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REVIEW ARTICLE

Genetic factors in the pathogenesis of gastroesophageal reflux disease

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Abstract Multiple factors play a role in the pathogenesis of gastroesophageal reflux disease (GERD). Two landmark studies showing higher concordance of disease in monozygotic than dizygotic twin pairs suggested the role of host genetic factors in its pathogenesis. Recent studies have shown that genetic polymorphism in genes influencing host's inflammatory response, drug metabolism, cell cycle regulation, xenobiotic pathways, DNA repair, mutagenesis, esophageal sensory function and gene silencing are associated with risk of GERD and its sequelae—Barrett's esophagus and esophageal adenocarcinoma. However, more studies on larger sample size are needed before reaching a definite conclusion on the role of an individual gene.

Keywords Anti-inflammatory cytokine · DNA hypermethylation · DNA repair · microRNA · Pro-inflammatory cytokine · Proton pump inhibitors · Xenobiotic metabolism

Introduction

Gastroesophageal reflux disease (GERD) is common all over the world. Multiple factors, which include host physiological, genetic and environmental factors, play a role in pathogenesis of GERD [1–4]. Two landmark studies showing higher concordance of disease in monozygotic than dizygotic twin pairs suggested the role of host genetic factors in the pathogenesis of GERD [5, 6]. Recently, several studies reported association between host genetic factors and GERD and its sequelae—Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC). The genetic factors include (a) role of polymorphisms in several genes encoding for pro- and anti-inflammatory cytokines, DNA repair pathway proteins, enzymes involved in xenobiotic metabolism, and cell cycle regulatory proteins, (b) gene silencing by DNA hypermethylation, and (c) microRNAs (miRNA) in disease progression. Recent studies on host genetic factors in pathogenesis of several other functional gastrointestinal diseases such as dyspepsia and irritable bowel syndrome also suggest that these functional diseases of the gastrointestinal tract, including GERD, are multifactorial in origin, and genetic factors play an important role in their pathogenesis [7].

A PubMed search using the key words "gastroesophageal reflux disease AND genetic polymorphisms" (retrieved 84 articles), "gastroesophageal reflux disease AND host genetics" (retrieved 12 articles), "gastroesophageal reflux disease AND genetics" (retrieved 453 articles), and "Barrett's esophagus AND miRNA" (retrieved 9 articles) was done. This article reviews the major studies on genetic factor in pathogenesis of GERD based on the current literature.

Interleukin-1B in pathogenesis of GERD

Interleukin-1B (*IL-1B*) is a gene located on chromosome 2q14, encoding for a pro-inflammatory cytokine interleukin-1beta (IL-1β). *IL-1B* has two bi-allelic polymorphisms at −511 and −31 promoter region representing C/T and T/C transitions, respectively. Studies have shown that these two regions are in near complete linkage disequilibrium. Linkage

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disequilibrium results in presence of combinations of some specific alleles or genetic markers in a population than would be expected from a random formation of haplotypes from alleles based on their frequencies (Fig. 1). Some studies revealed that the presence of *IL-1B*-511 T allele or *IL-1B*-31 C allele (pro-inflammatory) is protective against the development of GERD [8–10]. However, a recent study from Taiwan revealed contradictory results and showed *IL-1B*-511 T/T and −31 C/C genotypes, and *IL-1B*-511 T and −31 C alleles were associated with an increased risk of reflux esophagitis; the odds ratios in this study were very low [11]. Presence of pro-inflammatory allele may result in increasing degree and extent of gastritis destroying HCl secreting parietal cells; this results in reduced gastric acid secretion and hence, reducing severity of GERD (Fig. 2). Furthermore, it has been shown that presence of *H. pylori* infection along with pro-inflammatory *IL-1B*−511 T allele has been associated with reduced risk of GERD by the induction of atrophy in the gastric corpus [9, 10].

IL-1RN in pathogenesis of GERD

IL-1RN gene, located on chromosome 2q14.2, encodes for a non-signaling molecule IL-1 receptor antagonist (IL-1Ra) which competes for the receptor binding with the functional IL-1. Hence, the balance between IL-1β and IL-1Ra influences the net inflammatory response in the tissues, which has an important role in many diseases such as gastric atrophy [12], and intestinal metaplasia [13]. *IL-1RN* shows an 86-bp variable number of tandem repeats polymorphism (VNTR). A tandem repeat is a short sequence of DNA that is repeated in a head-to-tail fashion at a specific chromosomal locus; each of these variants acts as an inherited allele (Fig. 3b). VNTR polymorphism is present in intron 2 of *IL-1RN* gene, which leads to presence of 5 different alleles, i.e., allele 1 (4 repeats), allele 2 (2 repeats), allele 3 (5 repeats), allele 4 (3 repeats), and allele 5 (6 repeats). Each individual will have any two of these alleles (as humans have diploid chromosomes). The 4-repeat (*IL-1RN**1) and 2-repeat (*IL-1RN**2) alleles are the most common in a given population, whereas the other alleles occur at a combined frequency of <5%. The presence of *IL-1RN**2 has been associated with high IL-1Ra and low IL-1β release [14, 15]. Though initial studies showed that *IL1RN**2 alleles is protective against GERD among patients with *H. pylori* infection [8], a subsequent study suggested that in the presence of *H. pylori* infection, *IL-1B*-511*T/*IL-1RN**1 haplotype is protective against development of GERD [10]. A haplotype is a set of combination of alleles at more than one locus which is inherited by an individual from one of his parents and not easily separable by recombination (Fig. 3c).

COX-2 and risk of GERD

Cyclooxygenase-2 (*COX-2*) gene is located at 1q25.2-q25.3 and encodes COX-2 protein, which is the key enzyme in prostaglandin biosynthesis; it acts both as a di-oxygenase and peroxidase. It is involved in inflammation and mitogenesis. The *COX-2* 8473 T>C polymorphism in the 3′ untranslated region is associated with altered COX-2 expression in a murine model [16]. The only study

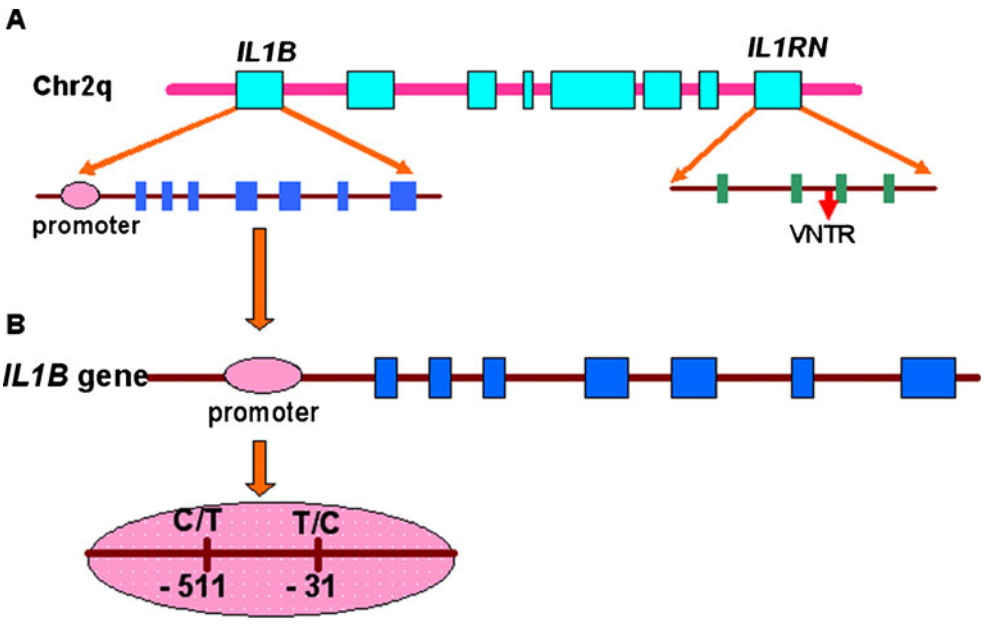

Fig. 1 As these two loci (−511 and −31) of *IL-1B* promoter region are very near to each other, there is very little chance of recombination/cross over occurring between them. Hence, they are said to be in near complete linkage disequilibrium i.e. if an individual has *IL1B*-511 C allele, he is expected to have *IL1B*-31 T allele and vice-versa

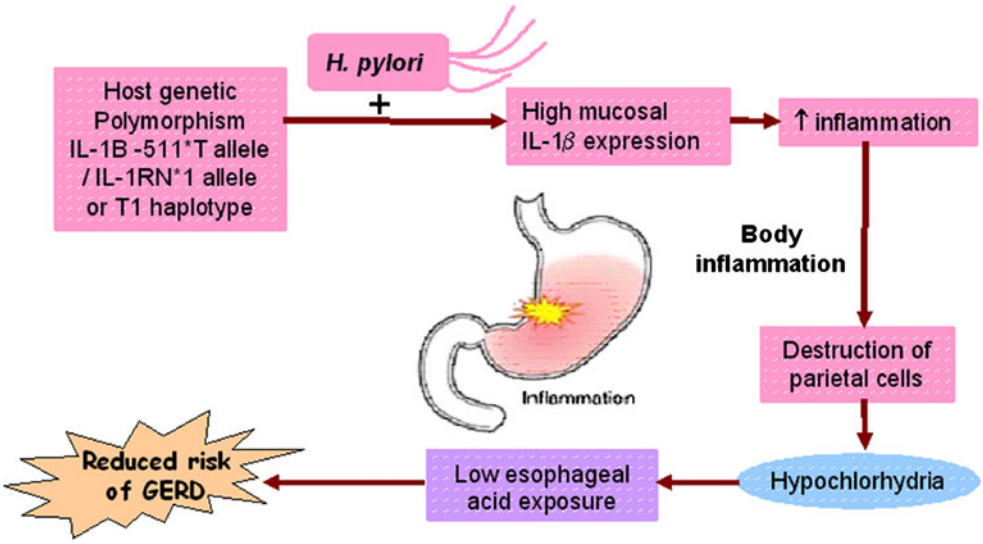

Fig. 2 Presence of pro-inflammatory allele (IL-1B-511*T and IL-1RN*1) may result in increasing degree and extent of gastritis destroying HCl secreting parietal cells; this results in reduced gastric acid secretion decreasing severity of gastroesophageal reflux disease

available on the role of this polymorphism in GERD and its sequelae showed that presence of *COX-2* 8473 C allele (variant) might predispose an individual to EAC but was not associated with risk of its precursor conditions BE or GERD [17]. *COX-2* also exhibits two polymorphisms in the promoter region i.e. at -765 C/G and -1195A/G. Increased COX-2 expression and enzyme activity is linked to the COX-2 CA haplotype. A single study has shown that COX-2 CA-haplotype is more frequently observed in patients with EAC than in patients with BE and GERD [18]. Hence, it could be possible that neoplastic progression (development of EAC) in patients with BE and reflux esophagitis be influenced by COX-2 activity.

IL-10 and risk of GERD

Interleukin-10 is an anti-inflammatory cytokine, encoded by gene *IL-10,* located at 1q31-q32 in humans. Polymorphism at -1082A>G variant genotype (high *IL-10* secretor) of *IL-10* is associated with BE and EAC than GERD [19]. A later study showed that presence of *IL-10* -1082 variant

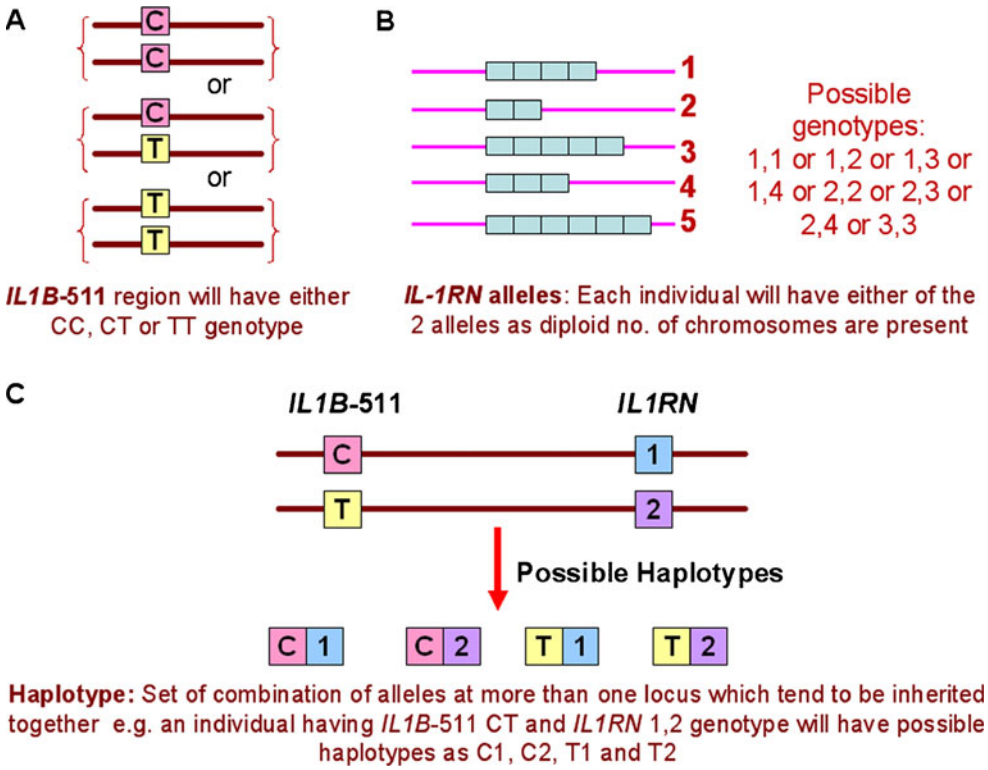

Fig. 3 a, b shows possible alleles and their combinations among *IL-1B*-511 and *IL-1RN* VNTR polymorphisms. **c** shows an example where an individual having *IL-1B*-511 CT genotype and *IL-1RN* 1, 2 genotype will have possible haplotype combinations as C1, C2, T1 and T2

genotype in association with *IL-12B* +1188A>C variant allele (pro-inflammatory; high IL-12p70 secretor) was associated with reduced risk of BE [20]. This study also showed that a combination of the *IL-12B* AA genotype and the *IL-10* AA or AG genotypes was associated with reflux esophagitis [20].

CYP2C19 and response to proton pump inhibitors

Proton pump inhibitors (PPIs) are the most potent drugs currently available for suppressing gastric acid secretion. However, response to this drug may be altered by its metabolism by the host. Variation in the host's genetic make-up may influence variation in its metabolism with consequent difference in response. Cytochrome P450 2 C19 (*CYP2C19*), a member of the cytochrome P450 mixed-function oxidase system, is involved in the metabolism of several drugs including PPIs. The genotypes of *CYP2C19* are classified into three groups: homozygous extensive metabolizer (homEM), heterozygous extensive metabolizer (hetEM), and poor metabolizer (PM). PPI-induced healing rates in GERD are apparently higher in PM/hetEM than in homEM. Metabolism of some PPIs such as omeprazole and lansoprazole depends on *CYP2C19* genotypes [21, 22]. On the other hand, rabeprazole does not undergo hepatic biotransformation by *CYP2C19*, thus offering significant advantages over the other PPIs due to its more efficacy [23, 24].

GST and risk of GERD

Glutathione-S-transferases (GSTs) are the most important phase II enzymes of the xenobiotic pathway. These enzymes catalyze the conjugation of potentially mutagenic electrophilic compounds, with nucleophilic glutathione yielding less toxic and more water-soluble compounds. Human GSTs can be divided into five main classes of enzymes: alpha, mu, pi, theta, and zeta. Of these, *GSTP1* (located on 11q13), *GSTT1* (on 22q11.23), and *GSTM1* (on 1p13.3) exhibit genetic polymorphisms that may lead to altered enzyme activity, which has been associated with many diseases [25–27]. *GSTP1* exhibits a polymorphism within its coding region (A to G transition at nucleotide +313, thus changing codon 104 from ATC [Ile] to GTC [Val]), which leads to decreased enzyme activity [28]. Both *GSTT1* and *GSTM1* genes exhibit null or deletion polymorphisms. Individuals homozygous for the null allele lack GST enzyme activity and hence may not be able to detoxify the chemicals [29, 30]. However, *GSTT1* and *GSTM1* polymorphisms may not be associated with risk of GERD, though *GSTP1* b allele was associated with susceptibility to GERD [31], especially to BE [32].

DNA repair genes and risk of GERD

Genetic polymorphisms in genes encoding for proteins in DNA repair pathways such as Nucleotide Excision Repair genes, *XPC* (xeroderma pigmentosum complementation group C, located on 3p25) and *XPD* (xeroderma pigmentosum complementation group D, located on 19q13.3), base excision repair gene, *XRCC1* (x-ray repair complementing defective repair in Chinese hamster cells 1, positioned at 19q13.2) have been shown to be altered in various diseases, and lead to defective DNA repair mechanisms.

A preliminary study on the role of DNA repair genes suggested that patients with GERD and BE had reduced frequencies of *XRCC1* Arg399Gln (G28152T) homozygous variant genotype than the asymptomatic controls [33]. The same study also showed that patients with EAC possess a significantly higher frequency of the *XPC* PAT [poly (AT) insertion/deletion polymorphism within intron 9] homozygous variant genotype and reduced frequencies for the *XPD* Lys751Gln (A35931C) homozygous variant genotype compared with asymptomatic controls [33]. However, later studies found that presence of *XPD* Lys751Gln variant genotypes were associated with more than two folds higher risk of developing EAC than the wild type [34, 35]. Large population-based studies are needed for deciphering the role of these DNA repair genes in pathogenesis of GERD and its sequel.

CCND1 gene and risk of GERD

CCND1 gene is positioned at 11q13 in humans; it encodes for Cyclin D1, a major cell cycle regulatory protein. This cyclin forms a complex with cyclin-dependent kinases (CDKs, a family of protein kinases) and functions as a regulatory subunit of CDK4 or CDK6, whose activity is required for cell cycle G1/S transition. It exhibits a polymorphism in exon 4 at G870A. Presence of A/A genotype has been associated with increased risk for GERD, BE, and EAC [36].

Epidermal growth factor (EGF) and risk of GERD

EGF gene is located at 4q25. The 53-aminoacid EGF peptide acts a potent mitogenic factor by binding the high affinity receptor at the cell surface. Two studies have suggested a possible role of *EGF* A61G polymorphism in susceptibility to EAC, which is known to result from BE. The homozygous G/G variant genotype of *EGF* A61G was associated with the greatest risk of EAC [37], especially among those with either severe or long-standing GERD [38]. However, this study has to be replicated in other populations.

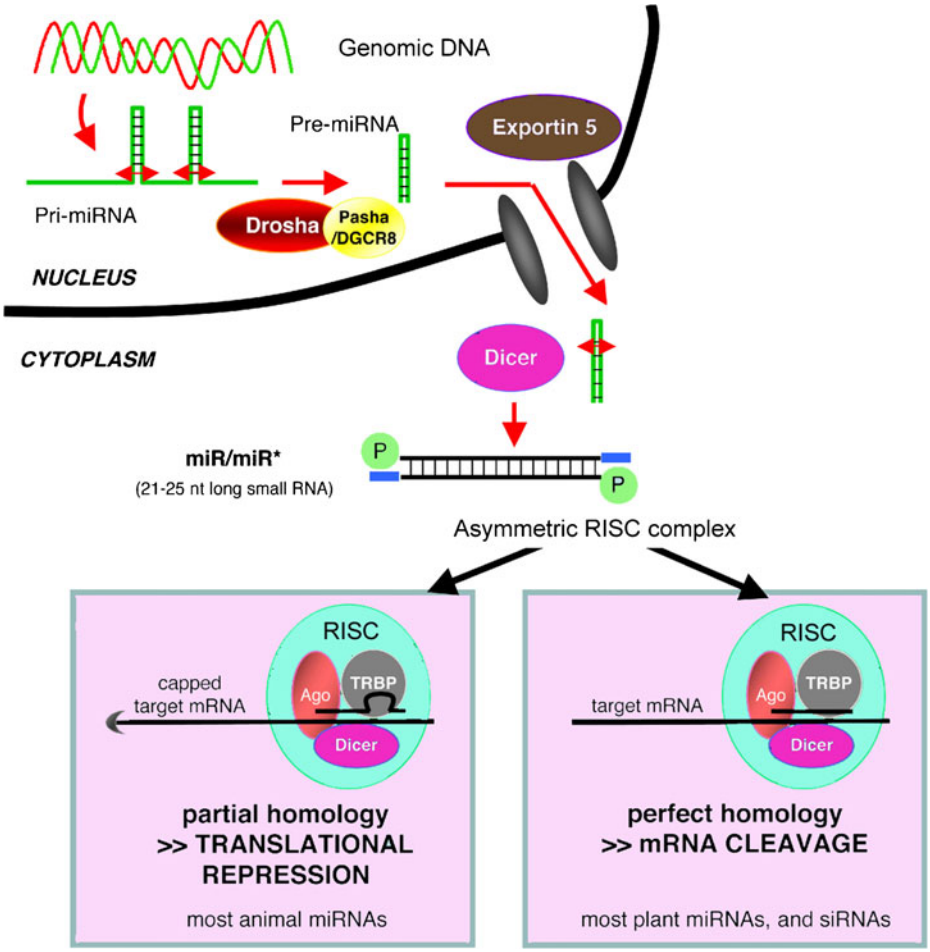

Fig. 4 Biogenesis of micro-RNA from host DNA: it begins with primary miRNAs (pri-miRs, inactive form), which are either transcribed by RNA polymerase II or are excised as portions of introns. Pri-miRs are processed in the nucleus by Drosha ribonuclease and the resultant precursor-miRNA (pre-miR) is then exported to the cytoplasm. In the cytoplasm, Dicer ribonuclease processes the pre-miR and a single RNA strand is transferred to an argonaute protein and TRBP within the RNA-induced silencing complex (RISC). The mature (active) miRNA-RISC complex targets complementary mRNA transcripts to repress translation. miRNA bind to the 3′UTR of target mRNAs through base pairing, resulting in target mRNAs cleavage or translation inhibition

GNB3 and risk of GERD

Guanine nucleotide binding protein (G protein), beta polypeptide 3 (GNB3), a gene located at 12p13 encodes for the beta subunit of G-protein. Beta subunits are important regulators of alpha subunits, as well as of certain signal transduction receptors and effectors. G-proteins mediate the response to acid, neurotransmitters and humoral factors modulating esophageal sensory function. Patients with GERD may have normal esophageal acid exposure, but their esophageal mucosa may be more sensitive to acid reflux, leading to heartburn and erosive esophagitis due to visceral neural pathway dysfunction [4, 39, 40]. A recent study revealed the role of host genetic polymorphism of GNB3 C825T in the enhanced perception of reflux events [41].

hMLH1 gene silencing and risk of GERD

hMLH1 is a human homolog of the *E. coli* DNA mismatch repair gene mutL. This gene is located at 3p21.3 in humans. MLH1 has no known enzymatic activity of its own. hMLH1 forms a heterodimer with other DNA repair

Table 1 Role of miRNAs in pathogenesis of sequelae of gastroesophageal reflux disease

miRNA	Role in BE and EAC	Suggested mechanism
miR-21 [47, 54]	Up regulated in BE and EAC	Targets other tumor suppressor genes
miR-143 [48, 53]	Down regulated in EAC	Altered cell's ability to direct the appropriate apoptotic responses
miR- 145 [48, 53]	Down regulated in EAC	Altered cell's ability to direct the appropriate apoptotic responses
miR-194 [49, 53]	Up regulated in BE and EAC	May be involved in intestinal epithelial cell differentiation
miR-196a [50]	Elevated levels in EAC, BE	Growth-promoting and anti-apoptotic functions
miR-203 [47]	Reduced in cancer tissue of EAC and not in SCC	Different mechanism of pathogenesis in EAC and SCC
miR-215 [51–53]	Down regulated in EAC	Reduced ability of cells to regulate proliferation

BE Barrett's esophagus, *EAC* esophageal adenocarcinoma, *SCC* squamous cell carcinoma

proteins which is responsible for the recruitment of the proteins needed for the excision and repair synthesis. Promoter hypermethylation has been suggested as the main cause of hMLH1 silencing. One study showed that patients with GERD had a higher degree of hMLH1 hypermethylation (88.8%) in the local tissue than in blood DNA, indicating that local environment due to reflux may promote hypermethylation [42].

miRNAs in BE and EAC

miRNAs are approximately 21 nucleotide long, non-coding segments of RNA that regulate gene expression. miRNA biogenesis begins with primary miRNAs (pri-miRs, inactive form), which are either transcribed by RNA polymerase II or are excised as portions of introns [43, 44]. Pri-miRs are processed in the nucleus by Drosha ribonuclease and the resultant precursor-miRNA (pre-miR) is then exported to the cytoplasm [45]. In the cytoplasm, Dicer ribonuclease processes the pre-miR and a single RNA strand is transferred to an argonaute protein and TRBP (human immunodeficiency virus [HIV-1] transactivating response [TAR] RNA-binding protein) within the RNA-induced silencing complex (RISC). The active miRNA-RISC complex targets complementary mRNA transcripts to repress translation [43, 46]. miRNA binds to the 3′ UTR (untranslated region) of target mRNAs through base pairing, resulting in target mRNAs cleavage or translation inhibition (Fig. 4). It is estimated that 1–4% genes in the human genome are miRNAs and a single miRNA can regulate as many as 200 mRNAs. Increasing evidences suggest that miRNAs play critical roles in many key biological processes, such as cell growth, tissue differentiation, cell proliferation, embryonic development, and apoptosis.

Several recent studies have documented the role of miR-21, miR-143, miR-145, miR-194, miR-203, miR-205 and miR-215 in BE and EAC [47–54] (Table 1). However, there is lack of studies on the role of miRNAs in the pathogenesis of GERD. Hence, there is a need for studies for evaluating the role of various miRNAs in progression of the GERD>BE>EAC pathway. Recently, it has been shown that genetic polymorphisms in miRNA encoding genes and miRNA binding sites (3′ UTR of genes) may have a role in the disease [55–59].

Insulin-like growth factor gene polymorphism and esophagitis

Reflux esophagitis and BE are risk factors for EAC. Insulin-like growth factor (IGF) axis plays a key role in cell development, proliferation and survival, and is implicated in the etiology of several malignancies. However, data on polymorphism in IGF axis gene on risk of esophagitis and EAC are scanty. A recent study [60] found a significant association of polymorphisms of two SNPs namely, IGF1 (rs6214) and growth hormone (GH) receptor (rs6898743) and a microsatellite repeat *IGF-1* $(CA)_{17}$ allele with disease status. Precisely, IGF1 SNP was associated with BE, GH receptor SNP was associated with EAC, and presence of IGF1 $(CA)_{17}$ 185-bp allele was associated with RE. This study suggested that the three polymorphisms of IGF genes were associated with EAC and its precursors [60]. However, this is a preliminary observation and has to be validated with further studies.

Conclusion and future directions

This review is aimed to focus on the role of various host genetic factors in the pathogenesis of GERD and its complications. These studies have to be replicated in different populations for interpreting the mechanism of pathogenesis of the disease. Studies related to gene silencing and miRNAs have been performed predominantly in patients GERD sequelae (BE and EAC) rather than in those with GERD. Future studies should explore the mechanism of gene alteration/mRNA alteration targeting the disease progression from healthy state GERD>BE>EAC.

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