REVIEW

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Oncoprotein metastasis: an expanded topography

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Abstract

In this survey, the initial insights on the sub- and transcellular process of oncoprotein metastasis (OPM) are linked to recent observations and advances in related fields. The six proteins described here, *i.e.* insulin, osteopontin, interleukin-6, anterior gradient-2 protein, cellular apoptosis susceptibility protein and hepatoma-derived growth factor, as well as distinct peptide fragments thereof might henceforth serve as pivotal biomarkers for OPM in clinical chemistry, molecular morphology, pathology and oncology and, as a result, guide as potential targets future structure-based interventions in cancer treatment.

Keywords: oncoprotein, metastasis, biomarker, cancer, diagnosis, prognosis.

Background

One of the first milestones in modern signal transduction research has been the report on the isolation of the (*cell membrane-bound*) insulin receptor in 1972, which thus precisely defined a binding partner for the (*extracellular and blood-borne*) key hormone insulin [1]. This led in the 1970s and 1980s to an initial widespread focus on *cell membrane* receptors for various *extracellular* (hormone or, respectively, growth factor) ligands as possible targets in molecular medicine.

Yet, in 1992, an additional important binding partner for (*internalized*) insulin was predicted based on bio-informatic studies: the *intracellular* (*mainly nuclear*) retinoblastoma tumor suppressor protein, briefly: RB [2]. This new paradigm for an *intracellular/nuclear* association between a hormone/growth factor and its tumor suppressor binding partner was subsequently validated through several experimental studies among which a pivotal one has been conducted in human hepatoma cells [3].

Within the same framework, it was predicted in 1994 through structural analysis that the (*extracellular*) RB-like insulin-like growth factor binding proteins 3 and 5 (*i.e.* IGFBP-3 and -5) *internalize into the nuclei* of cells where they may bind the (*nuclear*) insulin-like retinoblastoma-binding proteins 1 and 2, briefly RBP-1 and RBP-2 [4]. This prediction was then partly validated by the subsequent experimental demonstration of the nuclear localization of (IGF-bound) IGFBP-3 [5].

This dual, *i.e. extracellular and intracellular*, localization of various highly significant growth-regulatory proteins then provided the conceptual basis for formulating in 1994 a novel biophysical theory on cell growth regulation which encompassed the view on the existence of *mobile protein*-based *transcellular fields* – that precede changes in cellular morphology and migration (*e.g.* during carcinogenesis) – and was consequently coined "particle biology" [6].

As an outflow of the initial particle biology concept and its associated co-concept on "peptide strings", the term "oncoprotein metastasis" was initially proposed in 2007 [7], subsequently mentioned as one among several aspects of epigenetic or non-genetic regulation of cancer cell fate in 2008 [8] and more recently revisited in 2010 [9]. It denominates a tissue/organism-wide spread of oncoproteins both into the extra- and intracellular compartments as well as into both cancer cells and non/pre-malignant cells, thus ultimately contributing in a likely decisive way to tumor progression and cancer metastasis.

The fact that, besides the already described OPM candidate molecules insulin and osteopontin [9], four additional proteins have now been recognized to be putatively able to drive the OPM process and thus cancer metastasis altogether, hence underscoring the potential generality of the phenomenon, has prompted the present survey.

Recent advances

The following two tables summarize recent progress in this area and its related fields that mainly involves six highly mobile (onco)proteins or, in other words and in analogy to Barbara McClintock's "jumping genes", "jumping (onco)proteins" that are likely to crucially influence the metastatic process: insulin, osteopontin (OPN), interleukin-6 (IL-6), anterior gradient-2 (AGR-2) protein, cellular apoptosis susceptibility (CSE1L/CAS) protein and hepatoma-derived growth factor (HDGF).

These six proteins as well as distinct peptide fragments thereof could be regarded as candidate markers for OPM and might be developed further accordingly in order to expand cancer diagnosis and prognosis.

Table 1 – ***Subcellular localization of the candidate OPM markers insulin, osteopontin, IL-6, AGR-2 protein, CSE1L/CAS protein and HDGF as well as published evidence for such localization***

Candidate OPM marker	Extracellular	Intracellular
Insulin	[7–10]	[7–9, 11, 12]
Osteopontin	[9, 13]	[9, 13]
Interleukin-6	[14]	[14]
AGR-2 protein	[15]	[16]
CSE1L/CAS protein	[17, 18]	[17–19]
HDGF	[20]	[21]

The *numbers* in the table indicate the respective articles in the list of references.

Table 2 – ***Tissue localization of the candidate OPM markers insulin, osteopontin, IL-6, AGR-2 protein, CSE1L/CAS protein and HDGF as well as published evidence for such localization***

Candidate OPM marker	Normal-appearing, potentially premalignant tissue	Cancer tissue
Insulin	[7–9, 11, 12]	[7–9, 11, 12]
Osteopontin	[9, 13]	[9, 13]
Interleukin-6	[14]	[14]
AGR-2 protein	[15, 16]	[16]
CSE1L/CAS protein	[17–19]	[17–19]
HDGF	[22]	[22]

The *numbers* in the table indicate the respective articles in the list of references.

Interestingly, the likely functional counterparts to these six molecules presumed to be involved in OPM are highly mobile tumor suppressor proteins such as insulin-like growth factor binding protein 3, briefly: IGFBP-3 which is both the most abundant and important transport protein for the insulin-like growth factors (IGFs) in the blood circulation and, moreover, a growth-suppressive protein that translocates to the cell nucleus [4, 23].

Taken together, it could be that, in the future, the (*bacterial toxin-like*) cancer metastasis-driving onco-proteins, such as the six OPM proteins presented here, will be effectively neutralized by (*antitoxin-like*) tumor suppressor protein-derived (peptide) compounds, thereby potentially efficiently reversing the otherwise lethal course of cancer disease altogether and, at the same time, reciprocating in oncology the (serum therapy or, respectively, passive immunization) treatment strategy that Victor Babes and Emil von Behring successfully introduced for the treatment of various infectious diseases more than a century ago.

Note added in proof

In further support of the present concept of an expanding family of circulating and internalizing (onco) proteins that directly promote the systemic spread of the carcinogenic process, it has recently been suggested that IL-6 may act as a "phenotypic switch in blood" towards metastasis (Geng Y *et al.*, 2013 [24]), thus being consistent with a previous investigation on the ubiquitous distribution of IL-6 in colorectal cancer patients [14]. Moreover, another study has shown that HDGF acts as a pro-metastatic factor in an experimental model of malignant melanoma (Tsai HE *et al.*, 2013 [25]).

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