in normal proliferating cells, tumor cells resist to apoptosis [23]. One mechanism that can explain this resistance is the entry into a quiescent state, where the cell stops its division cycle [43,2]. This quiescent state is also a mean for the cancer cell to escape from the effects of chemotherapy [2,33,40]. Therefore, it participates to the aggressiveness of the tumors.

Iarcon et al. [1] proposed a simple model explaining why cancer cells can enter into quiescence under hypoxic conditions whereas normal cells follow their cycle. The authors introduce a difference between normal proliferating and cancer cells through the deregulation of the expression of a protein of the cell-cycle (p27) during tumorigenesis. However, this deregulation event is not a general feature of cancer. Indeed, this phenomenon was not observed in the majority of tumor cells [32,39]. Besides, it is not clear that p27 is necessary to induce hypoxia-induced cell cycle arrest [6,21].

The HiF-1α factor is the central protein involved in the intracellular signaling pathway of hypoxia [46]. It is a transcription factor, which enhances the expression of numerous genes. These genes enable the cell to adapt to the environmental conditions (angiogenesis, arrest of aerobic metabolism), or to enter into apoptosis [20,37].

HiF-1 is an heterodimeric protein, constituted of two sub-units: HiF-1β, which is constitutively expressed, and HiF-1α, which is the sensor of hypoxia. Indeed, in order to activate hypoxia genes, HiF-1α has to be in a reduced form. When the level of oxygen is sufficient, an enzyme called HiF-1α prolyl-hydroxylase is active and

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converts HiF-1α into an hydroxylated form. This oxygenated form of HiF-1α is rapidly degraded by the proteasom pathway [23,44,40].

The ways of actions of HiF-1α are numerous and complex [38]. A review of the huge molecular biology literature dealing with the effects of HiF-1α on the cell cycle enables us to retain several types of actions. First, it is clear that HiF-1α indirectly downregulates cyclin E activity, and this inhibition is the reason why HiF-1α causes slowing down or arrest of cell cycle [22,19,1]. The origins of this action on cyclin E activity remain poorly defined [22], even if some potential pathways are known. Notably, the upregulation of cyclins inhibitors, such as p21 and p27, are reported [17,22,20]. However, some authors showed that the action of HiF-1α on p27 is not so clear since the expression of p27 under hypoxia may be independent of HiF-1α [6,9].

The second important effect of HiF-1α is the interrelation between this factor and cyclin D [50,16]. Wen et al. [50] studied the effect of HiF stabilization on cyclin D level. They first found that after 24 h at 0.2%, the mean cylin D concentration in the whole cell population decreases with 50% compared to the normoxic condition. To confirm the implication of HiF-1, its activity was impaired by DN-HiF overexpression, which induces an increase of the cyclin D level. There is also an action of cyclin D on HiF-1α, due to the activation of the HiF-1 prolyl-hydroxylase activity [16]. Besides, the activation of cyclin D expression by HiF-2 underlines the rivalry in hypoxic tumor growth and progression between HiF-1 and HiF-2. Here, we choose to focus on the influence of cyclin D inhibition by HiF-1α, in order to show how this simple relationship can generate a serie of interesting results in agreement with data from the literature. Besides, the inhibition of the cyclins by HiF-1α under hypoxia is very well documented. As we previously said, hypoxia-dependent inhibition of cyclin E is considered as a cause of hypoxia-dependent cell-cycle arrest. Second, the increase of unphosphorylated versus phosphorylated form of the Retinoblastoma protein [19,20] under hypoxia is also a good evidence for the downregulation of cyclin D by HiF.

The increase of HiF-1α activity during tumorigenesis is well documented, since it seems to be a very common feature of cancers [53,29,8,42]. As a consequence, this factor became a new therapeutic target [45,47]. In some cases, its high level is simply due to the chronic hypoxia undergone by the tumor cells. In other cases, genetic mutations induce an over-stabilization of HiF-1. It is the case for the renal clear carcinoma [13]. As a consequence, for the same oxygen pressure, HiF-1 will have a higher level in cancer cells than in normal cells [15].

In a general way, a link was found between the aggressiveness of cancers and HiF-1α activity. This role of HiF in tumorigenesis is firstly due to the induction of anti-apoptotic and pro-angiogenic genes. Second, it mediates the entrance into quiescence of proliferating cells, which induces a hypoxia-dependent chemoresistance.

The aim of this work is to describe an example of a simple mechanism of HiF-1α-dependent entrance into quiescence under hypoxia. We make a link between the level of HiF-1α and the ability of the cell to enter into quiescence under hypoxia. In agreement with the literature, our model assumes the regulation of HiF-1α stability by the oxygen pressure [51,44,34]. We built a mathematical model of the G1/S transition in hypoxic conditions, which explicitly integrates the HiF-1α pathway. We focused on the relationships between HiF-1α and the cyclins, in order to propose a simple and biologically accurate mechanism of hypoxia-induced quiescence.

2. Model

2.1. Hypotheses

Our model is primary based on the models described in Alarcon et al. [1], Tyson and Novak [49], Novak and Tyson [36]. In those papers, the G1/S transition is modeled by a biological switch between a cyclin and an inhibitor complex. They considered that this inhibitor was APC/cdh1. However, this role of APC/cdh1 complex is not well admitted; classicaly, the complex addressing cyclin E for degradation is known to be the SCF complex [14]. As a consequence, it is more accurate to consider that the inhibitor of cyclin E is SCF. The switch that we aim to study is represented in Fig. 1. The G1 phase finishes when this molecular switch occurs. In our model, we differentiate the cyclin E and the cyclin D. The cyclin E is involved in the molecular switch where it inhibits and is inhibited by the SCF complex. Whereas Novak and Tyson [36] consider that two cyclins drive the G1/S transition (cyclin E and A), we consider here just one cyclin we named cyclin E. The concentration in active SCF complex is controlled by an evolution equation similar to that given by Tyson and Novak [49] for the APC/cdh1 complex. The cyclin D phosphorylates the Rb protein, which releases the transcription factor E2F. As Novak and Tyson [36], we supposed that at each time, $E2F_{Rb}$ is in an equilibrium relationship with E2F and Rb because the complexation/decomplexation of phopshorylated Rb and E2F are supposed to be very fast compared to the evolution of the cyclin concentration. Besides, free E2F can be in an unphosphorylated (active) form, or in a phosphorylated (inactive) form. A dynamic equilibrium ensures the transition from phosphorylated to unphosphorylated forms. The total concentration of E2F (free phosphorylated/unphosphorylated, and complexed with Rb) is supposed to be constant, as in [36]. Active E2F factor promotes the synthesis of the cyclin E, as assumed for the cyclin A by Novak and Tyson [36]. Besides, to take into account the cell growth in the progression through the G1 phase, we assume that the mass increases the cyclin E concentration. This assumption is taken from Alarcon et al. [1] and Novak and Tyson [36]. The oxygen pressure is taken into account with the variable P, which represents the percentage of oxygen among all the other gases in the cell environment. The effect of the oxygen pressure is modeled by the concentration of HiF-1α. This concentration increases when the oxygen pressure decreases, as well described in the literature [27,54]. Jiang et al. [27] show that *in vitro* cultured cells submitted to hypoxia exhibit an exponential relationship between the HiF-1 level and the oxygen pressure [27]. The experimental results from Zhou et al. [54] confirm that an exponential law is a good model for the hypoxia-induced HiF-1 stabilization. These authors also showed that this exponential law strongly depends on the cancer cell lines. We will discuss this point later. HiF-1α decreases the cyclin D activity by inhibiting its synthesis, as observed in experiments [50]. The evolution of the cyclin D level during the cycle, the influence of HiF-1α on its level, and the reaction of Rb phosphorylation are calibrated with data from the literature. We do not take into account the role of the p27 protein, contrary to Alarcon et al. [1]. As we said, the effects of hypoxia on this protein remain unclear; besides, we want to focus on the influence of cyclin D/HiF interactions which promote the entrance into quiescence. Fig. 2 gives a sketch of the molecular network.

2.2. Biological description

The variables used in the model are the cyclin D (*cycD*), the cyclin E (*cycE*), the Retinoblastoma protein (in its unphosphorylated form) (*Rb*), HiF-1α (*H*), the SCF complex (*SCF*), the mass of the cell, and the different chemical forms of the E2F transcription factor. E2F exists in phosphorylated and unphosphorylated (*E2F*) form, and free or linked to Rb ($E2F_{Rb}$). Thus, free E2F can be phosphorylated or unphosphorylated. The free and unphosphorylated form ($E2F_A$) is the active form. A chemical equilibrium drives the transition between the phosphorylated and unphosphorylated forms of E2F. We named $E2F_{tot}$ the total of all the chemical forms of E2F. As Novak and Tyson [36], we assume this total to be