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Mini-review

The esophagitis to adenocarcinoma sequence; the role of inflammation

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ABSTRACT

Esophageal adenocarcinoma (EAC) is the eighth most common cancer worldwide, and approximately 15% of patients survive 5 years. Reflux disease (GERD) and Barrett's esophagus (BE) are major risk factors for the development of EAC, and epidemiologic studies highlight a strong association with obesity. The immune, inflammatory and intracellular signaling changes resulting from chronic inflammation of the esophageal squamous epithelium are increasingly well characterized. In GERD and Barrett's, an essential role for T-cells in the initiation of inflammation in the esophagus has been identified, and a balance between T-cell responses and phenotype may play an important role in disease progression. Obesity is a chronic low-grade inflammatory state, fueled by adipose tissue derived- inflammatory mediators such as IL-6, TNF-α and leptin, representing a novel area for targeted research. Additionally, reactive oxygen species (ROS) and receptor tyrosine kinase (RTK) activation may drive progression from esophagitis to EAC, and downstream signaling pathways employed by these molecules may be important. This review will explain the diverse range of mechanisms potentially driving and maintaining inflammation within the esophagus and explore both existing and future therapeutic strategies targeting the process.

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1. Introduction

1.1. The esophagitis to adenocarcinoma sequence

Barrett's esophagus (BE), characterized pathologically by specialized intestinal metaplasia (SIM), is a pre-malignant condition arising from chronic reflux disease (GERD) [1,2]. It is generally accepted that GERD, which results in chronic mucosal damage, develops as a result of a direct caustic injury to the luminal surface of the squamous epithelium, caused by the reflux of acidic gastric juices into the distal esophagus [3,4]. The damage to the surface cells is thought to stimulate a proliferative response in the underlying basal cells resulting in the characteristic basal cell hyperplasia [5]. An inflammatory response is also present with histological reports showing an inflammatory infiltrate in the squamous epithelium and chronic mucosal inflammation characterized by IL-8 release [6]. As with other chronic inflammatory conditions, esophagitis is associated with an increased risk of developing cancer- patients with esophagitis have a relative risk of 4.5 for developing EAC, this increases to 29.8 in patients who have progressed to BE [7]. It is therefore important to examine the factors driving this inflammation and to understand pathways at play, which may increase the risk of developing cancer. This may include examining the immune cells present at each stage and investigating how they promote tissue damage and drive inflammation along the progression. As such this review will focus on the role of T-cells in driving inflammation in the esophagus and the progression from esophagitis to EAC. Obesity has previously been shown to result in the establishment of a chronic low grade inflammatory environment and is known to increase the risk of BE and EAC [8]. The effect of adipose tissue derived inflammatory mediators such as IL-6, TNF-α and leptin in esophagitis, BE and EAC will be discussed, in addition to the related signaling pathways; receptor tyrosine kinases (RTK), NF-κB and STAT3 (Fig. 1). Furthermore, existing and future treatments targeting this pathological inflammation will also be discussed.

1.2. The role of T-cells in the progression from esophagitis to EAC

T-cells play an essential role in the initiation, maintenance and termination of the inflammatory response. However, their emerging role in the progression from esophagitis to EAC has become a recent focus. In a rat model of reflux disease, T cells were found to infiltrate the sub mucosal layers prior to any tissue damage and prior to any other immune cells, suggesting that these cells may play a key role in the initiation of the inflammatory response in esophagitis patients [9]. In humans, levels of the T-cell chemoattractant, RANTES are increased in esophagitis patients, allowing for the recruitment of T-cells [10]. T-cell function, as measured by PHA-induced blastogenesis, is significantly reduced in patients with esophagitis and BE [11], with BE patients showing a reduction

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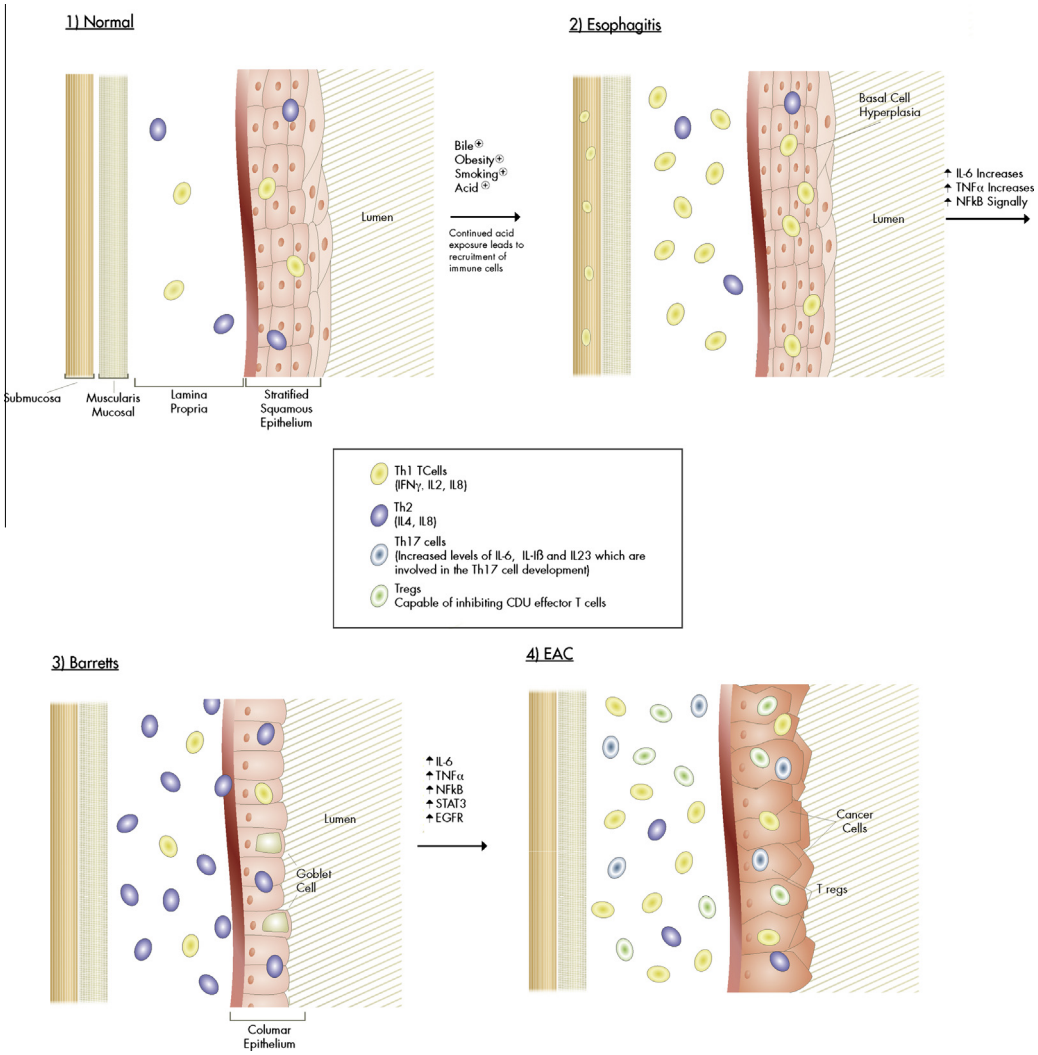

Fig. 1. The esophagitis to esophageal adenocarcinoma sequence. The continued exposure of the squamous epithelium to gastric acid and bile results in the production of inflammatory mediators such as IL-8 and IL-1β. This initiates the inflammatory response in the esophagus leading to lymphocyte recruitment and tissue damage. In esophagitis levels of IL-8, IL-1β and IFN-γ are increased indicating a pro-inflammatory response with Th1 cells predominating. The release of pro-inflammatory molecules such as IL-6, TNF-α and increased NFκB signaling are hypothesized to further drive the progression to BE, in which a predominantly humoral or Th2 response is seen. Continued increase in IL-6, TNF-α and NFκB, along with increased STAT3 and EGFR signaling are thought to promote the neoplastic conversion to EAC. Finally in EAC increased levels of Th1 cells are again seen along with increased Tregs which may dampen down the anti-tumor immune response thus providing a mechanism for immune evasion.

in systemic IL-2 production. As IL-2 is involved in clonal expansion of T-cells following activation, this suggests potential T cell dysfunction in BE [11]. However, further studies are required to elucidate the role of T cells and their function in disease progression.

$CD4^+$ T-cells can be further subdivided into subsets including Th1, Th2 and Th-17 depending on their cytokine profile. By producing IL-2, IFN-γ, and TNF-α, Th1 $CD4^+$ cells mediate tumor rejection and tissue destruction in part by driving the $CD8^+$ cytotoxic response [12]. Th2 $CD4^+$ cells produce IL-4, IL-6 and IL-10 facilitating a humoral response whilst suppressing cell-mediated immunity. The balance of these T cell responses has been suggested to play an important role in progression from oesophagitis to EAC. A recent paper by Souza et al. demonstrated that the epithelial layer was not directly damaged by the refluxed acid, but instead the acid triggered the production of chemokines and cytokines, including IL-8 and IL-1β, which mediated tissue damage [9]. In this study, reflux was induced in a rat model and at 3 days post-induction no damage to the surface epithelial cells was present, however basal cell hyperplasia was observed. Notably a lymphocytic infiltrate in the submucosa was detected by day 3 which increased in the lamina propria by week 1 and the epithelial layer only by week 3, suggesting that inflammation starts in the submucosa and progresses out towards the luminal surface. Furthermore they showed that exposure of squamous cells to acid and bile salts promote the secretion of the chemokine IL-8 and the cytokine IL-1β, which significantly enhance the rate of lymphocyte migration. This suggests that cytokine secretion by epithelial cells in response to acid exposure may initiate the inflammatory response, causing epithelial injury [9]. In humans, Fitzgerald et al. examined the cytokine profile and inflammatory cell infiltrate in both esophagitis and BE [1]. In esophagitis patients levels of IL-1β, IFN-γ and IL-8 were increased compared to controls, whereas Barrett's patients showed increased levels exclusively of IL-10 and IL-4. This suggests that while esophagitis is characterized by a pro-inflammatory cell-mediated cytokine profile, in Barrett's the predominant response appears to be an anti-inflammatory Th2 like response. This switch to a Th2 response has been proposed to drive the development of BE [13]. IL-4, which is increased in BE compared to esophagitis and normal esophageal

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