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Review

Focal adhesion signaling and therapy resistance in cancer

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ABSTRACT

Interlocking gene mutations, epigenetic alterations and microenvironmental features perpetuate tumor development, growth, infiltration and spread. Consequently, intrinsic and acquired therapy resistance arises and presents one of the major goals to solve in oncologic research today. Among the myriad of microenvironmental factors impacting on cancer cell resistance, cell adhesion to the extracellular matrix (ECM) has recently been identified as key determinant. Despite the differentiation between cell adhesion-mediated drug resistance (CAMDR) and cell adhesion-mediated radioresistance (CAMRR), the underlying mechanisms share great overlap in integrin and focal adhesion hub signaling and differ further downstream in the complexity of signaling networks between tumor entities. Intriguingly, cell adhesion to ECM is *per se* also essential for cancer cells similar to their normal counterparts. However, based on the overexpression of focal adhesion hub signaling receptors and proteins and a distinct addiction to particular integrin receptors, targeting of focal adhesion proteins has been shown to potently sensitize cancer cells to different treatment regimes including radiotherapy, chemotherapy and novel molecular therapeutics. In this review, we will give insight into the role of integrins in carcinogenesis, tumor progression and metastasis. Additionally, literature and data about the function of focal adhesion molecules including integrins, integrin-associated proteins and growth factor receptors in tumor cell resistance to radio- and chemotherapy will be elucidated and discussed.

1. Introduction

Oncologic diseases are still one of the leading causes of mortality in industrialized countries [1]. In line with aging of the population, the incidence of cancer is constantly increasing as is our knowledge about therapy resistance mechanisms and how cancer cells circumvent a therapeutic approach by activating prosurvival bypass signaling pathways [1,2].

The concept of the hallmarks of cancer provide a convincing view on developmental steps and determinants of progression of malignant tumors, and, beyond, illustrate a large plethora of potential cellular and non-cellular targets. With great differences in development and growth, genome and epigenome, therapy sensitivity and metastatic spread, we are currently more aware then ever before of the intra- and intertumoral complexity and heterogeneity of this disease. As one of the most important paradigms explaining therapy resistance, cell adhesion-mediated radioresistance (CAMRR) and cell adhesion-mediated drug resistance (CAMDR) were uncovered more than a decade ago [3–10]. Multiprotein and multifunctional focal adhesion complexes facilitating cell–ECM contact and connection between ECM and actin cytoskeleton play mechanistically the key role as they structurally and functionally control the cell's morphology and cytoplasmic signaling for survival, proliferation, differentiation, and motility [11–13].

The uniqueness of focal adhesions lies in the juxtaposition and cooperative connection between integrins and growth factor receptors accessing the cytoplasmic signaling network (Fig. 1). It seems that the exact orchestration of this receptor interplay and particularly the channeling of biochemical cues differ between tumor entities. Importantly, adhesion to ECM has been shown to essentially contribute to tumor cell resistance to radiation and

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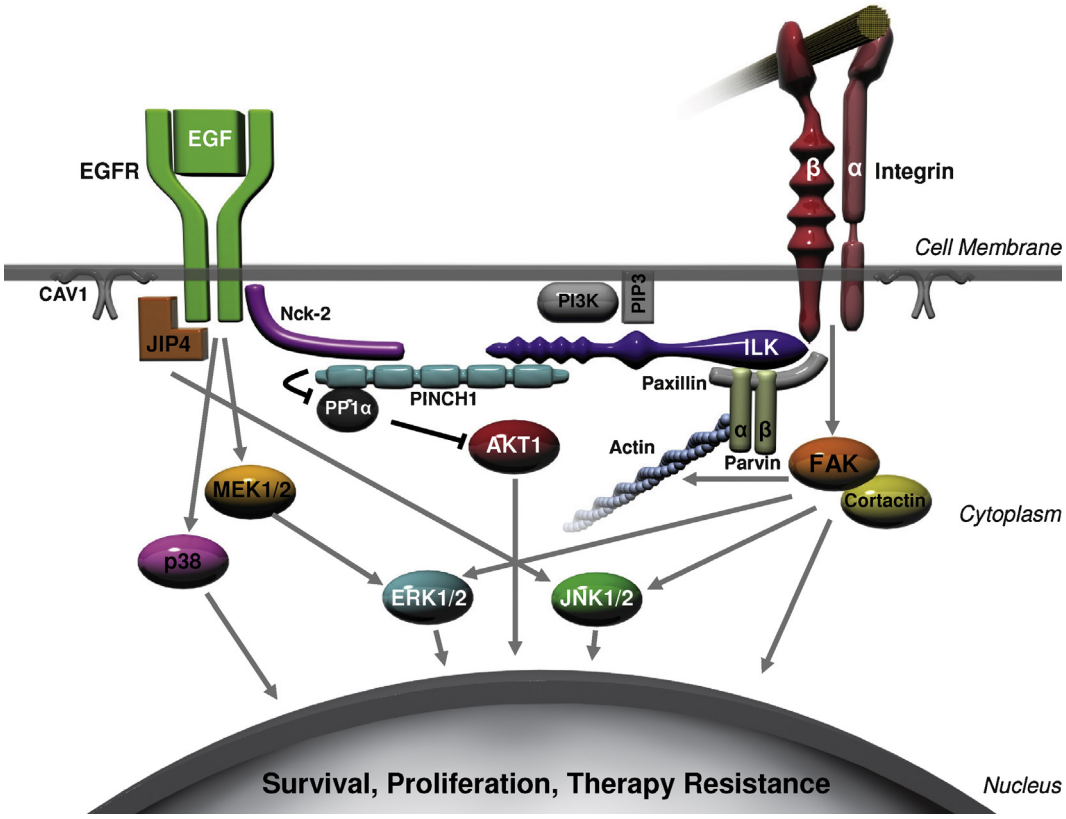

Fig. 1. Scheme of a focal adhesion multiprotein complex. Besides integrins and epidermal growth factor receptors (EGFR), several kinases and adapter molecules contribute to cell adhesion-mediated resistance mechanisms. CAV1, caveolin-1; ERK1/2, extracellular-signal regulated kinases 1/2; FAK, focal adhesion kinase; ILK, integrin-linked kinase; JIP4, JNK-interacting protein 4; JNK, c-Jun N-terminal kinase; MEK1/2, mitogen-activated protein kinase kinase; Nck-2, non-catalytic region of tyrosine kinase 2; PI3K, phosphoinositol 3-kinase; PINCH1, particularly interesting new cysteine-histidine-rich 1; PP1α, protein phosphatase 1α.

chemotherapy [3,5,14–18] as well as to targeted therapeutics [19–21]. Due to their most upstream localization, the receptors within focal adhesions seem to be an ideal starting point for therapeutic intervention. However, taken into consideration has to be the strong redundancy and complexity of downstream signaling and crosstalk, which is likely to challenge the efficacy of a particular molecular therapy. Recent work elegantly demonstrated how bypass mechanisms reduced the efficacy of the clinically used anti-EGFR antibody Cetuximab [19,20]. Reviewing the huge network of interacting proteins located in focal adhesions, pharmacological inhibition of one molecule could easily be circumvented *via* alternative pathways in tumor cells. Therefore, uncovering the molecular processes underlying focal adhesion hub signaling will enable us to better understand signaling bypasses and resistance mechanisms and foster the development of reasonable and feasible multimodal treatment options.

In this review we will give insight into the role of integrins in carcinogenesis, tumor progression and metastasis. Additionally, literature and data about the function of focal adhesion molecules including integrins, integrin-associated proteins and growth factor receptors in tumor cell resistance to radio- and chemotherapy will be elucidated and discussed.

2. Integrins in cancer

Integrins are obligate heterodimeric transmembrane receptors consisting of one α and one β subunit, which mainly serve as adhesion molecules for ECM proteins [22]. To date, 18 α and eight β integrin subunits have been found to form more than 20 different receptors. The combination of the subunits determines the binding region and impacts on the affinity of the receptor for a specific matrix protein [22,23]. Due to their expanded network of interaction partners including adapter and signaling molecules (Figs. 1 and 2), integrins not only connect the cellular cytoskeleton with the extracellular microenvironment but also control critical cell functions such as survival and migration through the activation of certain signaling mechanisms [13,24–28].

Particularly in epithelial tumors, integrins play a fundamental role for tumorigenesis [29–37]. Biopsies of normal cervix epithelium and squamous cell carcinoma revealed an enhanced and diffuse β4 integrin expression in dysplastic and malignant tissue [33]. In a mouse model, the expression pattern of integrins changed when skin carcinomas were induced either by viral oncogene transduction or application of chemical carcinogens [31]. Here, the laminin receptor α6β4 integrin was strongly upregulated, while the expression of other subunits like α5β1 and α3β1 integrin was decreased. According to these observations, depletion of β4 integrin delayed tumor onset and progress of mammary carcinomas *in vivo*. This was accompanied by downregulation of ErbB2 and STAT3 signaling [32], whereas re-expression of α2β1 integrin in poorly differentiated α2 integrin deficient breast cancer cells resulted in cell differentiation and reduced tumorigenicity [34]. Recently, Sachs and colleagues showed that chemically induced skin carcinogenesis is markedly impaired in α3 integrin knockout mice indicating that this molecule is critical for tumor initiation and epidermal turnover [35].

Integrins also impact on cancer metastasis through tremendous changes in the cellular and extracellular neighborhood occurring during tumor development and progression [38–43]. In a murine colon cancer model, inhibition of α5β1 integrin using a small