Long noncoding RNAs: novel links to inflammatory bowel disease?

Editorial Focus

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Inflammatory bowel diseases (IBDs), comprising ulcerative colitis and Crohn’s disease, are still largely idiopathic in nature. With the global incidence of these conditions on the rise, there is a pressing need to increase our understanding of their etiology and to develop improved therapeutic regimes. To this end, meta analyses of multiple genome-wide association studies have identified 163 genetic loci that are linked to the pathology of IBD(4). A surprising proportion of these loci are associated with regions of the genome that do not produce protein. Historically, these “non-coding” regions were thought to be extraneous and non-functional. However, they are now receiving increased appreciation for their roles as regulators of gene expression by diverse mechanisms. Thus, the single nucleotide polymorphisms (SNPs) identified as IBD risk loci may promote disease by altering these regulatory functions.

Among the non-coding elements are microRNAs (~22 nucleotides) and long non-coding RNAs (lncRNAs) (>200 nucleotides). Dysregulation of lncRNAs is broadly associated with inflammatory conditions. PCA3 is one of the first lncRNAs to be approved by the Food & Drug Administration as a biomarker for prostate cancer. Another excellent example is lnc13, which is significantly decreased in the small intestine of patients with Celiac disease (CeD) (1). Lnc13 is found in close proximity to the risk locus for CeD and normally represses the expression of key inflammatory mediators by binding to heterogeneous nuclear ribonucleoproteins. In CeD, lnc13 is thought to be degraded by a NF-κB-dependent mechanism, leading to greater expression of these genes by macrophages and exacerbated inflammation. Intervention of this pathway may therefore lead to new opportunities for therapeutic intervention in CeD.

While the pathological roles of microRNAs have been widely explored in IBD (reviewed in references 2 & 5), only a few studies have focused on the potential contribution of lncRNAs(6, 9). In the current issue, a study by Padua and colleagues reveals a novel lncRNA signature that is unique to patients with active UC compared to those with inactive disease and control patients. 767 lncRNAs were differentially expressed (either upregulated or suppressed), and of these, 31 were found to be within 250 base pairs of the IBD susceptibility loci. One of the most significant hits was interferon gamma antisense RNA 1 (IFNG-AS1). This lncRNA was previously identified as being significantly upregulated in IBD patients by Mirza and colleagues(6), though it was not investigated further. Padua and colleagues used qRT-PCR to confirm that IFNG-AS1 is significantly upregulated in the colon of UC patients. Expression of the mouse ortholog ifng-as1 was also shown to be increased in two independent mouse models of IBD (TNBS and IL10−/−). Intriguingly, IFNG-AS1 levels in patient colons positively correlated with the expression...
of several inflammatory cytokines, including interferon gamma (IFNG), IL-1, IL-6, and TNF-alpha.

IFNG-AS1 (also known at TMEVPG1 and NeST) has previously been linked with IFNG regulatory functions in Hashimoto’s thyroiditis(7) and Sjögren syndrome (8). Using a series of in vivo mouse models, Gomez et al. demonstrated a crucial role for T cell-derived ifng-as1 in the host response to pathogens such as Theiler’s murine encephalomyelitis virus and Salmonella typhimurium (3). Ifng-as1 can alter the methylation of histone 3 in the ifng locus, suggesting that it regulates IFNG gene expression epigenetically. Using both knockdown and overexpression approaches, the current study provides confirmation that, like mouse ifng-as1, human IFNG-AS1 can positively regulate IFNG production by CD4+ T cells.

From this study and others, it is clear that IFNG-AS1 is an emerging biomarker for inflammatory diseases, including IBD. While its direct role in the pathophysiology of IBD has yet to be shown, its positive regulation of IFNG, a key driver of inflammation, suggests that it is highly likely to play contributing roles. The involvement of IFNG-AS1 in the host response to microbes may be pivotal in IBD, which is at least partially driven by a compromised response to commensal gut bacteria. Functional studies in mouse models of IBD are warranted and could progress quickly given the availability of knockout and transgenic animals(3). If causative roles for IFNG-AS1 are identified, this IncRNA may represent a novel target for therapeutic intervention.

In addition to IFNG-AS1, this study has also uncovered many other IncRNAs that are dysregulated in UC. This list has exciting potential, as further validation may lead to the identification of a host of new biomarkers and therapeutic avenues for the diagnosis and treatment of IBD.

REFERENCES


