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Review article

Research progress on the biological basis of Traditional Chinese Medicine syndromes of gastrointestinal cancers

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ABSTRACT

Gastrointestinal cancers account for 11.6 % of all cancers, and are the second most frequently diagnosed type of cancer worldwide. Traditional Chinese medicine (TCM), together with Western medicine or alone, has unique advantages for the prevention and treatment of cancers, including gastrointestinal cancers. Syndrome differentiation and treatment are basic characteristics of the theoretical system of TCM. TCM syndromes are the result of the differentiation of the syndrome and the basis of treatment. Genomics, transcriptomics, proteomics, metabolomics, intestinal microbiota, and serology, generated around the central law, are used to study the biological basis of TCM syndromes in gastrointestinal cancers. This review summarizes current research on the biological basis of TCM syndrome in gastrointestinal cancers and provides useful references for future research on TCM syndrome in gastrointestinal cancers.

1. Introduction

Gastrointestinal cancers account for 11.6 % of all cancers, and are the second most frequently diagnosed cancers worldwide [1]. Gastric cancer (GC) was responsible for over 1 million new cases in 2020 and an estimated 769,000 deaths (equating to one in every 13 deaths globally), ranking fifth in incidence and fourth in mortality [1]. Colorectal cancer (CRC) was responsible for more than 1.9 million new cases and 935,000 deaths in 2020, representing approximately one in 10 cancer cases and deaths [1]. The incidence of gastrointestinal cancers increases annually [2], especially in China [3,4]. Prevention and treatment of gastrointestinal cancers is crucial, as they threaten the lives and health of patients [5].

Traditional Chinese medicine (TCM) combined with Western medicine [6] or alone [7], has unique advantages for the prevention and treatment of cancer [8], including gastrointestinal cancers. Chinese patients tend to seek TCM treatment [9], which can alleviate clinical symptoms, prolong survival, and reduce the adverse effects of conventional therapy [10]. Syndrome differentiation and treatment are the basic characteristics of theoretical TCM systems [11]. Zheng, short for zhenghou (TCM syndrome) in Chinese, is the

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generalization of pathophysiological changes, reactions, and conditions at a certain stage that are the result of syndrome differentiation and the basis of treatment. Treating the same disease using different methods and homotherapy for heteropathy are guided by treatments based on syndrome differentiation. This is similar to precise treatment in modern medicine. For example, the Food and Drug Administration has approved the use of pabolizumab in solid tumors of microsatellite instability/deficient mismatch repair, regardless of its origin [12], which is a typical example of " homotherapy for heteropathy." Thus, the biological basis of TCM syndromes warrants further study.

The central dogma of molecular biology [13], first proposed by Francis Crick, indicates that the direction of genetic information flow is from DNA-RNA-protein, i.e., to complete the process of transcription and translation of genetic information. It can also be transferred from DNA-DNA, i.e., to complete the DNA replication process (Fig. 1). Genomics [14], transcriptomics [15], proteomics [16], metabolomics [17], and serology [18], generated around the central law are used to study the biological basis of TCM syndromes in gastrointestinal cancers.

This review summarizes the current research progress on the biological basis of TCM syndromes of gastrointestinal cancers, to provide some useful references for their future research.

2. The relationship between TCM syndromes of gastrointestinal cancers and genomics

Genes form the material basis for heredity [19]. The occurrence and development of gastrointestinal cancers are related to changes in certain genes. Some are proto-oncogenes, such as *CDH1* [20], *NTHL1* [21–23], *CTNNA1* [24,25], *BRCA2* [25,26], *STK11* [25,27], *SDHB* [25], *PRSS1* [25], *ATM* [25], *MSR1* [25], *PALB2* [25], *MLH1* [27–31], *MLH3* [28], *MSH1* [32], *MSH2* [27–31], *MSH3* [21], *MSH6* [27–31,33], *PMS2* [27,28,30], MMR-D [34], *TGFβ1*-RII [34], *IGFIIR* [34], *hMSH3* [34], *hMSH6* [34], *BAX* [34], *Dzip1L* [35], *Pcolce2* [35], *Igsf10* [35], *Sucnr1* [35], *Or13C8* [35], *Epb41L4B* [35], Sec*16A* [35], *Notch1* [35], *Tas2R7* [35], *Sf3A1* [35], *Gal3St1* [35], *Triobp* [35], *TP53* [36–38], *EPCAM* [28,30], *TGFBR2* [28], *FBXO11* [28], *PRSS58* [28], *MUTYH* [27,30,39], *SMAD4* [27,40], *BMPR1A* [26,27], *PTEN* [27], *KRAS* [26], *BRAF* [26,41,42], *PPAP* [21], *NAD* [21], *NUDT1* [39], *ERCC2* [39], *SEMA4* [26], *NTS* [26], *RASSF9* [26], *GALNT12* [26], *RPS20* [26], *PMS1* [31], *PMS2* [31], *MYH* [33], *GAPDH* [43], *ADIPOQ* [44], and *SERPING1* [45]. Some of these are anti-oncogenes, such as *APC* [26,27], *HNA*-2 [46], *AXIN1* [47], *AXIN2* [47], and *HINT1* [48]. Some genes have a dual effect and can promote or inhibit the apoptosis of tumor cells, such *asTNFRSF1A* (TNFR superfamily 1A) [49].

Several studies on the relationship between TCM syndromes of gastrointestinal cancers and genomics have been conducted. A hospital-based population of 387 patients with GC showed significant differences in rs13689 genotype distributions among several pairs of TCM syndrome types of GC, although none of the four single nucleotide polymorphisms (SNPs) in the *CDH1* showed significant differences [50]. Zhang et al. [51] investigated 29 SNPs in EGF, TGFA, and EGFR and found that two SNPs, rs11466285 in TGFA and rs884225 in EGFR, were significantly associated with the distribution of TCM syndromes. The rs11466285 TT genotype increases the risk of damp heat with toxin (DHT) and deficiency of both *Qi* and *yin* (DQY) compared to obstruction of blood stasis (OBS) [51]. The rs884225 AA genotype can increase the risk of DQY and deficiency of both *Qi* and blood (DQB) compared with *yin* deficiency due to stomach heat (YDSH) [51]. Parallel comparison among the SNPs and syndrome types reveals that DQB is distinct from YDSH, disharmony between the liver and stomach, stagnation of phlegm muddiness (SPM), OBS, and other syndromes at several SNP loci [51]. *ELF3*, *KRT8*, *KRT18*, *KRT19*, *FN1*, *SERPINE1*, *TCF4* and *ZEB1* in Excess and Deficiency syndrome classification in CRC after detecting 662 cells isolated from 11 primary CRC tumors were divided into 14 different cell clusters [52].

Therefore, the TCM syndrome of gastrointestinal cancers is related to changes in *CDH1*, *EGF*, *TGFA*, *EGFR*, *MUC2*, *REG4*, *COL1A2*, *POSTN*, *SDPR*, *GPX1*, *ELF3*, *KRT8*, *KRT18*, *KRT19*, *FN1*, *SERPINE1*, *TCF4*, and *ZEB* (Table 1).

3. The relationship between TCM syndromes of gastrointestinal cancers and transcriptomics

Genetic information is transferred from DNA to RNA to complete its transcription [19]. The occurrence and development of gastrointestinal cancers are related to expression changes of MLH1 methylation [42], MicroRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA). Some miRNAs, lncRNAs, and circRNAs also act as competing endogenous RNA (ceRNA) [53,54]. Some have cancer-promoting effects, such as miR-27 [55], hsa-miR-29b-3p [56], miR-107 [57], miR-133a [58], miR-133b [59], miR-155-5p [60], miR-342-5p [61], Linc00284 [55], lncRNA PCAT1 [62], LINC01537 [63], LINC00857 [64], DUSP5P1 lncRNA [65], lncRNA LVBU [66], circ-133 [58], circ EZH2 [59], circ ALG1 [61], circ CEA [67], circ RID1A [68], has circ 0000437 [69], and circ CAPRIN1 [70]. Some miRNAs have anticancer effects, such as miR-155 [71], miR-21 [71], miR-30b [72], miR-34a [73], miR-181a-5p [74], miR-326 [75], miR-329-3p [62], miR-330-5p [75], lncRNA LIFR-AS1 [56], circ METTL3 [57], circ PPFIA1 [60], has-circ 0072309 (circ LIFR) [76].

Several studies on the relationship between TCM syndromes of gastrointestinal cancers and transcriptomics have been conducted.

Fig. 1. The central dogma of molecular biology.

Table 1
Researches on the relationship between TCM syndrome of gastrointestinal neoplasms and genomics.

TCM syndrome	Genomics	Time	Reference
spleen-stomach weakness (SSW), Yin deficiency due to stomach heat (YDSH), deficiency of both Qi and blood (DQB), obstruction of blood stasis (OBS)	SNP rs13689 (genotype TT and TC/CC) in CDH1	2013	[50]
damp heat with toxin (DHT), deficiency of both Qi and yin (DQY)	Te rs11466285 (TT genotype) in TGFA	2013	[51]
deficiency of both Qi and yin (DQY), deficiency of both Qi and blood (DQB)	Te rs884225 (AA genotype) in EGFR	2013	[51]
Excess, Deficiency and Deficiency-Excess syndromes	ELF3, KRT8, KRT18, KRT19, FN1, SERPINE1, TCF4 and ZEB1	2021	[52]

There is a correlation between the methylation rates of the c-myc and p16 genes and TCM syndrome types [77]. DNA methylation controls gene expression to a certain extent. The C allele at the miR-27a rs895819 locus may be an oncogene in GC related to TCM syndromes [78]. There is currently little research on the relationship between TCM syndromes of gastrointestinal cancers and the available mRNA.

Thus, TCM syndrome in gastrointestinal cancers is related to changes in the methylation rate of c-myc and p16 genes, and miR-27a rs895819 (Table 2).

4. The relationship between TCM syndrome of gastrointestinal cancers and proteomics

Genetic information is transferred from RNA to proteins to complete its translation [19]. The occurrence and development of gastrointestinal cancers are related to changes in the expression of certain proteins. Some have cancer-promoting effects, such as VEGF [69,79], c-Met [55], IGF2BP2 [59], HuR [60], PGF [61],Netrin-1 [62], CD146 [62], RIPK4 [63], ANXA11 [64], DUSP5P1 [65], p53 [67], CDK1 [67], IGF2BP3 [68], ACC1 [70], GEF-H1 [80], RhoA [80], KNG1 [81], AMBP [82,83], and FNDC3B [84]. Some of these have anticancer effects, including RUNX3 [57], PER3 [57], CDX1 [60], and TCL1A [74].

Several studies on the relationship between TCM syndromes of gastrointestinal cancers and proteomics have been conducted. In 100 cases of GC E-cad expression, the difference in E-cad expression is significant between the different syndrome differentiation types in TCM, and there is a significant difference in E-cad expression between the stagnation of the phlegm-damp type, the deficiency in both *Qi* and blood, and the deficiency-cold of stomach and spleen types, where E-cad expression was high [85]. Chen et al. [86] showed that the levels of VEGF expression in various syndrome types are significantly different. The highest expression shows in the phlegm-stasis-poisons stagnant type, the second in the Gan-Wei disharmony type, and the lowest in the Pi-Wei asthenia type. Comparison among these show significant differences after detecting 104 specimens of patients with GC. KNG1, AMBP, and SERPING1 are all differentially expressed in patients with both CRC and Yin deficiency of liver-kidney syndrome (YDLKS) and are closely associated with complement and coagulation cascade pathways [87]. C7 and SERPING1 independently have potential diagnostic value in distinguishing YDLKS from no obvious TCM syndromes (NS) in CRC, providing evidence for the material basis of "same TCM syndrome in different diseases" [87].

Thus, the TCM syndromes of gastrointestinal cancers are related to changes in VEGF, KNG1, AMBP, SERPING1, C7, and SERPING1 (Table 3).

5. The relationship between TCM syndromes of gastrointestinal cancers and metabolomics

The occurrence and development of gastrointestinal cancers are related to changes in the expression of some metabolites [17], such as tryptophan [88], bile acid [88], choline metabolism [88], leucylalanine [89], serotonin [89], imidazole propionate [89], perfluorooctane sulfonate [89], glutamine [64], lipid metabolism [70], cholesterol [90], and urea [66].

Several studies on the relationship between TCM syndromes of gastrointestinal cancers and metabolomics have been conducted. L-alanine, 1, 2-ethanediamine, urea, glycerol, glycine, aminomalonic acid, creatinine, and palmitic acid are exclusively altered in dampness and heat syndrome (DHS), whereas D-tryptophan is specifically altered in Spleen deficiency syndrome (SDS), and L-proline, 1, 2, 3-propanetricarboxylic acid, D-galactose, and 2-indolecarboxylic acids are specifically altered in liver and kidney Yin deficiency syndrome [91]. Researchers investigate the difference in metabolic profiles of serum by comparing patients with CRC with Non deficiency (ND), Qi deficiency (QD), and Yin deficiency (YD) [92]. The conversion obstruction of carbohydrates, fatty acids, and amino acids occurs in patients with QD and YD compared with ND. This demonstrates that patients with CRC and QD or YD are associated with metabolic disorders, and the variations of serum metabolic profiles may serve as potential biochemical markers for the diagnosis and prognosis of these patients [92].

Thus, TCM syndromes of gastrointestinal cancers are related to changes in metabolites such as L-alanine, 1, 2-ethanediamine, urea,

Table 2
Researches on the relationship between TCM syndrome of gastrointestinal neoplasms and transcriptomics.

TCM syndrome	Transcriptomics	Time	Reference
liver–stomach disharmony, deficiency of Qi and blood, deficiency of cold in spleen and stomach	the methylation rate of c-myc and p16 genes	2018	[77]
syndrome of spleen-qi deficiency	miR-27a	2022	[78]

Table 3
Researches on the relationship between TCM syndrome of gastrointestinal neoplasms and proteomics.

TCM syndrome	Proteomics	Time	Reference
the stagnation of phlegm-damp	*E*-cadherin (E-cad)	2007	[85]
Pi-Wei asthenia type, Gan-Wei disharmony type, phlegm-stasis-poisons stagnant type	VEGF	2007	[86]
Yin deficiency of liver-kidney syndrome	C7, KNG1, AMBP, SERPING1	2017	[87]

glycerol, glycine, aminomalonic acid, creatinine, palmitic acid, D-tryptophan, L-proline, 1, 2, 3-propanetricarboxylic acid, D-galactose, and 2-indolecarboxylic acids (Table 4).

6. The relationship between TCM syndromes of gastrointestinal cancers and intestinal microbiota

The microbiome and metabolomics influence each other [93]. The occurrence and development of gastrointestinal cancers are related to changes of the intestinal microbiota, such as *Flavonifractor plautii* [88], Neisseriaceae, Lentisphaeraceae, Victivallaceae, Ruminococcaceae [94], Peptococcaceae, *Streptococcus*, *Leptotrichia*, and *Micrococcus*.

Several studies on the relationship between TCM syndromes of gastrointestinal cancers and intestinal microbiota have been conducted. The intestinal microbiota contributes to the distinction between the two TCM syndromes of CRC because the dominant bacteria in the Zheng-Qi-Kui-Xu group are Neisseriaceae, Lentisphaeraceae, Victivallaceae, Ruminococcaceae, and Peptococcaceae, and the dominant bacteria in the Xie-Du-Yong-Sheng group are *Streptococcus*, *Leptotrichia*, and *Micrococcus* [95].

Thus, the TCM syndromes of gastrointestinal cancers are also related to the intestinal microbiota, such as Neisseriaceae, Lentisphaeraceae, Victivallaceae, Ruminococcaceae, Peptococcaceae, *Streptococcus*, *Leptotrichia*, and *Micrococcus* (Table 5).

7. The relationship between TCM syndromes of gastrointestinal cancers and serology

Some serology indicators reflect the occurrence and development of gastrointestinal cancers, such as the carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), glutamic pyruvic transaminase (GPT) [96], progesterone (PR) [97,98], trace elements [99], total bilirubin (TBIL) [100,101], uric acid (UA) [102], and fibrinogen (FIB) [103,104].

Several studies on the relationship between TCM syndromes of gastrointestinal cancers and serology have been conducted. A hospital-based population study of 387 patients with GC shows that GPT status is significantly associated with TCM syndrome differentiation in GC [50]. A study analyzed specimens from 72 patients and showed that there is a significant difference in PR expression among different TCM syndromes [105]. PR expression is significantly higher in yin deficiency syndrome due to stomach heat than in other syndromes, and PR expression in deficiency syndromes is significantly higher than that in excess syndromes [105]. The quantitative changes in Zn, Cu, ZnO, CuO, Zn/ZnO, and Cu/CuO are related to pathological changes and the TCM syndrome pattern, and there is a close internal relationship among Spleen deficiency, Qi stagnation, and GC [106]. A study with 122 patients showed that the differences in TBIL, hemoglobin (HB), UA, and hematocrit (HCT) among the three groups (excess syndrome, deficiency syndrome, and syndrome of intermingled deficiency & excess) are statistically significant; The TBIL, HB, UA, and HCT indices in preoperative patients with excess syndrome of CRC are higher than those in patients with syndrome of intermingled deficiency & excess and deficiency syndrome; and UA and HCT are different between the excess syndrome and deficiency syndrome groups [107]. Sex, tumor location, TNM stage, total protein (TP), red blood cell (RBC), HB, HCT, platelet (PLT), and FIB are risk factors affecting TCM syndromes in preoperative CRC [107]. Researchers have investigated the differences in serum by comparing patients with CRC with ND, QD, and YD [92]. The proportion of subjects with CEA is higher in the YD pattern, and the proportion of subjects with CA19-9 is higher in both YD and QD than that in ND. Metabolomics analysis showed that 25 metabolites display differences between QD and ND, whereas 25 metabolites display differences between YD and ND [92].

Thus, TCM syndromes of gastrointestinal cancers are related to changes in the serological indicators CEA, CA19-9, GPT, PR, Zn, Cu, ZnO, CuO, Zn/ZnO, Cu/CuO, TBIL, HB, UA, HCT, TP, RBC, HB, HCT, PLT, and FIB (Table 6).

8. Conclusion and future outlook

In summary, research on the biological basis of TCM syndromes in gastrointestinal cancers has made some progress in genomics, transcriptomics, proteomics, and metabolomics. The relationship between TCM syndrome differentiation type and pathology in 312 patients with gastric cancer was analyzed and showed that their difference is that in the deficiency of vitality syndrome type; the chief

Table 4
Researches on the relationship between TCM syndrome of gastrointestinal neoplasms and metabolome.

TCM syndrome	Metabolome	Time	Reference
Dampness and heat syndrome (DHS)	Creatinine, aminomalonic acid	2018	[91]
Spleen deficiency syndrome (SDS)	D-tryptophan	2018	[91]
Liver and kidney Yin deficiency syndrome (LKYDS)	D-galactose, 1, 2, 3-propanetricarboxylic acid	2018	[91]
Non deficiency (ND), Qi deficiency (QD), Yin deficiency (YD)	carbohydrates, fatty acids, amino acids	2017	[92]

Table 5
Researches on the relationship between TCM syndrome of gastrointestinal neoplasms and intestinal microbiota.

TCM syndrome	Metabolome	Time	Reference
Zheng-Qi-Kui-Xu (ZQKX)	Neisseriaceae, Lentisphaeraceae, Victivallaceae, Ruminococcaceae, Peptococcaceae	2020	[95]
Xie-Du-Yong-Sheng (XDYS)	Streptococcus, Leptotrichia, Micrococcus	2020	[95]

Table 6
Researches on the relationship between TCM syndrome of gastrointestinal neoplasms and serology.

TCM syndrome	Serology	Time	Reference
spleen-stomach weakness (SSW), dampness-heat-toxin accumulation (DHT), stagnation of phlegm-muddiness (SPM)	glutamic pyruvic transaminase (GPT)	2013	[50]
the syndrome of yin deficiency due to stomach heat	progesterone (PR)	2010	[105]
Spleen Qi deficiency, Spleen deficiency with Qi stagnation	Zn, Cu, ZnO, CuO	1989	[106]
excess syndrome, deficiency syndrome, and syndrome of intermingled deficiency & excess	total bilirubin (TBIL), hemoglobin (HB), uric acid (UA), hematocrit (HCT)	2022	[107]
Nondeficiency (ND), Qi deficiency (QD), Yin deficiency (YD)	CEA, CA199	2017	[92]

manifestation is in nest or spread infiltration type, which becomes serious by varying degrees. In contrast, in excess superficiality type, the reaction of lymphoidocytes around the cancer decreases. In most syndrome types of Spleen-Kidney Yang deficiency and phlegm-dampness and stagnation of toxicity, the tumor occurs in a wide range and the degree of tissue differentiation is low [108]. In genomics, the TCM syndromes of gastrointestinal cancers is related to changes in some genes. In transcriptomics, TCM syndromes of gastrointestinal cancers is related to changes in the methylation rate of the c-myc and p16 genes, and miR-27a rs895819. In proteomics, the TCM syndrome of gastrointestinal cancers is related to changes in some proteins. In metabolomics, the TCM syndrome of gastrointestinal cancers is related to changes in metabolites. TCM syndromes of gastrointestinal cancers are also related to the intestinal microbiota. In serology, the TCM syndrome of gastrointestinal cancers is related to changes in some serological indicators.

Some researchers have attempted to establish a quantified diagnostic standard for CRC in patients with Spleen Qi deficiency syndrome [109]. Although research on the biological basis of TCM syndromes of gastrointestinal cancers has achieved unexpected results, some problems remain. First, ancient TCM does not form a recognized theoretical system for cognitive cancer, and different opinions on the pathogenesis of cancer remain, resulting in different TCM syndrome classifications and unified dialectical standards. Second, most studies lack theoretical guidance on TCM. Third, the studies have small sample sizes, a single center, and lack a good design. TCM syndrome research directions and current results are still not systematic and systematic long-term research is lacking. To achieve systematic results, research should be conducted according to the central dogma of molecular biology, such as studying the regulation axis and signaling pathway, as in most modern medical basic research.

Syndrome differentiation and treatment are the basic characteristics of theoretical TCM systems [11]. Some TCM prescriptions have shown effective results in clinical trials. In contrast, others have been disappointing, as some TCM prescriptions are used to treat specific TCM syndromes, which may have their own biological basis. For example, the classification of Excess and Deficiency syndromes may be related to tumor heterogeneity and the CRC microenvironment.

Therefore, it is important to investigate the biological basis of these TCM syndromes. Our group is establishing a gastrointestinal cancers biobank and is conducting basic and clinical research on the biological basis of TCM syndromes of gastrointestinal cancers according to the pathogenesis theory of cancerous toxins [110]. The theory of cancerous toxins is one of the core TCM theories on cancer pathogenesis. Our group found that three tRNA-derived fragments (tRFs) (tRF-3022b, tRF-3030b, and tRF-5008b) showed an increasing trend in CRC tissues. tRF-3022b may affect CRC tumor growth and M2 macrophage polarization by binding to galectin 1 (LGALS1) and macrophage migration inhibitory factor (MIF) [111]. We hope that the TCM syndrome classification of gastrointestinal cancers will be determined, and their biological basis explored in future research using new technologies, such as genome, transcriptome, proteomics, metabolomics, and 16S rRNA sequencing. We urge that these should be conducted according to the central dogma of molecular biology, to provide evidence and references for TCM treatment and improve clinical efficacy.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Data availability statement

No data associated with the study has been deposited into a publicly available repository. Data included in article/supplementary material/referenced in article.

CRediT authorship contribution statement

Tianhao Guo: Conceptualization, Investigation, Methodology, Project administration, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Shuoqi Zhao:** Investigation, Software, Visualization, Writing – original draft. **Wenjian Zhu:** Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Hongguang Zhou:** Conceptualization, Funding acquisition, Resources. **Haibo Cheng:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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