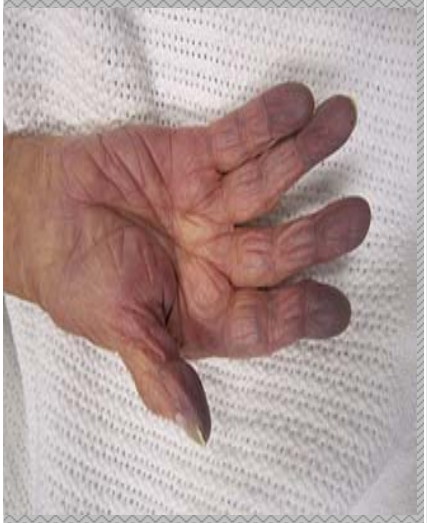

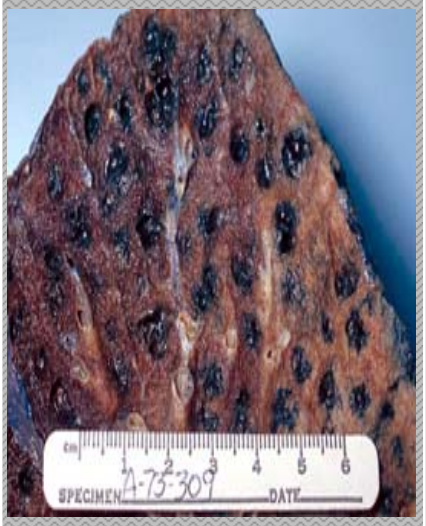

EMGEN Newsletter

Vol. 7, Issue 2

IN THIS ISSUE:

Eastern Mediterranean Health Genomics and Biotechnology Network (EMGEN) was created in 2004 with collaboration of representatives of selected centers of excellence in (health related) molecular biology, biotechnology & genomics in the Eastern Mediterranean region by recommendations and efforts of WHO/EMRO.

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COLORECTAL CANCER

Colorectal cancer (*CRC*) Sections which include:

1. Colon cancer
2. Rectal cancer

CRC is the most common type of malignant tumors that form inside the colon or rectum. The colon and the rectum are located in the lower part of the body's digestive system.

This malignancy is common in both genders and often classified as preventable cancer, so that in the recently decades, Early detection and a proper treatment are the vital factors, especially in developed countries.

CRC is a multifactorial gastrointestinal cancer. In most countries, the risk of developing cancers increases after age 40 because of heterogeneity, Many factors can play an essential role in *CRC* including: lifestyle factors, obesity, smoking, genetic factors, environmental exposures, family history and inflammation of the digestive tract. Often patients with *CRC* do not have any significant signs and symptoms during screening procedures until critical steps of cancer; however, common clinical signs and symptoms include:

1. Abdominal pain
2. Diarrhea
3. Change in bowel habits
4. Iron-deficiency anemia
5. Intestinal obstruction
6. Fatigue, weight loss (unknown etiology)

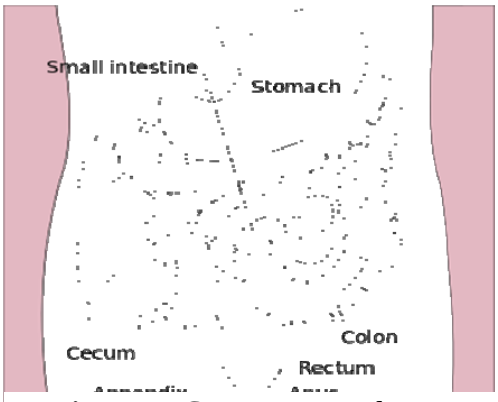

Figure 1. Gastrointestinal tract

The latest findings of essential developments in finding the biology and genetics pathway of colorectal cancer are slowly going into the clinical stage and being utilized for better screening, earlier prognostication and anti-cancer therapies (gene therapy and Nano drugs) .CRC is a good candidate for Gene and Cell Therapy. for example, gene replacement, virus enzyme therapy, immune drugs, siRNA targeting and Nano drugs.

Staging

Using the staging in *CRC* can help the doctor to select the best therapy and predict An appropriate diagnosis for each person. There are many stage definitions for *CRC* but the best one is *TNM*.

Table of *CRC* staging

(Tumor)T	Node (N)	Metastasis (M)	Grade (G)
TX: Primary tumor cannot be recognized. **Tis** **T0** **T1** **T2** **T3** **T4** The cancer cell slowly spread into other parts of the body	**NX:** The zonal lymph nodes cannot be recognized. **N0:** There is not any zonal lymph node metastasis **N1a:** The metastatic cell recognized in 1 regional lymph node. **N1b:** The metastatic cell recognized in more than 1(2 or 3) regional lymph nodes. **N1c:** The metastatic cell found in the sub-serosa and other structures near the colon. **N2a:** The metastatic cell recognized in 4 to 6 regional lymph nodes. **N2b:** The metastatic cell recognized in more than 6 regional lymph nodes.	**MX:** Without distant metastasis. **M0:** Without spread to distant parts of the body. **M1a:** Spread to 1 part of the body. **M1b:** Spread to more than 1 parts of the body.	**GX:** Unknown grade. **G1:** Well differentiation. **G2:** Moderately differentiation. **G3:** Poorly differentiation **G4:** Undifferentiation.

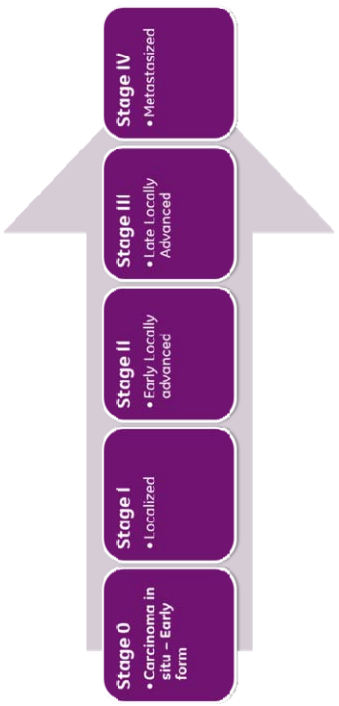

Figure 4: Staging of CRC

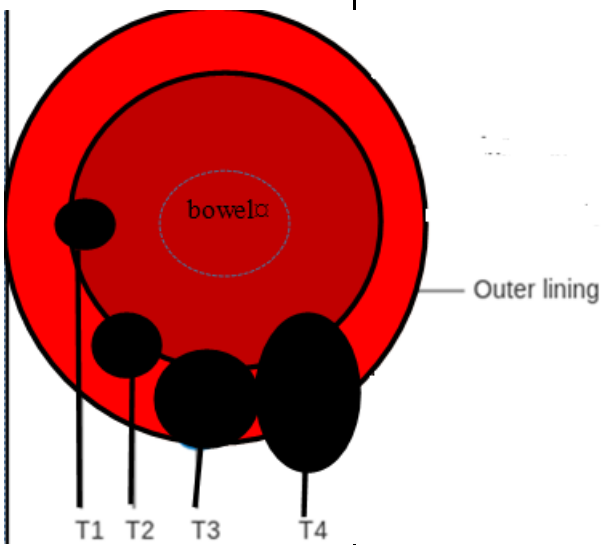

Figure 5. TNM classification

TNM staging system which includes 3 groups entitled as T,N and M. The origin of T,N and M are Tumor, Node and Metastasis, respectively. Some stages are classified by words or numbers. The higher the number after T, N and M indicates that the cancer is more progressive.

About 10 years ago, the only treatment for colorectal cancer was 5-fluorouracil in the developed countries. Then, the first chemical treatment for this cancer was 5-fluorouracil. Since then, several new drugs and treatments have been widely used in the developed countries, including the following items:

1. Avastin (Bevacizumab)
2. Bevacizumab
3. CAPOX
4. FOLFIRI
5. FOLFIRI-BEVACIZUMAB
6. Camptosar (Irinotecan Hydrochloride)
7. Capecitabine
8. Cetuximab
9. Eloxatin (Oxaliplatin)
10. Erbitux (Cetuximab)

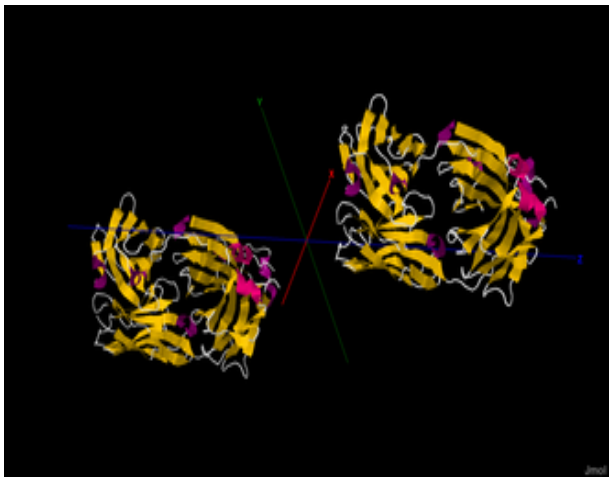

Figure 2. Erbitux (Cetuximab)

Doctors determine different stages of cancer by incorporating the T, N, and M grading and selecting their treatments by mentioned classifications .

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4. http://www.cancer.gov/about-cancer/treatment/drugs/colorectal
5. https://en.wikipedia.org/wiki/Cetuximab#/media/File:Cetuximab.png
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KRAS MUTATIONS IN COLORECTAL CANCER

Colorectal cancer (*CRC*) is one of the fatal cancers in the world. The *Kirsten-Ras (KRAS)* and *B-Raf* proto-oncogene (*BRAF*) genes are mutated in approximately 10-40% of colorectal cancers respectively. Some previous research have identified the correlation among *KRAS-BRAF* mutations and survival prognosis in the individuals with *CRC*.

KRAS

Ras proteins (also known as a small *GTPase* proteins) are a member of human homonymous genes which are represented in all cells in human organs. *Ras* has six beta strands, five alpha helices and 2 domains:

A G domain with 166 amino acids, five motifs binds to guanosine nucleotides, and a *CAAX-COOH* (C-terminal). *Ras* as dual molecular buttons that control intracellular signaling pathways, proliferation, differentiation, apoptosis, cell migration, metastasis, and actin cytoskeletal integrity. The most important parts of the *RAS* subfamily that are involved in many types of dangerous cancer and lead to invasion and metastasis are *hras, kras* and *nras*.

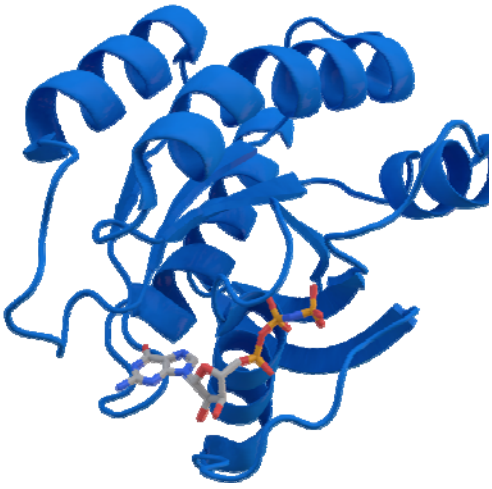

Figure 1. *KRAS* protein

KRAS or *V-Ki-ras2* is a *GTPase* protein that belongs to a mammalian *ras* gene family, encoded by the respective gene.

In turn, *KRAS* acts as a proto-oncogene and normal *Kras* gene has an essential duty in both healthy and tumor tissue. Furthermore, this important on/off switch molecule can activate several downstream signaling effectors such as *c-Raf, PI 3-kinase*, upregulates the *GLUT1* glucose transporter and binds to *GTP* under normal physiological conditions. Furthermore, KRAS gene has two different products with different structures: K-Ras4A and KRas4B. These proteins are different in both C -terminal regions and places of localization.The *KRAS* protein, (also known as *p21*), is placed on human chromosome 12 and contained 189 amino acids.

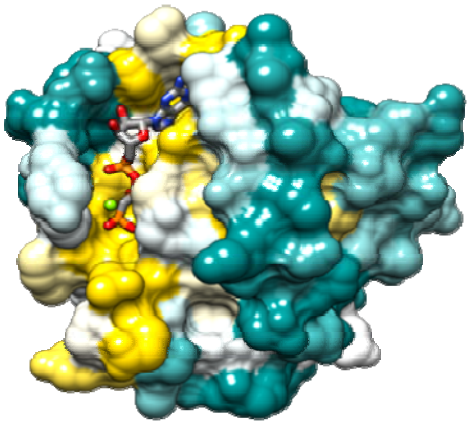

Figure 2. *H-ras* structure

Due to containing *GTP* cleaving enzyme, *KRAS* is necessary for intracellular signaling pathway, especially for *EGFR*-signaling activation. KRAS can interact with other oncogenes such as:

- C-Raf
- PIK3CG
- RALGDS
- RASSF2
- PLC$_{\epsilon}$
- RIN1

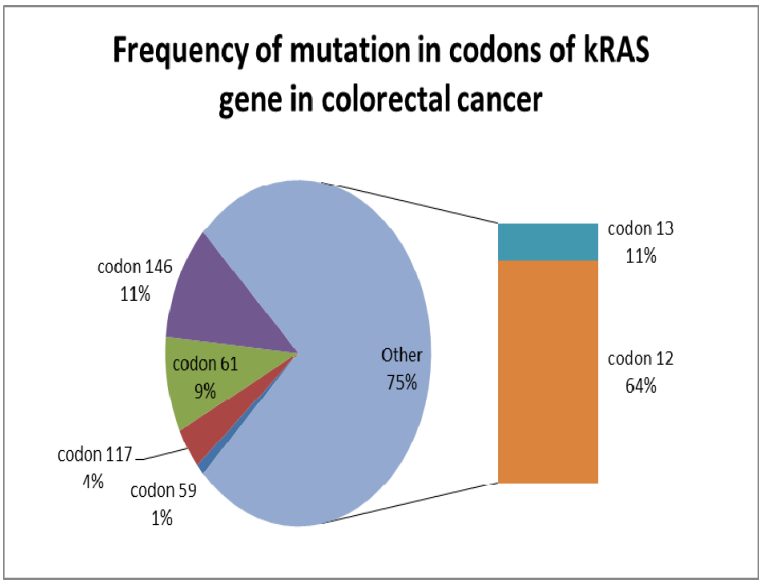

Diagram 1:Frequency of KRAS mutations in CRC

Similar to components of the *Ras* family,mutations in the *Kirsten Ras* can influence on *CRC* survival. Approximately 40% of *CRC* patients have *KRAS* changes and mutations in codon 12 and 13 are counting for about 95% of all mutation types. Mutations in other codons such as codon 61, 146 and etc. happen less frequently in patients with *CRC*. These mutations have a negative impact on the main *GTPase* activity of *KRAS* and they can prevent *GAPs* from leading *GTP* hydrolysis by *KRAS*, so that mutant *KRAS* proteins can activate downstream pro-proliferative signaling pathways.

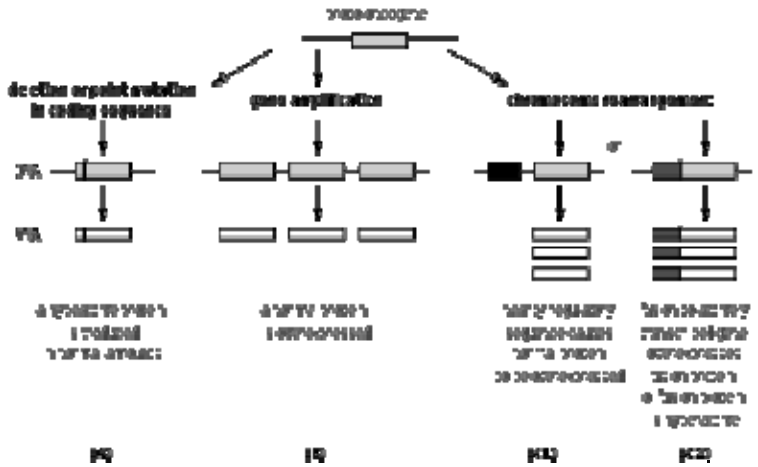

Figure 3:Oncogenes vs proto-oncogene

Because *KRAS* mutation is the most important changing factors in *EGFR* downstream molecules, it is regarded as a molecular biomarker for anti-*EGFR* therapy in *CRC*. Some recent studies indicated that anti-epidermal growth factor receptor (epidermal growth factor receptor-directed monoclonal antibodies, such as Cetuximab or Panitumumab) treatments in advanced colorectal cancer patients with *KRAS* mutations are not useful.

Drugs that target *VEGF*	Drugs that target *EGFR*
• Bevacizumab (Avastin) • Ramucirumab (Cyramza) • Ziv-aflibercept (Zaltrap)	• Cetuximab (Erbitux) • Panitumumab (Vectibix)

Conclusion

According to The Cancer Genome Atlas Network *APC, TP53, KRAS, PIK3CA, FBXW7, SMAD4, TCF7L2* and *NRAS,CTNNB1 , SMAD2, FAM123B* and *SOX9* genes have undergone mutations in *CRC*.

In recent decades, *KRAS* testing is an vital method for selecting an appropriate therapy in *CRC*; however, other factors such as the tumor sample selection, *BRAF, PIK3CA, PTEN* and *MSI* analysis are helpful in prognosis procedures too.

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2. Tan, C. and X. Du. (2012). KRAS mutation testing in metastatic colorectal cancer. *World J Gastroenterol* 18(37): 5171-5180.
3. https://en.wikipedia.org/wiki/KRAS#/media/File:KRAS_protein_3GFT.png
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ASSOCIATION BETWEEN EYE COLOR AND ALCOHOL DEPENDENCE

In 2015 the first study was published by Arvis Sulovari et al. about a relevance between eye color and the chance of becoming alcoholics.

Arvis Sulovari from Department of Microbiology and Molecular Genetics, University of Vermont, Burlington, Vermont and his colleagues believed that European American people with green, grey and light brown eyes had a higher rate of alcohol dependence than patient with dark brown eyes. "These results can be observed in the clinic for alcohol dependence detection" Sulovari says.

Li says, "the genetic components of eye color located on the same chromosome as the genes related to excessive alcohol use. However, these results are not enough and more research is needed."

In this study 1,263 European-Americans patients and Control groups for population stratification were used.

Researchers discovered that the genetic parts of eye color located on the same chromosome as the genes related to excessive alcohol use. Furthermore, they discovered linkage disequilibrium among an eye color genes, AD-related *GABA* receptor gene cluster, *GABRB3/ GABRG3, OCA2/HERC2* AD-related *GRM5* and pigmentation-linked *TYR*. However, these results are not enough and more research is needed.

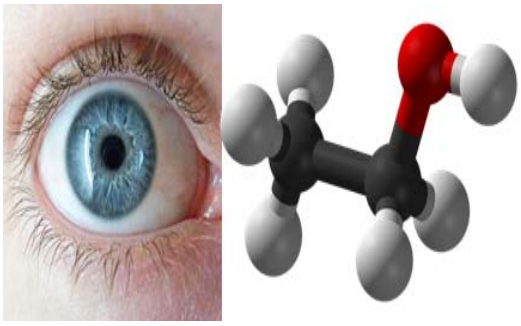

Figure 1. Association between Eye color and alcohol dependence.

References:

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NOVEL MUTATION GENE IN HEREDITARY COLON CANCER

Under the observation of Center for Hereditary Tumor Syndromes, University of Bonn, a team of human genetic scholars found a rare mutation in the *MSH3* gene in patients with hereditary colon cancer. This article published in The American Journal of Human Genetics. In this research many groups worked together including scientists from the Biomedical Research Laboratory, Goethe-University Frankfurt, the Howard Hughes Medical Institute and Yale University School of Medicine (USA).

They examined exome sequencing of leukocyte DNA from more than 100 patients with polyps and found compound-heterozygous loss-of-function (LoF) mutations(c.1148delA, c.2319-1G>A, c.2760delC, and c.3001 -2A>C) in 2 patients. It is known that polyps can raise the risk of malignancy, when they are left.

MutS Homolog 3 (*MSH3*) Also known as *DUP* and *MRP1* is a DNA mismatch repair protein that takes part in the mismatch repair (*MMR*) system.

The above-mentioned protein has two functions:

1.The first task of *MSH3* is preserving the genome from mutations

2.The second task is playing an important role as a tumor suppressor protein by repair of somatic mutations in DNA .

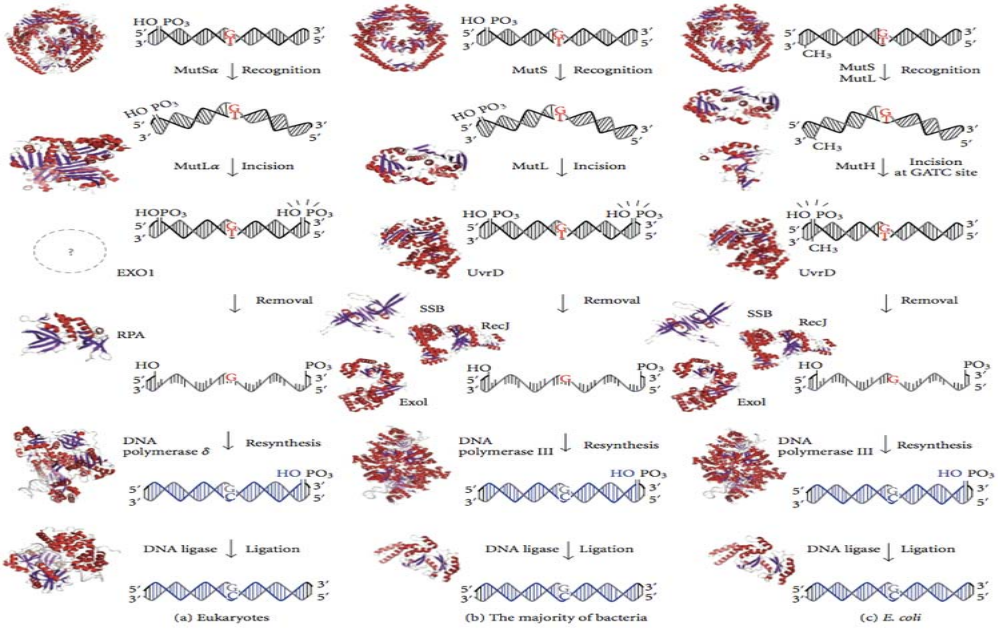

Figure 1. DNA mismatch repair pathways

The mutations lead to disorganization of the functional mentioned protein and the RNA levels in normal and tumor tissue, then genetic mutations accumulate in the most recurrent incidence of colorectal polyps. "In this hereditary colon cancer, the *MSH3* gene mutations have recessive inheritance. This means that the children of affected parents have a very low risk of expanding cancer and *MSH3* mutations show an extra category of colorectal adenomatous polyposis" explains *Dr. Isabel Spier* from the Institute of Human Genetics.

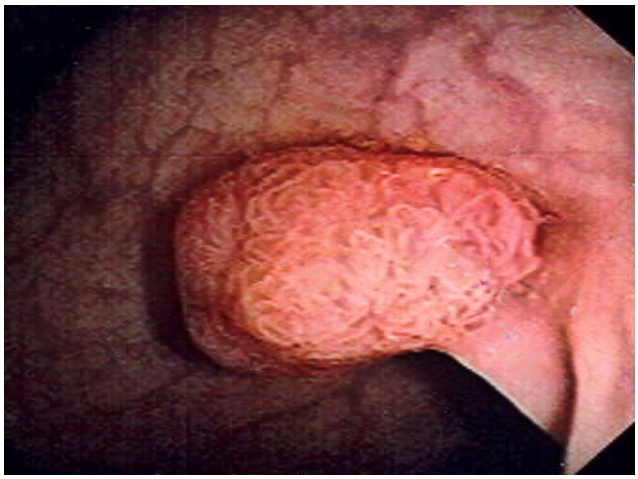

Figure 2. Polyp of sigmoid colon

References:

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3. https://en.wikipedia.org/wiki/MSH3
4. https://en.wikipedia.org/wiki/DNA_mismatch_repair#/media/File:DNA_mismatch_repair.png
5. https://en.wikipedia.org/wiki/Colorectal_polyp#/media/File:Polyp-2.jpeg
6. Stefan A. and et al. (2016). Exome sequencing identifies biallelic MSH3 germline mutations as a recessive subtype of colorectal adenomatous polyposis. *The American Journal of Human Genetics*, 99(2): 337-351.

MORE OXYGEN CAN CAUSE MORE TUMORS

At present, patients with lung cancer have the worst prognosis in the United States.

More than 100,000 new cases per year experience other types of cancer such as prostate and colorectal in this country. The specified risk factors in lung cancer include: smoking, genetic factors and long-term exposure to carcinogens.

According to results of Biological & Medical Informatics, University of California, San Francisco, the oxygen can diagnose as a stimulus of free radical damage, carcinogenesis, tumor cell invasion, angiogenesis and metastasis.

"To find out whether this vital molecule can play a significant role in human tumorgenesis according to age-adjusted cancer incidence, our teams collected patients by the National Cancer Institute through sections of the height-varying Western United States. Those positions differ in height from 11 meters under sea level to 3,473 meters above sea level. The height grows from the lowest area to the highest, the concentration of oxygen in the air drops by 34.9 percent" Kamen P.Simeonov says.

Under oxidative stress situations, excessive *ROS* leads to oncogenic stimulation, increased metabolic activity, serious lesions in cell, proteins, lipids, DNA and mitochondrial malfunction and contribute to carcinogenesis.

Breathed molecular oxygen (O_2) leads to organization of reactive oxygen species (*ROS*). *ROS* is also generated by radiation that has ionizing property or incomplete reduction of O_2 during normal metabolism of oxygen in cells.

ROS also known as a highly unstable molecule, has vital roles in cell signaling and homeostasis.

In this article Daniel S.Himmelstein et al. understood that for every kilometer of elevation achieved, lung cancer prevalence decreased nearly 13 percent and the rates of non-respiratory cancers did not indicate any association to elevation.

References:

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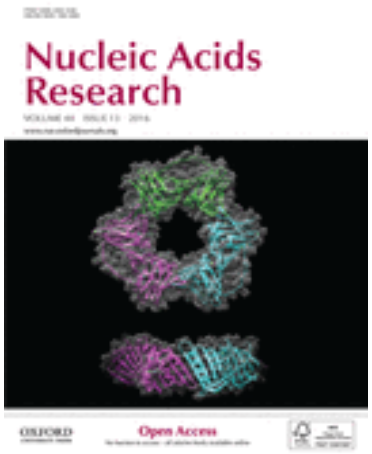
THE JOURNAL OF BIOCHEMISTRY

Impact Factor: 2.397

Scope: Covers about Biochemistry, Molecular Biology, Cell, and Biotechnology written in English.

ISSN: 1756-2651

NUCLEIC ACIDS RESEARCH (NAR)



Impact Factor: 9.202

Scope: Focus on physical, chemical, biochemical, biological aspects of nucleic acids and proteins involved in nucleic acid metabolism and their interactions for example contains:

CRISPR modification of DNA sequences, functional design of RNA, antibody, and protein structures, and etc.

ISSN: 1362-4962 (online), 0305-1048 (print)

THE JOURNAL OF IMMUNOLOGY

Impact factor: 4.92

Scope: Focus on innate and adaptive immunity, inflammation, clinical immunology, autoimmunity and etc.

ISSN: 1550-6606

GLYCOBIOLOGY

Impact factor: 3.283

Scope: Including results of biological functions of glycan, such as glycoproteins, glycolipids, proteoglycans and free oligosaccharides, and on proteins that specifically interact with glycan.

ISSN: 1460-2423

PROTEIN ENGINEERING, DESIGN AND SELECTION (PEDS)

Impact factor: 2.364

Scope: Publishes papers and review articles useful for the protein engineering in biotechnology and therapy, and for understanding protein fundamental properties of activity, stability, folding, misfolding and disease.

ISSN :1741-0134

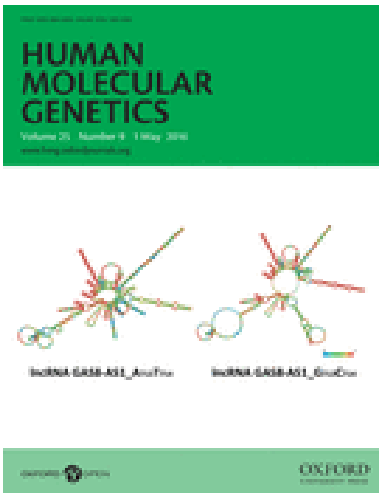
JOURNAL OF BIOTECHNOLOGY

Impact factor: 2.667

Scope: Focus on molecular biology, physiology/biochemistry, biotechnology, Genomics, bioinformatics and etc.

ISSN: 0168-1656

HUMAN MOLECULAR GENETICS



Impact Factor: 5.985

Scope: Including a wide access of subjects in all forms of genome-wide association studies, medical genetic disorders, developmental genetics, cancer genetics, neuro-genetics, genome-wide association studies and other types of therapy in genetic disorders and etc.

Online ISSN: 1460-2083

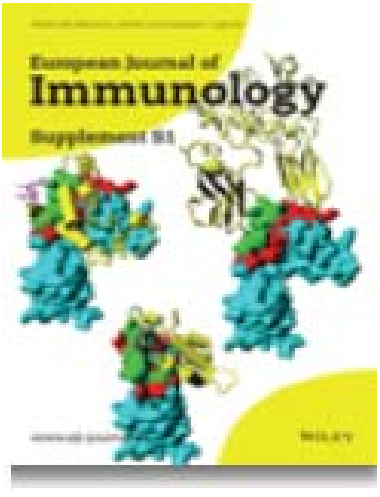
DNA RESEARCH

Impact Factor: 5.267

Scope: Covers about structures and functions of genes, genomes and nucleotide sequencing technologies

Online ISSN: 1756-1663

EUROPEAN JOURNAL OF IMMUNOLOGY



Impact Factor: 4.179

Scope: Allergy, inflammation, immunodeficiency, autoimmunity, tumor immunology and etc.

ISSN: 1521-4141

Announcements

http://www.genetics-gsa.org/conferences/

http://www.genetics-gsa.org/conferences/

http://www.genetics-gsa.org/conferences/

Announcements

2017 BIO International Convention

http://convention.bio.org/2017/

hgm
HUMAN GENOME MEETING

From Genomics to Therapy
5 – 7 February 2017
Hotel Barceló Sants, Barcelona, Spain

hgm 2017
HUMAN GENOME MEETING

http://www.hugo-hgm.org/

Helmholtz Zentrum München,
Munich, Germany
April 5—7, 2017

Chromatin and epigenetics:
from mechanism to function

https://www.eshg.org/830.0.html

HYPOXIA

Hypoxia is a situation in which whole or part of the body and tissues loses oxygen supply. Hypoxia could be regulated as either generalized or local Often hypoxia is a pathological position, but different forms of arterial oxygen concentrations can happen in human with normal physiology, for instance in a severe physical exercise with hypoventilation. Hypoxia is different from hypoxemia and anoxemia, so that hypoxemia and anoxemia refer to base or zero arterial oxygen store situation. Hypoxia may result from a breakdown at any phase in the transfer of oxygen to cells because of :

1. Reducing pressures of oxygen
2. Altitude
3. Ischemia
4. Anemia (insufficient available hemoglobin)
5. Carbon monoxide poisoning
6. Cyanide poisoning
7. Problems with a spread of oxygen in the lungs
8. Lack of hemoglobin
9. Problems with breathing rhythm and blood flow

Treatment and devices such as nasal cannula, simple oxygen facemask, non-rebreather mask for delivering oxygen and bag valve mask, depend on the cause of hypoxia.

References:

1. https://en.wikipedia.org/wiki/Hypoxia_(medical)
2. http://www.news-medical.net/health/Hypoxia-Treatment.aspx
3. https://en.wikipedia.org/wiki/Hypoxia_(medical)#/media/File:Cynosis.JPG

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD, or chronic obstructive pulmonary disorder, is an advanced disease that lead to breathing hard. In this disorder symptoms unexpectedly gets worse over time. Severe COPD can limit routine activities.

COPD has three main types:

1. Chronic bronchitis
2. Emphysema
3. Combination of both symptoms (seen in most people)

COPD may lead to coughing, breathing noisily, truncation of breath, chest hardness, and etc. COPD should be distinguished from asthma, congestive heart failure, pulmonary embolism, pneumonia, pneumothorax, bronchopulmonary, dysplasia, tuberculosis and produces much mucus. Cigarette, smoking, air pollution, job-related exposures and genetics are the leading reasons of COPD. This disease has not any special treatment yet. However, lifestyle changes help patients to fight their lung problems.

Reference:

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3. https://en.wikipedia.org/wiki/Chronic_obstructive_pulmonary_disease#/media/File:Centrilobular_emphysema_865_lores.jpg

PTEN GENE PRODUCT

Phosphatase and tensin homolog (*PTEN*) becomes a tumor suppressor by negatively controlling *Akt/PKB* signaling pathway that is changed in different cancers at high rates. The functional protein produced by this gene is a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase. *PTEN* binds the membrane through two domains: a phosphatase domain with the active site (includes of three loops, the *TI*- Loop, the *P*-Loop, and the *WPD* Loop), and a *C2* domain that attaches to the phospholipid membrane. During cancer growth, mutations and deletions in *PTEN* enzymatic activity site lead to increased and decreased cell proliferation and apoptosis respectively. Frequent *PTEN* mutation or inactivation occurs in many cancers such as glioblastoma, endometrial cancer, prostate, lung and breast cancer.

References:

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