Cancer stem cell and mesenchymal cell cooperative actions in metastasis progression and hormone resistance in prostate cancer: Potential role of androgen and gonadotropin-releasing hormone receptors (Review)

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Abstract

Prostate cancer (PCa) is the leading cause of male cancer-associated mortality worldwide. Mortality is associated with metastasis and hormone resistance. Cellular, genetic and molecular mechanisms underlying metastatic progression and hormone resistance are poorly understood. Studies have investigated the local effects of gonadotropin-releasing hormone (GnRH) analogs (used for androgen deprivation treatments) and the presence of the GnRH receptor (GnRH-R) on PCa cells. Furthermore, cell subpopulations with stem-like properties, or cancer stem cells, have been isolated and char-acterized using a cell culture system derived from explants of human prostate tumors. In addition, the development of preclinical orthotopic models of human PCa in a nonobese diabetic/severe combined immunodeficiency mouse model of compromised immunity has enabled the establishment of a reproducible system of metastatic progression in vivo. There is increasing evidence that metastasis is a complex process involving the cooperative actions of different cancer cell subpopulations, in which cancer stem-like cells would be responsible for the final step of colonizing premetastatic niches. It has been hypothesized that PCa cells with stemness and mesenchymal signatures act cooperatively in metastatic progression and the inhibition of stemness genes, and that overexpression of androgen receptor (AR) and GnRH-R decreases the rate the metastasis and sensitizes tumors to hormone therapy. The aim of the present review is to analyze the evidence regarding this cooperative process and the possible influence of stem-like cell phenotypes, AR and GnRH-R in metastatic progression and hormone resistance. These aspects may represent an important contribution in the understanding of the mechanisms underlying metastasis and hormone resistance in PCa, and potential routes to blocking these processes, enabling the development of novel therapies that would be particularly relevant for patients with metastatic and castration-resistant PCa.

Keywords

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