Commentary

Fasting inhibits human cancer progression via the epithelial-mesenchymal transition process: Important evidence unraveled

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ABSTRACT

Metastatic cancer disease is responsible for the majority of cancer-related deaths in human cancer patients. In parallel, recently it was pointed-out that fasting could play an important role during cancer treatment and progression via the deregulation of insulin-like growth factor-1 (IGF-1) as well as others growth factors and genes. Meanwhile, it is established that the epithelial-mesenchymal transition (EMT) is a major process for the progression of cancer cells from non-invasive to invasive form. We believe that fasting can inhibit cancer progression and metastasis though the reduction of IGF-1 level and consequently the inhibition of EMT; in this paper, we present some evidence to confirm this association.

Key words: Epithelial-mesenchymal transition, fasting, cancer invasion and metastasis

Carcinomas are tumors of epithelial origin and represent over 90% of human cancers. Metastatic carcinomas are responsible for the majority of cancer-related deaths, either directly due to tumor involvement of critical organs or indirectly due to complications of therapy to control tumor growth and spread. Alternatively, the epithelial-mesenchymal transition (EMT) is a highly conserved cellular program that allows polarized, immotile epithelial cells to convert to motile mesenchymal cells.[1] This important process was initially recognized during several critical stages of embryonic development and has more recently been implicated in promoting carcinomas invasion and metastasis.[1,2] On the other hand, it is well established that a hallmark of EMT is loss of E-cadherin, a key mediator of cell-cell adhesion, as well as other cell-cell junction proteins. Numerous studies have shown a high correlation between loss of E-cadherin and their associated proteins, catenins, and the gain of vimentin, fibronectin, and cancer invasiveness in malignant cells in cancer patients.[2,3] Meanwhile, accumulating evidence suggests that tyrosine kinase receptors (TKRs), such as epithelial growth factor-receptors (EGF-Rs), c-Met, insulin-like growth factor-receptor 1 (IGF-R1), fibroblast growth factor-receptors (FGF-Rs), and non-TKR c-Src can induce β-catenin's phosphorylation.[3-7] This results in their disassociation and degradation, providing a link between oncogenic activation of these kinases and the induction of EMT.[3,8,9] Thus a rational exists, since two decades, for the prevention of EMT and cancer progression through inhibition of these kinase receptors in the early-stage of carcinomas. Accordingly, we have demonstrated that a ligand-blocking monoclonal antibody (mAb) against the EGF-R1, LA1, inhibits cell growth, induces differentiation to a more epithelial phenotype, reduces the constitutive activation of EGF-R1 and up-regulates E-cadherin protein expression in two human lung cancer cell lines, H322 and A549.[10,11] This was associated with re-localization of the E-cadherin/catenins complex, and consequently the inhibition of cell motility in both cell lines. In contrast, epithelial growth factor (EGF) and heparin-binding (HB)-EGF, lignads of EGF-R1, induce cell proliferation and the epithelial-like to fibroblastoid (mesenchymal) conversion, slightly reduces the expression of E-cadherin and β-catenin, and stimulates cell motility.[10,11]

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More interestingly, we have noted that decreasing serum's quantity (serum starvation), from 10% to 1% in the cell medium, can provoke epithelial-like to a more epithelial phenotype of H322 and A549 cells [unpublished data]; we believe that this change is the result of decreasing several growth factors such as EGF and insulin-like growth factor-1 (IGF-1) and consequently the inactivation of their respective receptors.

Additionally, and in order to determine the role of *Src* as an important pathway of EGF-R1 and a major target in the treatment of human metastatic cancers, we examined the effect of *Src*/*Abl* inhibitor, SKI-606 on cell proliferation, cell cycle progression and cell invasion and motility in numerous human carcinoma cell lines including breast, prostate, cervical, and lung.[12-14] We reported that SKI-606 significantly affects these processes in the studied cancer cells. More specifically, we reported that *Src*/*Abl* inhibitor induces mesenchymal-epithelial transition (MET) and consequently up-regulates E-cadherin expression and inhibits cell invasion ability of human breast, prostate, cervical, and lung cancer cells. Moreover, we demonstrated that this effect occurs through the conversion of β-catenin's role from a transcription regulator to a cell-cell adhesion molecule, and consequently restore the E-cadherin/catenin complex expression patterns via *Src* dephosphorylation.[12-14] Collectively, our data confirm that EGF-R1 and/or its pathways inactivation play an important role in the regulation of cell invasion and metastasis of human carcinoma cells through the MET event.

Alternatively, several lines of evidence implicate IGF-R1 signaling is an important driver of the EMT.[5] For instance, in numerous human carcinoma cells, constitutively active IGF-R1 caused cells to undergo EMT, which is associated with dramatically increased migration and invasion, and this transition was mediated by the induction of Snail and down-regulation and E-cadherin.[5,15] These effects are mediated, at least in part, by its ligand, IGF-1. This growth factor is known to influence cell adhesion through the phosphorylation and transcriptional activation of β-catenin and dissociation of E-cadherin from the cell membrane [Figure 1].[16] In addition to disruption of homotypic cell adhesion, IGF-1 has also been shown to promote tumor invasiveness via secretion of matrix metalloproteinases or crosstalk with integrin signaling pathways.[17,18]

IGF-R1 signaling promotes Akt phosphorylation and protection from apoptosis, which is predicted to limit the efficacy of care standards of chemotherapies. In addition, it was reported that the IGF-R1 pathway (PI3k/Akt/mTOR) is also instrumental in EMT and angiogenesis during tumorigenesis.[5,19,20] Thus, there is a strong rationale for development of IGF-R1 targeted therapies, and IGF-R1

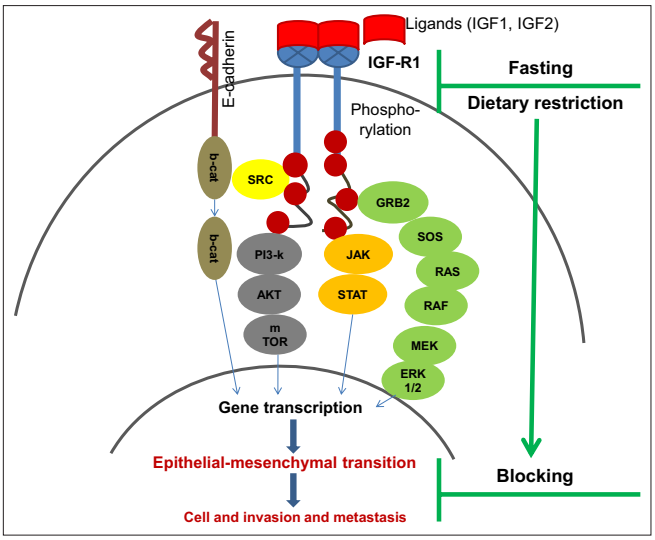

Figure 1: Schematic overview showing the effect of fasting and dietary restriction (DR) on IGF-R1 signaling pathways in cancer cells. Fasting and DR decrease IGF-1 secretion which consequently can reduce IGF-R1 activation. Thus, IGF-R1 downstream-signaling pathways, including *Src*/β-catenin, PI3k/Akt/mTOR, and GRB2/ERK pathways, can be turned-off which lead to blocking of the EMT process and consequently to decrease cell invasion and metastasis abilities in cancer patients

inhibition might be expected to enhance the effect of cytotoxic chemotherapies or other molecular targeted therapies. All of this implicates insulin and IGF-1 in the progression of human carcinomas. Alternatively, it is established that dietary restriction triggers highly conserved survival mechanisms that enhance the protection of organisms against various types of stress and/or disease. This counterintuitive effect is mediated in part by the reduction of conserved nutrient-signaling pathways that include several mitogenic components, especially the IGF-R1 and its downstream effectors,[19,21] which can block the EMT process and consequently cancer cell migration and invasion in cancer patients [Figure 1]. Meanwhile, there are several recent studies demonstrating that fasting can enhance the chemotherapy effect in cancer patients.[21,22] While, presently it is established that chemotherapy is the most widely used strategy for the treatment of human cancers but the toxicity of the treatment makes it only partially effective particularly with advanced malignancies. Meanwhile, it has been recently demonstrated that fasting selectively protects normal cells and organisms from chemotherapy toxicity, while simultaneously sensitizing tumors.[22,23] This is occurring via the reduction of insulin and IGF-1 and consequently IGF-R1 inactivation.[24,25] For instance, a recent study described 10 cases of patients affected by different types of tumors, ranging from stage II breast cancer, stage IV esophageal, prostate, to lung malignancies showed that fasting in combination with chemotherapy is safe and could reduce common side-effects associated to chemotherapy.[26] Taken together, this suggests that fasting has the potential to be translated into a mode of clinical intervention to protect patients against

chemotherapy-induced toxicity. Moreover, because of its effects on a variety of proteins, including IGF-I and insulin, which can affect cell-cell adhesion molecules, fasting also has the potential to be involved in cancer progression through EMT with or without chemotherapy [Figure 1].

In conclusion, we firmly believe that fasting could be an important approach to control cancer progression by blocking cancer invasion and metastasis via EMT procedure and the increasing efficiency of chemotherapy in cancer patients. However, we think that more molecular and cellular biological studies in addition to developing new animal models are necessary to determine the exact role of fasting in the progression of human carcinomas.

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