SAFETY OF SUBLINGUAL IMMUNOTHERAPY

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Sublingual immunotherapy (SLIT) is now recognized as a viable alternative to the classical injection route and it is currently used in everyday clinical practice in Europe. Sublingual administration is particularly attractive for children since it is completely pain-free. To date, no fatalities from SLIT have been reported, but two cases of anaphylaxis to inhalant allergens have been reported. The large majority of the adverse events reported in literature is described as mild. Most of them involve the mouth (burning or itching) or the gastrointestinal tract (stomach ache, nausea) and usually self-resolve in a few days without any intervention. At present, SLIT represents the main option for allergists, however, tablet immunotherapy could become an interesting alternative to sublingual drops.

IMPACT OF IL-18 ON INFLAMMATION

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IL-18 is produced by many cell types, such as Kupffer cells, keratinocytes, macrophages, dendritic cells, and activated T cells stimulated by LPS. It is an important regulator of both innate and acquired immune responses. IL-18 plays a central role in rheumatoid arthritis because of the T cells and macrophages that invade the synovial fluid. These finding support a role for IL-18 in inflammation, allergy and immune diseases.

A RE-EVALUATION OF THE MITOGENIC EFFECT OF SEROTONIN ON VASCULAR ENDOTHELIAL CELLS

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Serotonin is an extracellular mediator recognized by seven different types of receptors, thus giving rise to pleiotropic intracellular responses. One of these responses is the activation of proliferation for a number of cell types. The induction of proliferation of otherwise quiescent endothelial cells is a key step of angiogenesis. Previously published work concerning the effect of serotonin on endothelial cell proliferation is controversial. The present work is aimed to re-evaluate the mitogenic role of serotonin on endothelial cells, since a pro-angiogenic role for serotonin could be hypothesized if its mitogenic potential on these cells were confirmed. By using three different types of endothelial cells and three different experimental approaches, we demonstrate that serotonin cannot be considered a general mitogen for endothelial cells.

HORMONES OF HYPOTHALAMIC-PITUITARY-THYROID AXIS ARE SIGNIFICANT REGULATORS OF SYNTHESIS AND SECRETION OF VITAMIN K-DEPENDENT PLASMA COAGULATION FACTORS

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Present data about hormonal regulation of haemostasis are often contradictory and are mostly based on clinical observations. The aim of the current research is to study the effects of the hormones of hypothalamic-pituitary-thyroid (HPT) axis on plasma levels (i.e. on the synthesis and secretion) of vitamin K-dependent coagulation factors in rats. The study was carried out on 65 male Wistar rats, divided into five groups. The animals were injected subcutaneously (s.c.) once daily for three consecutive days as follows: the first group was injected with Thyrotropin releasing hormone (TRH), in a dose of 0.06 mg/kg b.w.; the second group by Thyroid stimulating hormone (TSH), with a dose of 1 MU/kg b.w., the third and the fourth group respectively with Liothyroninum (Trijodthyronin – T_3) and Levothyroxinum (Thyroxin – T_4) with a dose of 0.08 mg/kg b.w. each. The control group rats were injected with saline (the solvent of the hormones), following the same schedule and volume per kg b.w. The necessary quantity of blood was acquired by a cardiac puncture under ether narcosis, and antigen levels of plasma factors II, VII, IX and X (FII:Ag, FVII:Ag, FIX:Ag and FX:Ag) were determined by ELISA kits (Diagnostica Stago, France). TRH, TSH, T_3 and T_4 significantly decreased the plasma antigen levels of FII and FVII ($p<0.001$). TRH, T3 and TSH reduced significantly FIX:Ag level($p<0.001$ for TRH and T_3 and $p<0.05$ for TSH) while T_4 did not exert significant changes ($p>0.05$). FX:Ag level was also significantly reduced by TRH, T_3 ($p<0.001$), TSH and T_4 ($p<0.01$). Plasma levels of vitamin K-dependent coagulation factors FII:Ag, FVII:Ag, FIX:Ag and FX:Ag are significantly reduced under the influence of the hormones of hypothalamic-pituitary-thyroid axis which signifies their decreased synthesis and secretion. T_4 does not induce substantial changes in FIX:Ag plasma level.

EFFECT OF PHYTOCHEMICAL CONCENTRATIONS ON BIOLOGICAL ACTIVITIES OF CRANBERRY EXTRACTS

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Plants of cranberry (*Vaccinium macrocarpon*) furnish edible fruits and derivates that have been used for the prevention and treatment of urinary tract infections. In the present work we compare two commercial extracts that contain proanthocyanins (PACs) at 4% and 20% for antimicrobial, antiproliferative, antiradical and protective properties against oxidative stress on cell lines. Both extracts showed antimicrobial activity (MIC values range 3-100 µg/ml). Extract at 20% PACs showed higher antiproliferative activity against HepG2 and MCF7 cells, but not against C2C12 cells. Both extracts showed a dose-dependent free-radical scavenging capacity, and a protective effect on the cell damage was also revealed by reduction of intracellular active oxygen species release. Cranberry extracts confirmed antioxidative proprieties and efficacy in reduction of cell viability that resulted stronger against tumor cells. The pretreatment with cranberry extracts, furthermore, reveal an increase of cell resistance against oxidative stress, suggesting a potential role as a dietary supplement in preventing free-radical damage. The proanthocyanidin content is critical to determine the extract efficacy. In cellular experiments the extracts resulted clearly differentiated in their activity, and the activity was strongly influenced by PACs content. Only in DPPH test the free radical scavenging activity seemed to be directly related to proanthocyanidins content.

EFFECT OF A FERMENTED NUTRACEUTICAL ON THIOREDOXIN LEVEL AND TNF-α SIGNALLING IN CIRRHOTIC PATIENTS

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The aim of this study is to gain further insights into the possible nutraceutical effect on redox balance via thioredoxin (Trx) modulation and on the intrinsic susceptibility of monocytes to generate an inflammatory response. The study group consisted of thirty-two patients with compensated Child A-C, HCV-related cirrhosis. The patients were supplemented for 6 months with 6g/day of a certified fermented papaya preparation (FPP). Fifteen unsupplemented, age/gender-matched healthy subjects served as controls. The patients filled in a detailed diet-life style questionnaire, and blood samples were collected to test routine biochemistry, Trx, redox status (GSH, GSSG, GSH/GSSG ratio, 4-HNE and α-tocopherol). Moreover, isolated monocytes were tested for *ex-vivo* LPS-stimulated TNFα production and TNFα mRNA. As compared to control, patients with liver cirrhosis showed a significantly higher serum level of Trx. A significant correlation occurred with GSH/GSSG ratio in Child B and C patients. FPP supplementation brought about a significant reduction of Trx with levels comparable to the ones of healthy controls. Ten patients Child C (31.2%) showed borderline low levels of α-tocopherol while all cirrhotic patients, as a whole, showed a significantly abnormal redox balance. Supplementation with FPP did not modify α-tocopherol depletion but significantly improved redox balance parameters. Patients with liver cirrhosis showed a significantly upregulated TNF-α production in a time-dependent manner and this effect was more pronounced in more advanced stages of the disease and showed a significant correlation with α-tocopherol level. Supplementation with FPP significantly, although partially, downregulated TNF-α production from monocytes. Taken altogether, it would appear that the typical oxidative-inflammatory biochemical milieu of these patients is mirrored by a significant TNF-α upregulation at a monocyte level while a targeted nutraceutical might be a potentially amenable intervention to be part of validated scheduled treatments.

CIRCULATING LEVELS OF CYTOCHROME C, GAMMA-GLUTAMYL TRANSFERASE, TRIGLYCERIDES AND UNCONJUGATED BILIRUBIN IN OVERWEIGHT/OBESE PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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Non-alcoholic fatty liver disease, characterized by hepatocyte apoptosis, is distinct in fatty liver and non-alcoholic steatohepatitis, the more severe form. Apoptotic cell death is caspase-dependent and associated with mitochondrial membrane depolarization and cytochrome c release. Adhering to the hypothesis that the exposure of hepatocytes to free fatty acids, resulting in increased ROS production and mitochondrial damage, is balanced by the presence of antioxidant substances, circulating levels of gamma-glutamyl transferase, cytochrome c, triglycerides and unconjugated bilirubin were explored in patients suffering from non-alcoholic fatty liver disease with different severity. One hundred and eighty-six consecutive patients who presented recent ultrasound feature of "bright liver" without any liver disease of known origin were enrolled, eighty-nine of whom underwent liver biopsy. Forty-five subjects were allocated on the basis of histology in fatty liver group while 44 patients formed the group with non-alcoholic steatohepatitis. A cohort of 27 young, lean, apparently healthy individuals was selected as control group. The levels of gamma-glutamyl transferase were normal or slightly increased, while unconjugated bilirubin concentrations were elevated in all the spectra of non-alcoholic fatty liver disease. Comparing the present results with relevant findings from other studies dealing with diseases characterized by apoptosis, we did not find high circulating levels of cytochrome c in non-alcoholic fatty liver disease. What is more, our patients, categorized as suffering from simple fatty liver or from the more severe non-alcoholic steatohepatitis, had similar levels of cytochrome c and gamma-glutamyl transferase, p=0.19 and 0.11. Serum triglycerides were higher in patients with non-alcoholic fatty liver disease than in the healthy group, p=0.001. These findings likely reflect a balance between oxidative stress and anti-oxidant response rather than a lack of reliability of cytochrome c as a reliable biomarker of mitochondrial damage.

VASCULAR ENDOTHELIAL GROWTH FACTOR ENHANCES *IN VITRO* PROLIFERATION AND OSTEOGENIC DIFFERENTIATION OF HUMAN DENTAL PULP STEM CELLS

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Mesenchymal stem cells (MSC), isolated from dental tissues, are largely studied for future application in regenerative dentistry. In this study, we used MSC obtained from human dental pulp (DPSC) of normal impacted third molars that, when cultured in lineage-specific inducing media, differentiate into osteoblasts and adipocytes (evaluated by Alizarin Red S and Red Oil O stainings, respectively), thus showing a multipotency. We confirmed that DPSC, grown under undifferentiating conditions, are negative for hematopoietic (CD45, CD31, CD34, CD144) and positive for mesenchymal (CD29, CD90, CD105, CD166, CD146, STRO-1) markers, that underwent down-regulation when cells were grown in osteogenic medium for 3 weeks. In this condition, they also exhibit an increase in the expression of osteogenic markers (runx-2, alkaline phosphatase) and extracellular calcium deposition, whereas the expression of receptors (VEGFR-1 and -2) for vascular endothelial growth factors (VEGF) and related VEGF binding proteins was similar to that found in undifferentiated DPSC. Exposure of DPSC growing under undifferentiating or osteogenic conditions to VEGF-A_{165} peptide (10-40 ng/ml) for 8 days dose- and time-dependently increased the number of proliferating cells without inducing differentiation towards endothelial lineage, as evaluated by the lack of expression of specific markers (CD31, CD34, CD144). Additionally, exposure of DPSC cultured in osteogenic medium to VEGF-A_{165} for a similar period enhanced cell differentiation towards osteoblasts as evaluated after 14 and 21 days by Alizarin Red S staining and alkaline phosphatase activity quantification. These findings may have clinical implications possibly facilitating tissue repair and remodeling.

PHYSIOLOGICAL ANALYSIS OF 8-ISO-PGF2 ALPHA: A HOMEOSTATIC AGENT IN SUPERFICIAL BLADDER CANCER

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Recent studies underscore the importance of oxygen supply in bladder cancer. Tumour growth stimulates the production of vasoactive factors to increase oxygen delivery to tissues by vasodilatation. Any vasoconstrictive mediator could impair this vasodilatation reducing the oxygen supply. 8-Iso-PGF2 alpha is a potent vasoconstrictive agent. The aim of this work is to determine 8-Iso-PGF2 alpha release in healthy bladder mucosa and in superficial bladder cancer in order to investigate a pathophysiological vasoconstrictor answer of the superficial bladder cancer. The study was conducted on a sample of 12 patients; for every subject studied 8-Iso-PGF2 alpha release was assayed in healthy bladder mucosa and in superficial bladder tumour. 8-Iso-PGF2 alpha release was significantly reduced ($p < 0.001$) in superficial bladder cancer compared with healthy bladder mucosa. The inhibition of the production of a powerful vasoconstrictor such as 8-Iso-PGF2 alpha in the vascular homeostatic mechanism of bladder cancer can represent a response of the tumor tending to contrast an antagonist effect of vasodilatation and the necessity to support the oxygen supply.

INCREASED SERUM LEVEL OF XANTHINE OXIDOREDUCTASE IN LIVER TRANSPLANTED PATIENTS

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Xanthine oxidoreductase (XOR) leakage into serum has been observed in various types of liver pathology as well as after liver transplantation (LT). We determined the amount of XOR associated with LT to investigate the changes in serum enzyme level during the LT procedure and the post-operative period. Additionally, we examined whether there was any correlation between XOR levels and the surgical technique. XOR levels were measured by a competitive ELISA. In a first group of patients, the portal vein was flushed before the liver and systemic reperfusions, which occurred simultaneously. In the second group, the graft was flushed with blood from the portal vein before the systemic reperfusion. XOR showed a marked elevation in the caval effluent collected during LT and was higher compared to control serum levels at all time points that were examined after LT. The XOR levels during LT were also higher than samples taken pre-LT or from the portal blood flush before reperfusion. The XOR level was higher in Group 2 than in Group 1. Enhancement of the XOR serum level during LT was not derived from enterocytes, and it should be attributed to enzyme leakage from graft liver cells. We report the elevation of serum XOR during the three weeks following LT for the first time, as well as the influence of the graft reperfusion technique on XOR serum level.

HIGH ARTICULAR LEVELS OF THE ANGIOGENETIC FACTORS VEGF AND VEGF-RECEPTOR 2 AS TISSUE HEALING BIOMARKERS AFTER SINGLE BUNDLE ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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Various factors may account for the positive association between meniscal repair and anterior cruciate ligament reconstruction, one being the modulation of healing response of meniscal fibrochondrocytes by growth factors released with intra-articular bleeding and fibrin clot formation. Analysis of vascular endothelial growth factor (VEGF) and its receptors, VEGFR1 and VEGFR2, may be useful in the clinical assessment of bone and soft-tissue remodeling. We measured systemic and local levels of VEGF (VEGF165), VEGFR1 and VEGFR2 after either arthroscopic partial meniscectomy (APM) or single-bundle anterior cruciate ligament reconstruction (ACLR) in order to determine the local effect of bone tunnelling and notchplasty on the release of these growth factors. The study population included 40 patients: 20 consecutive patients had undergone ACLR with hamstring grafts and 20 had undergone APM. Thirty minutes after the end of the operation, knee joint fluid samples were collected via the drainage tube and at the same time venous blood samples were drawn. In both sets of samples, VEGF, VEGFR1 and VEGFR2 concentrations were determined by enzyme-linked immunosorbent assay (ELISA). No significant differences in VEGF, VEGFR1 or VEGFR2 concentrations in the venous blood were observed between the two treatment groups. In contrast, VEGF and VEGFR2 levels were significantly higher in the knee joint fluid of the ACLR group; furthermore, VEGF and VEGFR1 were significantly higher in the knee joint fluid than in the venous blood, whereas VEGFR2 was lower in the knee joint fluid than in the venous blood. Local release of VEGF and its angiogenetic receptor VEGFR2, but not the negative regulator VEGFR1, was significantly higher after ACLR than after APM, indicating a better vasculogenic potential for enhanced bone-graft and meniscus healing. These results could suggest that VEGF and VEGFRs could be considered as good biomarkers of tissue healing after knee joint surgery.

HISTIDINE-TRYPTOPHAN-KETOGLUTARATE SOLUTION HELPS TO PRESERVE ENDOTHELIAL INTEGRITY OF SAPHENOUS VEIN: AN IMMUNOHISTOCHEMICAL AND ULTRASTRUCTURAL ANALYSIS

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The aim of the study is to demonstrate the ability of HTK (Histidine-tryptophan-ketoglutarate) solution to preserve endothelium. Ten saphenous veins (SVs) were prospectively collected from 10 patients who underwent coronary artery bypass grafting (CABG). The SVs were divided into two sets of segments, one of which preserved in HTK solution at 4°C (group A), and the other preserved at 4°C in saline solution NaCl 0.9% (group B); ten pieces from the SVs were processed as control. The control sample was fixed in 10% neutral buffered formalin immediately after harvesting. The observation lasted up to the 5th postoperative day. A morphological, ultrastructural, and immunohistochemical analysis (CD31) was performed on each piece. Immunohistochemical analysis demonstrated significant protection on endothelium in group A compared to group B starting from the 1st observational day. Ultrastructural data confirmed immunohistochemistry. These preliminary results represent a basis for further analysis. They suggest the protective role of HTK solution in preserving endothelial integrity and may imply some clinical benefits in organ protection.

DIGESTIBILITY, PALATABILITY AND EMOTIONAL STATUS AFTER INGESTION OF AN ICED DESSERT: ANALYSIS OF SUBJECTIVE RESPONSES IN 100 HEALTHY VOLUNTEERS

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Food choices are influenced by many factors, perhaps the most important being availability. However, the desire to consume one item over another may be viewed as an outcome of sensory hedonic likes, situation and current internal state. In a previous preliminary report, an improvement of joy and mood, associated with good data of digestibility and palatability, was observed in a group of 30 healthy female subjects who consumed a coffee-flavoured iced dessert immediately after a standardized meal. The aim of this study is to confirm the results previously obtained in a smaller population and to investigate whether any differences between male and female subjects could be observed concerning the digestive process and emotional status. One hundred volunteers, after ENT and psychological assessment, were asked to fill out a Psycho-Emotional Questionnaire to assess their basal emotional pattern before the consumption of an iced coffee-flavoured dessert after a standard meal. After the meal they completed an Organoleptic-Sensory questionnaire, a Dynamic Digeribility questionnaire and again the Psycho-Emotional Questionnaire. In our study, most of the 100 subjects found the tested coffee-flavoured iced dessert pleasant according to the Organoleptic-Sensorial Questionnaire (OSQ), in terms of taste, aspect, texture and smell; moreover, the Dynamic Digestibility Questionnaire (DDQ) showed a good digestive experience in 71 subjects. According to the Psycho-Emotional Questionnaire (PEQ), an improvement of joy, activation and mood, associated with good data of digestibility and palatability was recorded. All these observations are statistically significant and the results seem to show a positive correlation between pleasure in eating such a product and emotional status. No statistically significant differences were recorded between male and female subjects.

MAJOR DEPRESSIVE DISORDER, ANHEDONIA AND AGOMELATINE: AN OPEN-LABEL STUDY

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Despite a wide range of available antidepressants, the effect of the treatment is often suboptimal and there is a need for more effective and better tolerated drugs. Unlike other antidepressants, agomelatine represents a new approach to depression with an innovative mechanism of action. It is an agonist of melatoninergic receptors MT1 and MT2 and a selective antagonist of 5-HT2c receptors. In this open-label 8-week study we aimed to investigate the efficacy of agomelatine on depressive symptoms in patients with major depression. Secondary endpoints were the effect of agomelatine on anhedonia. Thirty major depressive patients received a flexible dose (25-50 mg; per os, daily) of agomelatine. Depressive (Hamilton Depression Scale) and anxious (Hamilton Anxiety Scale) symptoms, anhedonia (Snaith Hamilton Rating Scale), and sleep quality (Leeds Sleep Evaluation Questionnaire) were assessed. Twenty-four patients (80%) completed 8 weeks of treatment. Significant improvements were seen at all visits on the HAM-D ($p<.05$), HAM-A($p<.01$), SHAPS ($p<.05$), LSEQ ($p<.05$). Nine subjects (30%) were responders and 5 (17%) remitters at week 1; 18 (60%) were remitters by the end of the trial. There was no serious adverse event. No aminotrasferase elevations were noted. In line with previous studies, in which agomelatine was associated with early clinical improvement, this study also provides evidence of an early response and the findings of improvements in depression scores. Moreover, this is the first study where agomelatine was effective in the treatment of anhedonia. Additional trials are needed to delineate the place of agomelatine in the contemporary pharmacotherapy for depressive disorders.

NEUROGENIC POTENTIAL OF MESENCHYMAL-LIKE STEM CELLS FROM HUMAN AMNIOTIC FLUID: THE INFLUENCE OF EXTRACELLULAR GROWTH FACTORS

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Amniotic fluids contain human stem cells, among which mesenchymal stem cells could be isolated. These cells have multipotent differentiation ability and no tumorigenic potential after transplantation in mice. These features make them good candidates for *in vitro* studies and for therapeutic purposes. The aim of this study was to isolate mesenchymal stem cell-like cultures from different amniotic fluids in order to study *in vitro* their neurogenic potential and assess if this process could be reproducible and standardized. We focused attention on the possible differential effects of soluble growth factors. Immunophenotypical and molecular characterization showed that the 31 amniotic fluid-derived cultures expressed mesenchymal markers as well as some stemness properties. These cells also appeared to be responsive to purines or acetylcholine showing an intracellular calcium increase, also reported for mesenchymal stem cells derived from other sources. Interestingly, in the presence of retinoic acid, these cells assumed a neuronal-like morphology. In addition, functional and molecular analyses revealed that retinoic acid-treated cells showed immature electric functional properties, the expression of neuronal markers and stemness genes. In conclusion, even if further investigations are required, the results presented here contribute to support the finding that amniotic fluid contains cells able to differentiate *in vitro* towards neural-like lineage in the presence of retinoic acid. The ability of retinoic acid to induce a possible neuronal progenitor culture makes the model useful to study a possible *in vivo* transplantation of these cells and to contribute to define the protocols for cell therapy.

A GREENSTICK OSTEOPOROTIC TIBIAL FRACTURE WHILE ON CHEMOTHERAPY IN A 12-YEAR-OLD GIRL WITH OSTEOSARCOMA OF THE KNEE: DOES A PREVENTIVE ROLE EXIST FOR AGENTS THAT REDUCE IATROGENIC BONE LOSS AND SKELETAL-RELATED EVENTS?

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In patients with osteosarcoma several causative factors are implicated in the occurrence of osteoporosis, such as no weight-bearing, pre- and post-surgical immobilization, and neoadjuvant and adjuvant chemotherapy. Nevertheless, osteoporotic fractures are a rare complication in young patients. We report the case of a spontaneous greenstick fracture of the distal tibia occurring during adjuvant chemotherapy in a 12-year-old Caucasian girl. Among the various drugs, the main role of methotrexate was investigated. A review of the literature is also presented along with a discussion about the role of preventive agents able to reduce the occurrence of osteopenia and/or osteoporosis following cancer treatment.

THE TIMING CLOCKWORK OF LIFE

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[1] First God made heaven and earth [2]
The earth was without form and void,
and darkness was upon the face of the deep;
and the Spirit of God was moving over the face of the waters. [3]
And God said, "Let there be light"; and there was light. [4]
And God saw that the light was good;
and God separated the light from the darkness. [5]
God called the light Day, and the darkness he called Night.
And there was evening and there was morning, one day. [6]
(Genesis, 1,6)

Many aspects of human physiology, metabolism and behaviour vary over the 24-hour day and can have a major impact on our health and well-being. Circadian rhythms are observed at all levels of cellular organization. There are daily oscillations in the levels of enzymes and hormones that affect the timing of cell function, division, and growth. Recent progress in understanding the molecular mechanisms underlying circadian rhythms has been remarkable. In its most basic form, circadian clocks are comprised of a set of proteins that generate a self-sustaining transcriptional-translational feedback loop with a free-running period of about 24 h. One or more of the clock components is acutely sensitive to light, resulting in an oscillator that can be synchronized to local time. The disruption or the reinforcement of the host circadian timing system, respectively, accelerates or slows down cancer growth through modifications of host and tumor circadian clocks.