

IL-17 and Triple Negative Breast Cancer

Abstract

Interleukin-17 (IL-17) is a pro-inflammatory cytokine mainly produced by a subset of T helper lymphocytes called Th17. The role of IL-17 and its receptor IL-17R has been well established and therapeutically exploited with success in chronic inflammatory disease such as psoriasis. Because inflammation is tightly correlated with cancer progression, growth and metastasis, several studies have investigated the involvement of the Th17 pathway in tumours. Triple negative breast cancer (TNBCs) is an aggressive form of breast cancer characterized by a young age of patients, and a grim prognosis. Since TNBCs lack expression of oestrogen and progesterone receptor and do not over express the human epidermal growth factor receptor 2 (HER2), the only systemic treatment available is chemotherapy to which they rapidly become resistant. Therefore new targets are needed to develop new therapies. In this article we review the current knowledge of IL-17 role in triple negative breast cancer.

Keywords: IL-17; Triple negative breast cancer; Tumour microenvironment; Anti-cancer Immunotherapy

Abbreviations: IL-17: Interleukin 17; IL-17R: Interleukin 17 Receptor; HER2: Human Epidermal Growth Factor Receptor 2; TNBC: Triple Negative Breast Cancer; Th17: T Helper Lymphocyte 17; BC: Breast Cancer

Introduction

Rouvier et al. [1] discovered interleukin 17 (IL-17) in 1993 and originally termed it CTLA-8 from their experiences on rodent hybridoma cDNA [1]. Later, other cytokines resembling it were discovered to form the IL-17 family, which comprises 6 members from its archetype IL-17 or IL-17A, to IL-17F. IL-17 is secreted mainly by T helper lymphocytes as a homodimer or a heterodimer, but secretion by other cells like neutrophils, TCR- $\gamma\delta$ lymphocytes, CD8+ T cells, natural killers and mast cells has also been reported [2]. The different isoforms of IL-17 have pleiotropic functions and signal through a ubiquitous transmembrane receptor, the IL-17R of which 5 subunits exists: IL-17RA, IL-17RB, IL-17RC, IL-17RD, IL-17RE. The importance of the Th17 axis has been extensively studied and demonstrated in chronic inflammatory disease of the skin or the joints. Antibodies directed against IL-17 or IL-17R is clinically effective and has shown therapeutic responses never seen before in psoriasis [3]. Besides, several studies have reported IL-17 and IL-17R to play roles in diverse cancer types though some results are conflicting [4]. Triple negative breast cancer (TNBC) is a very aggressive form of breast cancer (BC) characterized by a young age of patients, frequent relapse, and poor prognosis. Similarly as other cancer types, TNBC builds on inflammation in the tumour microenvironment to progress, grow and metastasize. Since they lack expression of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2), systemic treatments are limited to chemotherapy to which TNBC rapidly become resistant [5].

Therefore, IL-17 has been investigated in TNBC as a potential target for anti-cancer treatment and several studies have already highlighted its pro-tumoral functions.

Review Section

From patients' material, it is Zhu et al. [6] who initially reported the expression of IL-17 in human BC microenvironment. Though molecular type of tumour was not specified, most of the patients had grade III lesions. Eight out of 19 tumours had a strong staining for IL-17 positive cells, and this occurred in half of the grade III samples but none of the grade II. Inflammatory infiltrate was also more intense in higher-grade tumour. To note, no staining was detected on cancer cells themselves. The authors also assessed the impact of IL-17 on 4 BC cell lines (luminal A MCF-7 and T47D, and triple negative MDA-MB435 and MDA-MB231). Exposure to IL-17 provoked an increase of metalloproteinase (MMP)-dependant invasion of matrigel exclusively in TNBC cell lines though no direct impact on MMPs synthesis was observed [6]. Another study showed that in mice, IL-17 levels were raised in TNBC grafts and correlated with the stage of the disease. Besides, in this model, IL-17 infusion accelerated TNBC graft growth and angiogenesis as measured by microvascular volume density [7]. Concerning IL-17 signaling, in a first paper, our team reported ubiquitous presence of IL-17RA and RC in TNBC cell lines (BT20, MDA-MB468, MDA-MB157, and MDA-MB231). When exposed to IL-17A, 3 of the 4 studied TNBC cell lines showed an activation of ERK1/2 and ERK1/2-dependent resistance to docetaxel-induced

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cell death. As reported before, we also observed IL-17-promoting effects on TNBC cells migration and invasion on Boyden chambers assay [8]. In our following study, we detected that IL-17E similarly to IL-17A, promoted phosphorylation of ERK, Raf and p70S6 kinase [9]. IL-17E did not induce apoptosis but promoted resistance to docetaxel conversely to previous report by other authors [10]. Recently, we discovered that IL-17E and HER1 had crosstalk, probably through PYK-2, Src and STAT3 kinases activation. Besides, IL-17E-mediated IL-17RA/RB activation successfully resulted in pEGFR translocation to the nucleus, a known mechanism of resistance to anti-HER1 therapies [11]. Concerning the impact of IL-17B on TNBC, fixation on its receptor IL-17RB/RB induced nuclear factor- κ B (NF- κ B) pathway, which promoted BC cells tumorigenicity and resistance to chemotherapy [12]. In addition to direct effects on cancer cell signaling, IL-17 may have an indirect role by inducing tolerance in innate immune cells. The article by Coffelt et al. although not directly focused on TNBC, demonstrated that TCR- γ δ lymphocytes stimulated by IL-

1 β , produced IL-17, which induced neutrophils to suppress CD8+ T cells and thus allow tumour growth and distant metastases [13].

Conclusion

Since its discovery, investigation of the IL-17 family of cytokine has brought critical advances in the knowledge of inflammation and its related diseases. In breast cancers and particularly in its most feared form, triple negative breast cancer, pro-inflammatory cytokines are at the centre of the tumour development process. IL-17 family members and their associated receptors have been successfully detected in TNBC cells lines. Cell cultures as well as mice infusion with IL-17 has been reported to promote tumour growth, invasion, chemotherapy resistance, angiogenesis, to crosstalk with growth factor receptors and even to influence immune cells to tolerate cancer cells (Figure 1). These results argue in favour of the pursuit of further *in vivo* and *in vitro* studies to better understand the role of IL-17 in TNBC and propose it as a novel target for anti-cancer treatment.

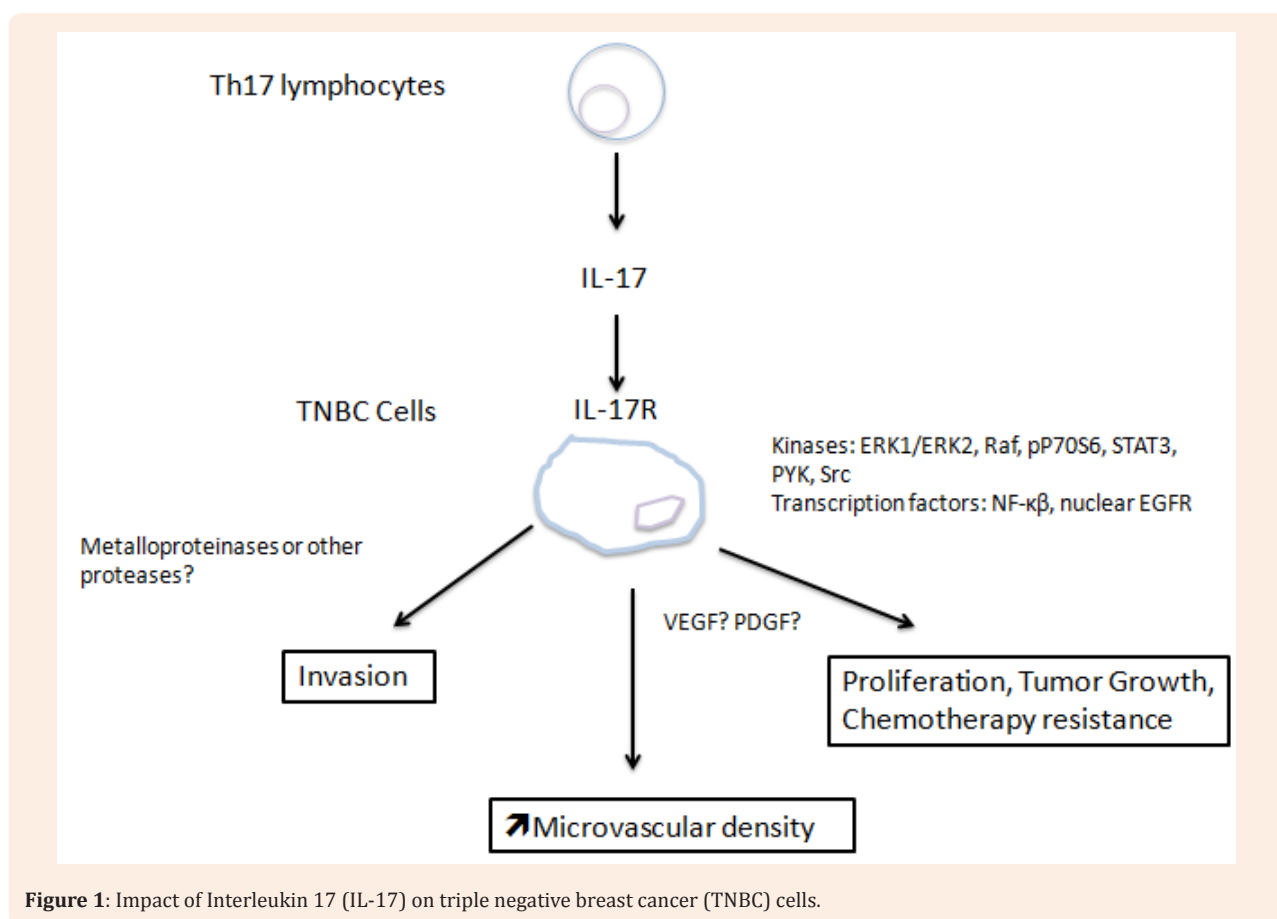


Figure 1: Impact of Interleukin 17 (IL-17) on triple negative breast cancer (TNBC) cells.

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