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Chemokines in triple-negative breast cancer heterogeneity: New challenges for clinical implications

Umar Mehraj [a], Umar Mushtaq [b,1], Manzoor A. Mir [a,1], Afnan Saleem [c], Muzafar A. Macha [d], Mohammad Nadeem Lone [e], Abid Hamid [b], Mohammed A. Zargar [b], Syed Mudasir Ahmad [c], Nissar Ahmad Wani [b,*]

[a] Department of Bioresources, School of Life Sciences, University of Kashmir, Srinagar, Jammu & Kashmir, India
[b] Department of Biotechnology, School of Life Sciences, Central University of Kashmir, Ganderbal, Jammu & Kashmir, India
[c] Division of Animal Biotechnology Faculty of Veterinary Sciences and Animal Husbandry, Shuhama Sher-e, Kashmir University of Agricultural Sciences and Technology, Kashmir, India
[d] Watson-Crick Centre for Molecular Medicine, Islamic University of Science & Technology Awantipora, Jammu & Kashmir, India
[e] Department of Chemistry, School of Physical & Chemical Sciences, Central University of Kashmir, Ganderbal, Jammu & Kashmir, India

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ABSTRACT

Tumor heterogeneity is a hallmark of cancer and one of the primary causes of resistance to therapies. Triple-negative breast cancer (TNBC), which accounts for 15–20% of all breast cancers and is the most aggressive subtype, is very diverse, connected to metastatic potential and response to therapy. It is a very diverse disease at the molecular, pathologic, and clinical levels. TNBC is substantially more likely to recur and has a worse overall survival rate following diagnosis than other breast cancer subtypes. Chemokines, low molecular weight proteins that stimulate chemotaxis, have been shown to control the cues responsible for TNBC heterogeneity. In this review, we have focused on tumor heterogeneity and the role of chemokines in modulating tumor heterogeneity, since this is the most critical issue in treating TNBC. Additionally, we examined numerous cues mediated by chemokine networks that contribute to the heterogeneity of TNBC. Recent developments in our knowledge of the chemokine networks that regulate TNBC heterogeneity may pave the way for developing effective therapeutic modalities for effective treatment of TNBC.

1. Introduction

While the death rate from breast cancer (BC) has fallen significantly during the last two decades, recent cancer data indicates that the disease remains a significant global public health burden [1,2]. Despite advances in early diagnosis and therapies, BC continues to be the most significant cause of tumor-related death [2]. Breast cancer and distant metastases are heterogeneous, a key reason for therapeutic failures [3,4]. The heterogeneity might be due to the occurrence of driver mutations and alterations in cancer genes, prompting clonal evolution and dissemination of polyclones to metastatic niches [5]. Combinatorial assessment of the histopathology of the primary tumor and the expression pattern of hormone receptors (estrogen and/or progesterone receptors; ER/PR) and epidermal growth factor receptor 2 (HER2/Neu), as well as additional genomic and transcriptomic profiling, enabled for the identification of subtypes of breast cancer and paved the way for the development of targeted therapies [6]. Based on gene expression, BC has been categorized into four subtypes: luminal A, luminal B, HER2-enriched, and TNBC. TNBC is a highly aggressive subtype that accounts for approximately 15–20% of all diagnosed cases, with limited access to targeted therapy owing to the lack of hormonal receptors (ER and PR) and HER2 amplification [7,8]. TNBC is a highly heterogeneous BC subtype, classified into six stable subtypes based on gene expression profiling, namely basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM) subtype, and luminal androgen subtype (LAR) [8,9]. TNBC is a substantial clinical challenge due to its poor prognosis, high recurrence, and, most importantly, high incidence of metastatic disease [8]. The breast tumor heterogeneity maintained by different molecular cues in tumor cells by tumor microenvironment (TME), promote aggressive tumor phenotype

* Correspondence to: Department of Biotechnology, School of Life Sciences, Central University of Kashmir, Ganderbal 191201, India.
E-mail addresses: waninh@yahoo.co.in, waninh@cukashmir.ac.in (N.A. Wani).
[1] The authors contributed equally.

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