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Original Article

Genetic Polymorphisms of Glutathione S-Transferase Genes and Risk of Colorectal Cancer in the Saudi Population

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الاشكال المتعددة لجين الجلوتاثيون س – ترانسفيريز ومخاطر الإصابة بسرطان قولون المستقيم في السعوديين

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الملخص

سرطان القولون والمستقيم من أكثر أنواع السرطان انتشارا لدى المجتمع السعودي، فعدد الحالات المسجلة سنويا يبلغ 1000 حالة تقريبا، وهو يعتبر أكثر أنواع السرطان انتشارا لدى الرجل السعودي، وثالث أنواع السرطان انتشارا لدى المرأة السعودية.

تمثل الجلوتاثيون الرابطة بجموعة الكبريت مجموعة كبيرة من الانزيمات المتشابهة والتى تعمل على التخلص من سمية كثيرمن المواد الكيمائية الضارة التى يتعرض لها الانسان خلال حياته سواء من داخل الجسم البشرى او من البيئة المحيطة.

فهناك حالة جينية (عدم ظهور النمط الجيني) لهذا الانزيم تجعله غير فعال و غير قادر على اداء وظيفته و يعتقد ان وجود مثل هدة الحالة الجينية تجعل الانسان اكثر عرضة لاصابة بانواع مختلفة من الاورام السرطانية.

ولقد اجريت دراسات عديدة للوقف على طبيعة الارتباط بين هذة الحالة الجينية التى ينتج عنها انزيم عديم الفاعلية و خطورة الاصابة بسرطان القولون والمستقيم ولكن مجمل هذة الدراسات متناقض في نتائجها على طبيعة هذا الارتباط و من اجل ذلك فقد قمنا بهذة الدراسة للوقوف على حقيقة هذا الامر في المملكة العربية السعودية بمنطقة مكة المكرمة.

وقد شملت هذه الدراسة 170 شخصاً مصاباً بسرطان القولون والمستقيم ، وكذلك 170 شخصاً اخر سليماً . وتم تحديد الحالات الجينية المختلفة بواسطة تقنية التفاعل البلمرة المتسلسل المعقد.

هذه الدراسة لم تظهرارتفاع ملحوظ بفارق إحصائي في معدل الحالة الجينية للانزيم الجلوتاثيون الرابط بمجموعة الكبريت من انواع م١ و ت١ في مرضى سرطان القولون والمستقيم قياساً بالمجموعة الضابطة . و بناءا على معطيات ونتائج الدراسة تم استنتاج عدم وجود علاقة بين تباين الحالات الجينية (ظهور النمط الجيني او عدم ظهور النمط الجيني) للانزيم الجلوتاثيون الرابط بجموعة الكبريت من انواع م١ و ت١و خطورة الاصابة بسرطان القولون والمستقيم للمرضى السعوديين في المملكة العربية السعودية بمنطقة مكة المكرمة. وعلى الرغم من هذة النتيجة فانه لا يمكننا اهمال دور هذة الجينات بالكلية فى عملية تطور وظهور اعراض سرطان القولون والمستقيم فقد يوجد تفاعل جينى لهذة الجينات موضع الدراسة مع جينات اخرى قد يودى هذا الى ظهور هذا الارتباط بسرطان القولون والمستقيم. وايضا فانه يوجد حاجة للقيام باعداد كثيرة من الدراسات على نفس النمط فى باقى بقاع المملكة لوقف على حقيقة هذة النتائج و هذا الارتباط من عدمه. وايضا مع الاخذ فى الاعتبار العوامل البيئية الاخرى و نمط الحياة اليومى وعلاقته بخطورة الاصابة بسرطان القولون والمستقيم.

ABSTRACT

Background:
Glutathione S-transferases (GSTs) are an important family of isoenzymes involved in the detoxification of many environmental carcinogens. The GSTs null deletion polymorphism of the GSTs genes that lead to diminished of enzymatic activity have been associated with increased susceptibility to develop several cancers.GSTM1 & GSTT1 status have been extensively studied as a risk factor for colorectal cancer (CRC), although inconsistent associations between GSTM1 & GSTT1 genotype and CRC risk have been observed .

Methods:
To re-examine this controversy, we have undertaken a case-control study investigating the relationship of GSTM1 & GSTT1status (null/ non-null genotype) and CRC risk, involving a total of two 170 CRC cases and individual controls. Genotyping assay was performed by multiplex PCR followed by gel electrophoresis.

Results:
The OR of CRC and GSTM1 & GSTT1 null genotype were 0.85 (0.45 – 1.59) and 1.13 (0.56 – 2.29) in the Saudi population, respectively. Hence, the results of this analysis does not support the hypothesis that either GSTM1 or GSTT1 have been associated with CRC, and suggests that GSTM1 & GSTT1 status have no effect on the risk of developing CRC .

Conclusion:
There may be interactions between GSTM1 & GSTT1and other polymorphisms that may influence the risk of developing CRC. Further investigation in different regions of the Kingdom of Saudi Arabia are required to verify or refute these results, and to identify more definite risk groups and determine factors of importance in the development of CRC.

Keywords: *GSTM1 & GSTT1*; colorectal cancer; polymorphism; genotype; KSA.

INTRODUCTION

Colorectal cancer (CRC) is considered as the fourth leading cause of cancer mortality both worldwide and in the Kingdom of Saudi Arabia (KSA). Moreover,The incidence seems to be increasing; with approximately 500,000 annual deaths (1,2). Although CRC is less frequent in the KSA than in its counterpart Gulf Cooperation Council States and in the West, this disease was the second most common malignancy after breast cancer. It ranks first among men and third among women between 1994 and 2004 (3). An increasing number of epidemiological studies

indicate that cigarette smoking; alcohol use; decrease physical activity, and the consumption of diets high in red meat are probably important etiological factors increasing the risk of developing CRC4. However, it is now widely accepted that CRC risk is determined by a complex interaction of both genetic and environmental factors such as susceptibility genes, carcinogen exposure and dietary factors (4-6).

Drug metabolizing enzymes modifies chemical compounds in cigarette smoke or diets, and some of the metabolites may be the cause of CRC. Polycyclic aromatic hydrocarbons (PAHs) and other tobacco-related carcinogens are activated by phase I enzyme cytochrome P450 that is termed high risk gene and is detoxified by phase II enzyme glutathione S-transferases (GSTs). The metabolic balance between phase I and phase II enzymes may be of importance to determine genetic susceptibility to colorectal carcinogenesis, as well as lung cancer (7-9). Following phase I reaction, phase II enzymes such as GSTs are responsible for detoxification of activated forms PAH epoxides and protect cells from reactive chemical intermediates and oxidative stress.

GSTs are constitutively found in a wide variety of tissues, with different characteristic patterns of GST isozymes. *GSTs* also form a superfamily of genes consisting of eight distinct families, termed alpha (α), mu (μ), pi (Π), theta (θ), sigma (δ), zeta (ζ), kappa (k) and gamma (γ) (http:www.OMIM.org). Certain genes within the *GSTM*, *GSTT* and *GSTP* subfamilies (*GSTM1*, *GSTT1* and *GSTPI* genes, respectively) are polymorphic in humans. GST expression varies between individuals, and expression is tissue and sex specific. *GSTM1* and *GSTT1* are expressed in normal colon tissue. The phenotypic absence of *GSTM1* and *GSTT1* activity is due to homozygosity for deletion of these genes, termed the null genotype (9, 10). Inheritance of null alleles in the *GSTM1* (chromosome 1p13.3) and *GSTT1* (chromosome 22q11.2) genes is common in the population, varies by ethnicity, and is associated with the loss of enzyme activity and cytogenetic damage. The homozygous deletion of *GSTM1* gene has been shown to occur in approximately 50% of the populations of various ethnic origins (11-17), while the homozygous deletion of *GSTT1*gene has distributed between 10 and 64 % of various ethnic groups (11-13,15).

The frequency of the *GSTT1* null genotype in Caucasian populations is 30% or less, but that in Oriental populations may be similar to the frequency of the *GSTM1* null genotype (15). In an earlier study based on phenotyping, the *GSTM1* null genotype was found to yield increased risk for CRC, {(OR) of 2.32 (95%CI: 0.88-6.15)} in English groups (8). In the next study, an excess of the individuals with null genotypes were observed in CRC but this was not a significant. When the patients were divided into cancers occurring in the proximal or distal colon, the null genotype became a significant risk factor among the subgroup with distal colorectal tumors11. Therefore, two (8,11) of eight (8,11-17) revealed approximately 2-fold increased risk for colorectal cancer.

Five published studies (11-13,15,17) have examined the relationship between *GSTT1* null genotype and colorectal cancer risk. Only one (17) of these studies showed the *GSTT1* null genotype was related to significantly increased risk CRC. It is likely

that individuals with more reactive phase I enzymes and less efficient phase II enzymes might be at higher risk for different types of cancer than individuals with the opposite combination (18-23). Recently, lots of meta-analysis and case control studies claimed that the null genotypes of *GSTM1* and *GSTT1* and the dual null genotype of *GSTM1*/*GSTT1*, were all not risk factors in CRC among the Central European (24), Chinese (25), and South Indian populations (26). Whereas, another study in same year suggested that GSTs measurement might be useful as a colorectal marker in CRC (27). The aim of this study was to explore the most real possible association between*GSTM1*& *GSTT1* status and CRC risk in Saudi population.

METHODS

Blood samples of this case-control design study were obtained from seventy Saudi patients newly diagnosed with CRC. One hundred matched controls were selected consecutively. All cases and controls were Saudis over 30 years of age and represented both sexes. The selection of controls was matched to the cases in relation to both age and sex. A case was defined as a newly-diagnosed CRC patient who is free from other chronic diseases such as diabetes, hyperlipidemia, hypertension, cardiac, liver and renal diseases. Female cases were not pregnant or lactating. Controls were free from cancer or chronic diseases. The study was approved by the ethical committee of the Medical School of Umm Al-Qura University. All patients and controls gave informed, written consent to participate in the study.

Laboratory methods

Genomic DNA was extracted and purified from EDTA-peripheral blood using the QIAmp DNA Blood Mini Kit (Qiagen, Valencia, CA) according to the manufacturer's instructions. The purified genomic DNA was quantified and stored at -80°C until required. For genotyping assay, PCR was performed in which GSTM1 and GSTT1 were co-amplified using the primers M1F: (5'-GAA CTC CCT GAA AAG CTA AAG C-3') and M1R: (5'- GTT GGG CTA AAT ATA CGG TGG-3') and T1F: (5'-TTC CTT ACT GGT CCT CAC ATC TC-3') and T1R: (5'-TCA CCG GAT CAT GGC CAG CA-3'), generating fragments of 215 and 480 bp, respectively, based on a previously described method23. Length specific PCR amplifications of the primer sets used were confirmed by an in silico search of the Genome sequence using the UCSC genome browser In-Silico PCR software (28). The absence of one PCR product for one gene indicated a null genotype for this gene. The amplification of GSTM1&GSTT1 genes were carried out by mixing 50 ng of the isolated DNA, 25 ng of primers, 1X Master Mix from Thermo Scientific Inc. (Maxima Hot Start Green) containing Maxima Hot Start Taq DNA Polymerase, optimized hot start PCR buffer, Mg2+, and dNTPs. A total of 35 cycles of PCR using the DNA Engine Dyad thermal cycler from Bio-Rad laboratories Inc. with denaturation at 94oC for 30 sec, annealing at 580C for 60 sec, and extension at 72oC for 60 sec was performed. An initial denaturing was carried out at 95 oC for 4 minutes and a final extension step at 72oC for 10 minutes.

Early experiments for optimizing the annealing temperature were performed to successfully co-amplify the two target genes.

Genotypes were identified by electrophoresis of the amplified fragments through 2% agarose gels containing ethidium bromide (0.5 mg/mL). A quality control study was performed to validate the results. DNA samples were quantified by absorbance measurement and this allowing samples concentration to be normalised to produce consistent results. The genotypes for all samples were reassessed twice to confirm the results and ensure reducibility.

GSTs genes status

The following nomenclature have been used to specify the genotypes at GSTM1: non-null (wild-type (WT) or heterozygous deletion), null (homozygous deletion); and GSTT1: non-null (wild-type (WT) or heterozygous deletion), null (homozygous deletion).

Statistical analysis

The genotype and allelic frequencies for all the individuals from the CRC group were separated and compared statistically with the corresponding data for the control group. For this purpose, we used the $\chi 2$ test with SPSS 16. Results were considered to be statisti¬cally significant when the P value was less than 5% ($P < 0.05$). ORs were calcu¬lated for disease susceptibility associated with specific genotypes.

RESULTS

Genotyping data after multiplex PCR and gel electrophoresis as illustrated in figure 1 were recorded and tabulated to make it ready for statistical analysis. The frequency of the GSTM1 null genotype was 62.8% and 59.0% in CRC and control groups respectively. The frequency of the *GSTT1* null genotype was 24.3% and 27.0% in CRC and control groups respectively. The frequency of the *GSTM1*non-null genotype was 37.2% and 41.0% in CRC and control groups respectively.

The frequency of the *GSTT1* non-null genotype was 75.7% and 73.0% in CRC and control groups respectively. The frequency of the dual null genotype of *GSTM1/GSTT1*was 87.1% and 86.0% in CRC and control groups respectively.

The statistical analysis of the results demonstrated t no statistically significant association of *GSTs* genotypes with CRC cases as shown in table1. This analysis shows that the null genotypes of *GSTM1* and *GSTT1* and the dual null genotype of *GSTM1/GSTT1*were all not risk factors in CRC patients in our population.

Table1: GSTM1 and GSTT1 genotype frequencies in cases and control groups

Status	Type	CRC	OR (95%CI)	P	Control
GSTM1	Non-null null	26 (37.2 %) 44 (62.8%)	0.85 (0.45 – 1.59)	0.61	41 (41.0%) 59 (59.0 %)
GSTT1	Non-null null	53 (75.7 %) 17 (24.3 %)	1.13 (0.56 – 2.29)	0.73	73 (73.0 %) 27 (27.0 %)
GSTM1/T1	Dual null	61 (87.1%)	1.01 (0.41 – 2.12)		86 (86.0%)

Data are reported as numbers of subjects with percent in parentheses. CRC: colorectal cancer; OR= Odd

Ratio; 95% CI = confidence interval at 95%.

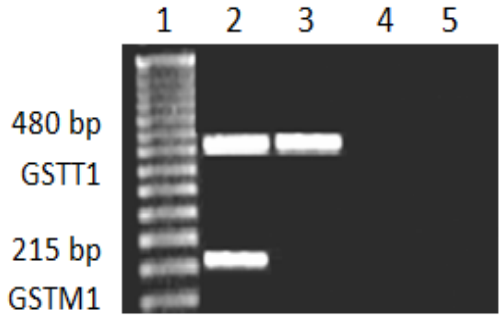

Fig.1. Example of GST genes genotypes obtained. Lane 1: DNA ladder; Lanes 2 (dual none—null) & 3 control (null *GSTM1*), Lane 4: CRC case (dual null); Lane 5: negative control

DISCUSSION

Although in this study the GSTM1 and GSTT1 status were not associated with an increased risk of CRC, the influence of the these genes in the devel¬opment of CRC cannot be excluded, since haplotypes involving many metabolic genes could contribute in a distinct manner to carcinogenesis.

The first report in 1991, evaluated a possible association between the GSTM1 and GSTT1 null genotypes and CRC (7). Since then, the GSTM1 and GSTT1 functional-loss deletion polymorphisms have been regarded as a risk factor for developing CRC by a number of researchers. It is not uncommon for the initial small size studies to over-estimate risk or effect on CRC susceptibility, which subsequent larger studies cannot confirm and thus lead to incorrect conclusions (29).

The inconsistency about the effects of GSTM1and GSTT1 null genotypes on susceptibility to CRC prompted this analysis in order to explore a possible association between GSTM1and GSTT1deficiency and CRC risk. The results of this study suggest that GSTM1and GSTT1 null genotyping is not associated with an increased risk of developing CRC.

GSTs are a superfamily of phase II isoenzymes believed to protect cells from reactive chemical intermediates and oxidative stress resulting from a wide range of electrophilic xenobiotics (e.g., tobacco-related carcinogens) and endogenous intermediates (e.g., reactive oxygen species). GSTM1and GSTM1deficiency has been evaluated as a risk factor in individual susceptibility to several cancers by a number of epidemiological studies.

Although GSTM1 and GSTT1 null genotyping did not display an association with increased risk of developing CRC in this study, it is not surprising because the evidence to support the role of GSTM1 and GSTT1 status as a colorectal cancer risk factor is not strong. It is conceivable that the influence of GSTM1 and GSTT1 genotypes may seem to be relevant to the expression levels in other tissues as GSTM1 and GSTT1 are only expressed at low levels in colon tissue (30). It is known that the primary site for the expression of GSTM1 and GSTT1 are the human liver (31). Therefore, increased CRC risk directly related to the lack of enzymes activity would be mediated by blood-borne metabolites from hepatic system.

It has been taken into consideration that the design of this case-control study in evaluating GSTs deficiency as a risk factor for CRC was far from perfect. From this data, it could be assumed that these functional-loss polymorphisms in GSTs do not alter the risk of CRC. However as with all analysis there are areas that can affect outcome and may

confound the results of analysis, giving false positives or reporting no association where there is one.

These factors have been reviewed by Cardon and Bell (32). Consideration of sample size is crucial in the design of case-control studies in order to clarify an association between genotypes and cancer risk. If GSTs deficiency is associated with 1.5-fold increase in CRC risk, this study is obviously under-powered to demonstrate such a moderate effect. Some case-control studies analyzed were based upon cancer cases and hospital based controls. The use of healthy controls is more appropriated as controls with non-malignant disease might influence the frequencies of the GSTM1and GSTT1genotypes in determining the susceptibility to cancer risk. It has been reported that hospital based controls are, in general, not desirable because they are a more or less biased population.(33)

In addition, it is now widely accepted that differences in ethnic distribution between case and control groups among the studies may be another source of a potential bias of the results from the analysis. So, the association between cancer and a particular polymorphic site in one ethnic group might be of limited value as a genetic marker for cancer in another ethnic group.

The frequencies of GSTM1 and GSTT1 deficiency varied between ethnic groups: in Caucasian populations (34). The frequency of the GSTM1 deficiency ranges from 40.8% to 58.6%; in Asian populations (11,35), from 21.6% to 55.9%; and in African populations (36), it was 66.6%. The frequency of the GSTT1 null genotype in Caucasian populations is 30% or less, but that in Oriental populations may be similar to the frequency of the GSTM1 null genotype. Ethnic specificity in this analysis would be taken into consideration during investigating the association between GSTs deficiency and CRC risk in Saudis.

As the KAS is considered as multiethnic country, affecting the outcome and may confound the results of this analysis. Depending on the control and cases, individuals may be related to different ethnic groups that may contribute to this negative association.

Glutathione S-transferases represent a complex grouping of proteins. Two entirely distinct superfamilies of enzyme have evolved that possess transferase activity (37). The first enzymes to be characterized were the cytosolic or soluble, GSTs385. To date at least 16 members of this superfamily have been identified in humans (37). On the basis of their degree of sequence identity, the soluble enzymes have been assigned to eight families (37,39,40). The second more recently defined superfamily, is composed of microsomal transferases and has been designed membrane-associated proteins in glutathione metabolism, or MAPEG for short (41).

In humans, MAPEG superfamily has at least six members. Evolution of a large number of soluble GST and MAPEG members has allowed diversification of function, regulation and subcelluler localization in the two superfamilies. GSTM1 and GSTT1 genotype is only two of key enzymes involved in the detoxification of a number of environmental carcinogens such as polycyclic aromatic hydrocarbons (PAHs). Other isoenzymesmay have a function in the

detoxification of PAHs. Thus, the lack of an association between GSTM1and GSTT1 deficiency and CRC risk may imply that GSTM1and GSTT1 genotype might have small impact on modifying CRC susceptibility.

It is conceivable that CRC risk related to any one locus will be small because gene gene interactions are likely to operate. Therefore, the effect of the GSTM1and GSTT1 genotype on susceptibility to CRC could be minor. In this study, we only addressed the question of the GSTM1 and GSTT1 status and CRC risk. We were unable to evaluate whether the presence of a gene-environment interaction differs when stratified by levels of smoking exposure, dietary and lifestyle characteristics among the studied subjects.

Such data were not available during this analysis, so any general conclusions could not be drawn based on such information. It has been reported that a sedentary lifestyle and a diet low in fruits and vegetables, and high in animal red meat and saturated fat, appeared associated with high risk of CRC (42-44). Moreover, it should be noted that some studies reported that cigarette smoking is a risk factor for CRC and fail to show an association with the GSTM1and GSTT1deficiency (45, 46). Therefore, it is likely that cigarette smoking may be an independent risk factor for CRC regardless of genotype status.

In conclusion, this study does not support the hypothesis that the GSTM1 and GSTT1 genotypes are independently associated with an increase in the risk of developing CRC. It may reflect a relatively small effect of GSTM1 and GSTT1 genotypes on CRC risk. Nevertheless, it is clear to know that the metabolism of carcinogens is complex, and interaction with other "high-risk" genes and environmental exposures may be important when assessing the risk of developing CRC.

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Original Article

Biology of Interleukin 33 (IL-33)

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العلم الحيوي لانترلوكين 33

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الملخص

انترلوكين 33(IL-33) هو عضـو جديد من عائلة محفز الخلايا انترلوكين1 (IL-1) والذي يبدي وظيفة حيوية من خلال مستقبل الخلايا الخاص به وهو ST2 .

الفكرة البدائية كانت توضــح أن انترلوكين 33 يبدي وظيفة حيوية في خلايا تي المســاعدة 2 (Th2) الحاملة لـــــ CD4 والمرتبط إيجابياً مع ST2 الذي على سطحها من خلال انتاجَ IL-5 وَ IL-13 .

من المثير للاهتمام أن الدراسات الأخيرة تقترح أن انترلوكين 33 أيضاً قد يكون مسؤولاً عن استجابة خلايا تي المساعدة 1 (Th1) في المناعة الطبيعية والحالات المرضــية . على أي حال , ســواءاً انترلوكين 33 قادراً على تحفيز خلايا تي المساعدة 1 أو لا , والذي لا يزال مجهولاً حالياً .

ABSTRACT

Interleukin-33 (IL-33) is a new member of the IL-1 cytokine family which exerts biological function via its cellular receptor ST2. The initial thought was that IL-33 exerts a vital function in ST2-positive type 2 $CD4^+$ T helper (Th2) cells response through the induction of IL-5 and IL-13. Interestingly, recent studies have suggested that IL-33 may be also involved in Th1 cell responses in immunity and disease. However, whether IL-33 can polarise Th1 cells or not is currently unknown.

Keywords: IL-33, Th1/Th2, St2 receptor

INTRODUCTION

IL-33 was discovered as a new member of the IL-1 family in 2005 (1).
The members of the IL-1 cytokine family including IL-1α, IL-1β and ……. IL-18, possess similar homological structure and nucleotide sequences and play a critical role in immunity, infection and inflammation (2-3). IL-33 is produced as a pro-protein about 32KDa which can be further matured by undefined enzymes to produce 18KDa mature protein (1).

Pro-IL-33 contains a DNA-binding domain which allows the protein to interact with chromosomal DNA in the nucleus may play a regulatory role in gene function (1). There is 55% identical homology at the amino acid level between murine and human *IL-33* (1). The mRNA level of IL-33 can widely detected in tissues such as lung, brain, stomach, spin cord and skin (1). However, the expression of IL-33 mRNA is only observed in a few cell types such as epithelial cells, smooth muscle cells (SMC), activated macrophages and dendritic cells (DC) (1).

METHODS

RECEPTOR FOR IL-33

IL-33 is thought to perform its biological function through a receptor complex consisting of ST2 and IL-1 receptor accessory protein (IL-1RAP) (1, 4). Even though IL-1RAP is necessary for signalling of IL-33, IL-33 mainly signals via ST2 (1). ST2 is a member of IL-1 receptor (IL-1R) family and is mainly on innate immune cells such as mast cells and basophils (5), eosinophils (6) and DC (7). It also preferentially induced and expressed on Th2 cells, but not Th1 cells (8-9). IL-33 also is expressed by structural cells, such as epithelial cells, endothelial cells and fibroblasts which play a major role in the immune system (10).

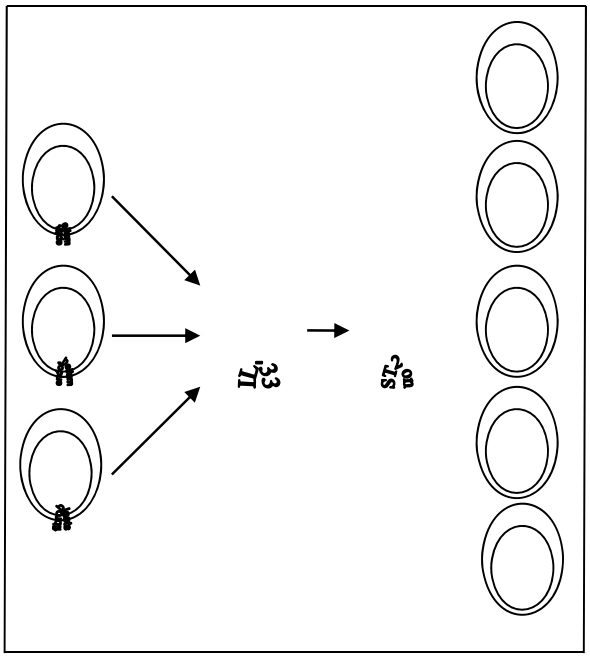

Figure1: IL-33 production and receptors

FUNCTION OF IL-33

The interaction between IL-33 and its receptors initiates the recruitment of myeloid differentiation primary-response protein 88 (MYD88) complexes to activate the transcription factor nuclear factor- kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), leading to cytokine production and cellular activation (1). It has been reported that IL-33 can drive production of Th2-secreted cytokines such as IL-5 and IL-13 but not IL-4 by either polarised Th2 cells or naïve T cells independent of IL-4 (1, 11). Furthermore, increased mRNA levels of IL-5 and IL-13 can be observed in spleen, thymus and lung by stimulation with IL-33 *in*

vivo (1). Schmitz and colleagues also reported that IL-33 can induce high level of serum IgE production, splenomegaly and eosinophilia in mice. These findings indicate that IL-33 may be a key factor for Th2 response in immunity and disease.

In addition, IL-33 can stimulate Th2-associated cytokines and protect against parasite infection and arthrosclerosis (2, 12). IL-33 also play a critical role in allergic disease and asthma due to its important function on Th2 cells, mast cells, basophils and eosinphils in allergic responses (11, 13-17).

However, several studies have revealed that IL-33 might also be involved in the Th1-mediated response (18-20). It has been reported that IL-33 can induce IFN-γ from invariant natural killer T (iNKT) cells as well as natural killer (NK) cells in the presence of IL-12 (19). It can also promote the production of pro-inflammatory cytokines such as IL-17, TNF-α and IFN-γ in mice of collagen-induced arthritis (CIA), a model for human rheumatoid arthritis (21). Thus, IL-33 can mediate Th1 cells response separately from its function in Th2 cells responses. It is also reported that IL-33 can activates the $CD8^+$ T cells and NK cells that could directly kill tumor cells. These observation show that IL-33 function like as IL-18 that can activate both Th1 or Th2 base on condition and act as a alarmins for immune system(22).

'Alarmins' are a group of endogenous proteins or molecules that are released from cells during cellular demise to alert the host innate immune system. It also activates the indirect anti-tumor immune cells such as dendritic cell (DC)(23).

Cell activation	Cytokine and Ab production	Disease
Th2	IL-5 and IL-13	Protect against parasite infection and arthrosclerosis
Th2 cells, mast cells, basophils and eosinphils	high level of serum IgE	allergic responses
$CD8^+$ T cells and NK cells	------	kill tumor cells
NK and iNKT cells in the presence of IL-12	IFN-γ	------
------	IL-17, TNF-α and IFN-γ in mice of CIA	------

Table 1: Function of IL-33

CONCLUSIONS

Cytokines play a critical role in the control of the innate and adaptive immune responses. IL-33, the most recently discovered member of the IL-1 superfamily including IL-1 and IL-18 and have been linked to several human pathologies. Il-33 strongly bind to ST2 receptor that is mainly expressed on stromal cell and Th2 cells. IL-33 has shed new light on the intricacies of immune system regulation. These novel cytokines have pleiotrophic actions ranging from antiviral immunity to the regulation of Th2 immune responses. For example, the discovery of IL-33 has significantly improved our understanding of the factors regulating the polarization of the T helper cell responses and IL-33 appears to be an important regulator of Th2 responses.

On the other hand, IL-33 considered to be critical for mounting an efficient antiviral response, which are yet to be fully characterized, are emerging as important components of the inflammatory response in allergy and autoimmunity. IL-33 and other cytokine/receptor combinations may, therefore, serve as novel targets for the

treatment and control of allergy, autoimmune diseases, and some cancers.

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