F-actin

F-actin (also called microfilament or actin filament) is a double-stranded, right-handed helix with 14 actin molecules per strand and turn. F-actin has a diameter of 8 nM and is polarized with a pointed (minus) and a barbed (plus) end.

►Cytoskeleton

Fab Fragments

Fab fragments are variable (specific) regions of antibodies.

►Humanized Monoclonal Antibodies

Factor IIa

►Thrombin
►Coagulation/Thrombosis
►Anticoagulants

FAD

Flavin Adenine Dinucleotide

►Flavin Adenine Dinucleotide
►Vitamin B_2 (Riboflavin)
►Monoamine Oxidases and their Inhibitors

Familial Alzheimer's Disease

This type of disease occurs in families and begins unusually at early age (i.e., onset below the age of 60). Approximately 10% of Alzheimer's disease are familial and are inherited in an autosomal dominant manner with high penetrance. Deterministic genes directly cause the disease. Mutations in three different genes encoding for the amyloid precursor protein (APP) and the presenilins 1 and 2 (PS1 and PS2) have been identified to be responsible for early-onset familial Alzheimer's disease.

In addition, other genes (risk genes) remain to be discovered. Risk genes, such as the apoliprotein E-e4 (APOE-e4) gene, increase the likelihood of developing the disorder.

►Alzheimer's Disease

Familial Hypocalciuric Hypercalcemia (FHH)

A form of PTH-dependent hypercalcemia that results from the presence of one or two CaR alleles bearing inactivating mutations.

►Ca^{2+}-Sensing Receptor (CaR)

Fanconi-Bickel Syndrome

Fanconi-Bickel syndrome (FBS) is a rare type of glycogen storage disease which is caused by homozygous or compound heterozygous mutations within the *SLC2A2* gene encoding GLUT2. More than 100

patients have been reported in the literature. Most patients have the typical combination of clinical symptoms: hepatomegaly secondary to glycogen accumulation, glucose and galactose intolerance, fasting hypoglycemia, a characteristic tubular nephropathy, and severely stunted growth. A total of 34 different *SLC2A2* mutations have been identified with none of them being particularly frequent. No specific therapy is available for FBS patients. Symptomatic treatment is directed towards a stabilization of glucose homeostasis and compensation for renal losses of various solutes.

►Glucose Transporters

Farnesyl Transferase Inhibitors (FTIs)

►Lipid Modifications

FAS Ligand (FasL)

The Fas ligand or FasL is a type II transmembrane protein that belongs to the tumor necrosis factor (TNF) family. The binding of Fas ligand with its receptor induces apoptosis.

►Matrix Metalloproteinases
►Tumor Necrosis Factor
►Apoptosis

FAT10

F-adjacent Transcript-10 (FAT10) is composed of two ubiquitin-like domains and capable to mark conjugated proteins for proteasomal degradation independent of ubiquitin. FAT10 is inducible by IFN-γ and TNF and induces apoptosis when over expressed.

►Ubiquitin/Proteasome

Fatty Acid Transporters

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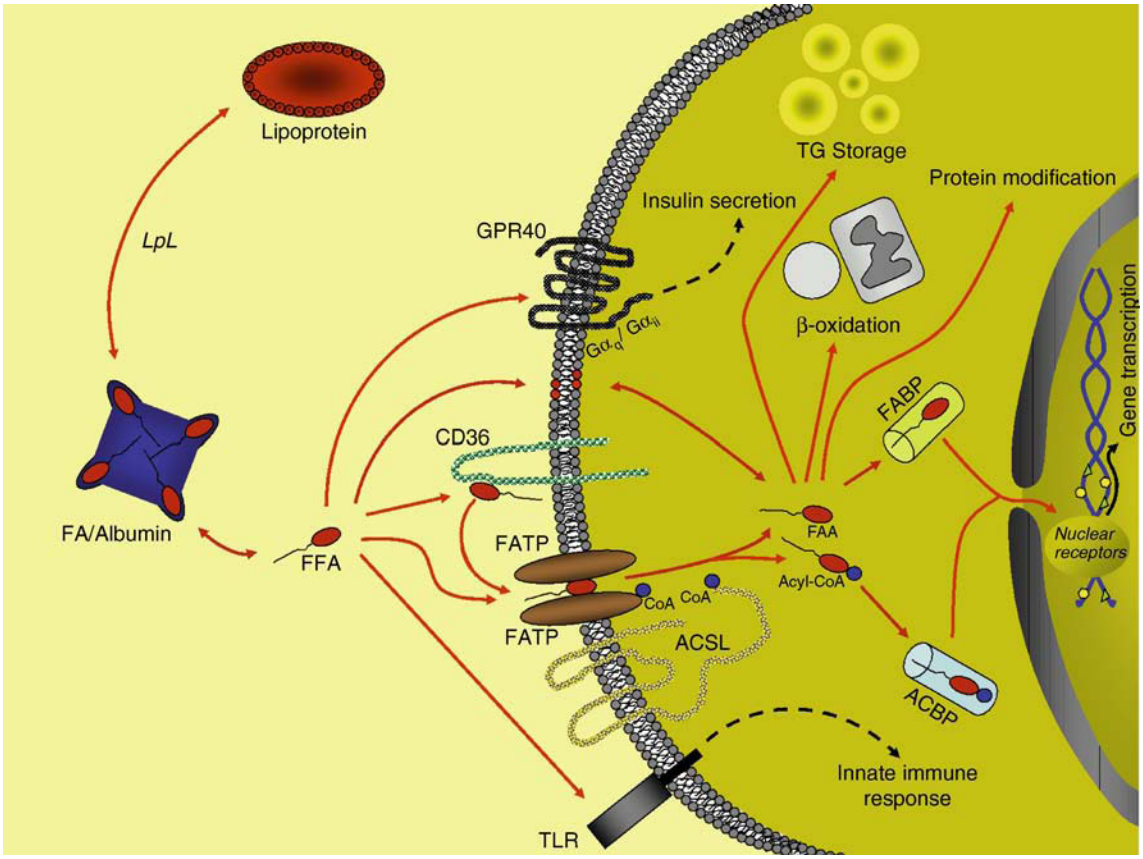
Acronym
FATP

Synonyms
Fatty acid transport protein paralogues 1–6; FATP1–6; Gene symbols SLC27A1–6; Solute carrier family 27A; Very long-chain acyl-CoA synthetase; VLCS

Definition
Fatty acid transport proteins (FATPs) are an evolutionary conserved family of integral membrane proteins found at the plasma membrane and on internal membranes. FATPs facilitate the unidirectional uptake and/or intracellular activation of unesterified long-chain and very ►long-chain fatty acids (LCFAs) into a variety of lipid-metabolizing cells and tissues.

Basic Mechanisms
Introduction
LCFAs are vital components of our diet and contribute to cellular processes including metabolic energy generation and storage, plasma membrane synthesis, and protein anchoring. While in some tissues and cell types LCFAs can signal through membrane receptors, they typically have to first cross the plasma membrane to elicit cellular responses. In general, the uptake of fatty acids from the circulation into cells includes the sequence of (i) localized generation of free fatty acids through hydrolysis of triglycerides (TGs) from lipoproteins by lipases inside the endothelial lumen and rapid binding of fatty acids to albumin, (ii) fatty acid dissociation from albumin followed by passive or active transport across the plasma membrane, and (iii) their association with intracellular binding proteins and subsequent participation in metabolic and signaling processes (Fig. 1).

Uptake of LCFAs across the lipid-bilayer of most mammalian cells occurs through both a passive diffusion of LCFAs and a protein-mediated LCFA uptake mechanism. At physiological LCFA concentrations (7.5 nM) the protein-mediated, saturable, substrate-specific, and hormonally regulated mechanism of fatty acids accounts for the majority (>90%) of fatty acid uptake by tissues with high LCFA metabolism and storage such as skeletal muscle, adipose tissue, liver,

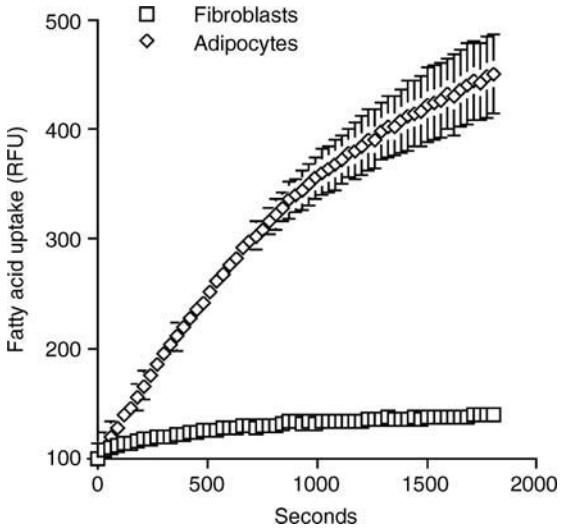


Fatty Acid Transporters. Figure 1 Free fatty acid uptake and action in mammalian cells. Serum free fatty acids (FFA) are generated from lipoproteins by the action of endothelial lipoprotein lipase (*LpL*). At physiological conditions, the majority of FFAs is bound to albumin while the concentration of unbound FFAs in this equilibrium is low. Plasma membrane traversing of FFAs into the cell under these conditions occurs mainly by a protein-mediated mechanism, either by interaction of the FFAs directly with FATP complexes or by a preceding binding to cell-surface proteins, such as CD36, which subsequently hands the FFAs on to the FATPs. On the cytosolic site, FFAs are quickly activated and coupled to coenzyme A (CoA) by the catalysis of long-chain fatty acyl-CoA synthetases (ACSLs) or the by FATPs itself. Fatty acid binding proteins (FABPs) or acyl-CoA binding proteins (ACBPs) facilitate an intracellular unloading of the transporters and the synthetases and can also function as an intracellular fatty acid buffer. In the cell, FFAs can act at different subcellular localizations and have functions in energy generation and storage, membrane synthesis, protein modification, and activation of nuclear transcription factors. In addition to acting intracellularly, unbound FFAs can also signal extracellularly in certain cell types (e.g., by stimulating the G-protein coupled receptor GPR40 in β-cells to induce insulin secretion, or by activating toll-like receptors – TLRs) to initiate the innate immune response).

and heart. The relative contribution of passive diffusion is thought to be higher in cell types that lack fatty acid transporters such as fibroblasts (see Fig. 2) and may be elevated as a result of super-physiological fatty acid concentrations. While several fatty acid handling proteins have been identified (see Fig. 1), recent in vivo studies have particularly highlighted the contribution of FATPs to LCFA uptake, lipid metabolism, and lipid-associated disorders [1].

The Family of FATPs

In humans and mice, the FATP family is comprised of six structurally related members (FATP1–6; 33–57.1% identity in mice) that are found in all fatty acid-utilizing tissues of the body. While substrate preferences are comparable among the different FATPs paralogues, they differ widely in their tissue expression pattern [2]. FATP1 was the first FATP to be identified and is highly expressed in adipose tissue, skeletal muscle and, to a lesser extent, in heart. FATP2 is predominantly expressed in liver and kidney cortex. FATP3 shows a broader expression pattern with high mRNA and protein levels in lung. FATP4 is the only FATP expressed in small intestine and is localized to the apical brush border of the epithelial cells, where it is implicated in the absorption of dietary lipids. FATP4



Fatty Acid Transporters. Figure 2 Quencher-based real-time fatty acid uptake assay with a fluorescently labeled FFA analogue (C1-Bodipy-C12). Predominantly protein-mediated fatty acid uptake by 3T3-L1 adipocytes (diamonds) was compared with diffusion-driven uptake by fibroblasts (squares) using the QBT Fatty Acid Uptake reagent (Molecular Devices Corp., CA, USA), which contains C1-Bodipy-C12 as substrate in conjunction with a cell impermeable quencher. Uptake kinetics was recorded using a Gemini fluorescence plate reader. Error bars indicate the standard deviations from 12 independent wells. RFU: relative fluorescence units.

is also expressed to a lesser extent in other tissues including adipose tissue, liver, skin, and heart. Furthermore, FATP4 together with FATP1 are the predominant FATP paralogues in brain. FATP5 is expressed solely in liver. Confocal immunofluorescent microscopy with isolated primary hepatocytes demonstrated that FATP5 is localized to the plasma membrane of these cells, which was confirmed by immunoelectron microscopy of liver sections, showing a predominant localization of FATP5 protein to basal microvilli in the space of Disse. FATP6 is expressed specifically in heart where it is the predominant FATP paralogue. Immunofluorescence microscopy studies of FATP6 in primate and murine hearts have shown that the protein is exclusively located on the sarcolemma, where it is restricted to areas of the plasma membrane juxtaposed to small blood vessels [1]. In addition to vertebrates, FATP orthologs have been identified in invertebrate, fungi, and prokaryote genomes such as *Caenorhabditis elegans*, *Saccharomyces cerevisiae*, and *Mycobacterium tuberculosis*.

FATP Structure and Mechanism of Transport

Due to the high overall sequence similarity, the presumed secondary structure of all FATP members is assumed to be similar, with an extracellular N-and an intracellular C-terminus. Because of the hydrophobic nature of a protein that strongly interacts with fatty acids, the exact topology of the FATPs is difficult to predict. Studies with FATP1 revealed at least one α-helical transmembrane domain and several membrane-associated domains [3]. However, FATPs do not show any obvious similarities to other transporter families, e.g., the polytopic membrane transporters for hydrophilic substrates such as members of the GLUT family, or transporters of amphipatic and hydrophobic substrates, e.g., bile and cholesterol transporters. It has been demonstrated that FATP1 forms homodimers, and possibly higher-order complexes, most likely by interactions in the cytoplasmatic loop. Coexpression experiments of nonfunctional FATP1 mutants with wild-type FATP1 revealed that oligomerization is required for their transport function. A 311-amino acid sequence motif is conserved in all mammalian FATP family members and is essential for the function of these proteins. An AMP-binding sequence (IYTSGTTGXPK), likely facing the cytosol, is found at the beginning of this sequence motif. This 11-amino acid motif is conserved in a number of proteins that either bind ATP or catalyze reactions that proceed through adenylated intermediates.

In vitro and ex vivo studies have shown that FATPs transport LCFAs and very long-chain fatty acids (VLCFAs) but no medium-chain fatty acids, fatty acid esters, or lipid-soluble vitamins [4]. LCFA transport is inhibited by prior protease treatment. Synthetic substrates for FATPs include ^{14}C-labeled fatty acids and the fluorescently labeled fatty acid analogue C1-BODIPY-C12. Using the latter substrate, differences in fatty acid uptake kinetics between FATP expressing 3T3 L1 ►adipocytes and 3T3 L1 fibroblasts, which are devoid of FATPs, can be readily appreciated (Fig. 2).

It has been shown that FATP1, -2, -3, -4, and -5 can also catalyze the formation of CoA thioesters of hydrophobic substrates such as VLCFAs and unconjugated bile acids. However, it is still an ongoing debate whether FATPs are (i) solely transmembrane transport proteins mediating LCFA uptake, possibly in close association with other proteins such as long-chain acyl-CoA synthetases (ACSLs), or (ii) are themselves membrane-bound long-chain and very long-chain ACSLs that trap LCFAs inside the cell following fatty acid diffusion across the plasma membrane, or (iii) combine the transport with acyl-CoA synthetase activity for optimal uptake, or (iv) are multifunctional proteins that mediate LCFA uptake independently of their esterification activities. Clearly, further investigations of the enzymatic and transport activities of FATPs are needed to resolve these important questions. Extrapolating from our current knowledge, it is likely that in vivo several fatty acid handling proteins such as fatty acid translocase (FAT/CD36), long-chain ACSLs, fatty acid binding proteins (FABPs), and acyl-CoA

binding proteins (ACBPs) interact with FATPs to facilitate efficient uptake of fatty acids (Fig. 1). In accordance with this hypothesis, FATP1 has been shown to associate with ACSL1 [5], suggesting that both proteins are essential for FFA uptake. As a model for LCFA uptake we have suggested the following mechanism [3]. In addition to a small, diffusional component, LCFAs are either directly transported by FATP complexes across the plasma membrane or, alternatively are first accumulated on the plasma membrane by binding to CD36, which subsequently hands on the fatty acids to FATPs. Within the cells, LCFAs are rapidly activated and metabolized by ACSLs or FATPs. Subsequent binding of fatty acids to intracellular LCFAs handling proteins facilitates the unloading of transporters and synthetases and acts as an intracellular fatty acid buffer.

FATP Null Mutants and FATP Polymorphisms

►Knockout mice have been reported for several FATPs [1]. As ►insulin desensitization has been closely linked to excessive fatty acid uptake and intracellular diacylglycerol and TG accumulation, these animal models were particularly evaluated in the context of protection from diet-induced type 2 diabetes (►Type 2 Diabetes Mellitus (T2DM)). In addition, studies on human subjects have also established genetic links between ►polymorphisms in FATP genes and metabolic alterations [1].

In hyperinsulinemic-hyperglycemic clamp studies, FATP1 KO mice were protected from the insulin-desensitizing effects of lipid injections. FATP1 KO mice were completely resistant to long-term diet-induced ►obesity, insulin-desensitization, and other parameters of the metabolic syndrome. Loss of FATP1 function reduced muscle TG content and prevented a lipid bolus induced reduction of IRS-1 tyrosine phosphorylation and PI-3 kinase association. FATP1 is also expressed on the plasma membrane of brown adipose tissue (BAT) and FATP1 KO mice showed reduced basal fatty acid uptake and displayed smaller lipid droplets in BAT. As a consequence FATP1 KO mice failed to upregulate fatty acid uptake and to defend their core body temperature following cold exposure suggesting that FATP1 is required for thermogenesis [6].

As yet, no human diseases have been identified as a result of FATP1 mutations. However, genetic polymorphisms in the human FATP1 gene have been linked to dyslipidemia. An A/G exchange at position +48 in intron 8 of the FATP1 gene has been shown to result in increased TG concentrations in female but not in male subjects. In a second study, the same polymorphism was linked to increased postprandial TG concentrations and smaller low density lipoprotein (LDL) particles. To date, it is still unknown if this polymorphism is associated with altered levels of FATP1 expression and/or function.

A FATP2 KO mouse has been generated and investigated in the context of the neurodegenerative endocrine disorder X-linked adrenoleukodystrophy. However, no association between FATP2 function and X-linked adrenoleukodystrophy was found. FATP2 KO mice exhibited a decreased peroxisomal very long-chain acyl-CoA synthetase activity and decreased peroxisomal VLCFA β-oxidation in liver and kidney. However, no VLCFA accumulation in either of these organs was observed. The consequences of FATP2 loss for hepatic and renal LCFA uptake are presently unknown.

To date, four studies on murine FATP4 deletions have been published. Both the introduction of a premature stop codon in exon 3 due to a spontaneous mutation as well as the deletion of exon 3 by gene manipulation resulted in an early neonatal lethality due to symptoms strikingly similar to restrictive dermopathy, a rare human genetic disorder. Neonate mice exhibited thickened, tight skin, and a disrupted epidermal barrier as well as facial deformations and breathing difficulties. Additional analyses of the genetically engineered mice demonstrated reduced esterification activities for C24:0, but not C16:0 or C18:1 (very) long-chain fatty acids in dermal and intestinal lysates from FATP4 null mice. No effects on LCFA uptake have been examined in these two studies. A third study described a deletion of exons 1 and 2 of the murine FATP4 gene resulting in embryonic lethality occurring before day 9.5 of gestation. This phenotype was ascribed to the absence of FATP4 in the yolk sac where it is normally expressed by the cells of the extra-embryonic endoderm, likely resulting in an impaired absorption of maternal lipids by the embryo during early embryogenesis. Isolated primary enterocytes from heterozygote mice had a 48% reduction in FATP4 expression and a 40% reduction in LCFA uptake. However, no malabsorption of lipids was detected in vivo. A fourth report describing an epidermal-specific conditional FATP4 KO mouse showed that these mice develop a hyperkeratosis with a disturbed epidermal barrier suggesting that epidermal FATP4 is essential for the maintenance of a normal skin structure and function. In humans, a polymorphism in exon 3 of the FATP4 gene leads to an amino acid exchange (G209S) that has been linked to decreased parameters for TG and insulin levels, body mass index (BMI), and systolic blood pressure.

FATP5 KO mice have been characterized in two studies focusing on the role of FATP5 in hepatic lipid and bile metabolism. LCFA uptake in primary hepatocytes isolated from FATP5 KO mice was reduced by 50% and hepatic lipid content in the KO mice was significantly reduced despite an increased fatty acid de novo biosynthesis. Detailed analysis of the hepatic lipidome of FATP5 KO mice revealed significant

quantitative and qualitative alterations among lipid classes. Similarly to FATP1 KO mice, homozygote deletion of FATP5 resulted in resistance to high-fat diet-induced weight gain and insulin-resistance. FATP5 KO mice displayed both decreased caloric intake and increased energy expenditure on this diet. How changes in hepatic lipid metabolism lead to altered feeding behavior is currently unknown. While the total bile pool in FATP5 KO mice was unchanged, a distinct shift from conjugated to unconjugated bile acids occurred as a result of FATP5 deletion. The remaining conjugated bile acids were exclusively derived from de novo synthesis, implying a role of FATP5 in the reconjugation of bile acids during enterohepatic recirculation.

Pharmacological Intervention

Insulin

Insulin stimulates FATP1-mediated fatty acid transport on the protein level but negatively regulates FATP1 mRNA transcription through a cis-acting insulin response promoter sequence, albeit no changes in FATP1 protein levels have been reported following insulin exposure. In basal adipose and muscle cells, most of the FATP1 protein is sequestered in an intracellular perinucelar compartment, where it colocalizes with the insulin-sensitive glucose transporter GLUT4. Insulin stimulation induces the translocation of FATP1-containing vesicles to the plasma membrane resulting in an increase in cellular LCFA uptake.

Phloretin

Phloretin inhibits FATP-mediated traversing of fatty acids across lipid bilayers. Phloretin is the aglycon of phlorizin and has been used to terminate the uptake of LCFAs and VLCFAs in timed in vitro uptake assays with cultured cells or in ex vivo uptake assays with isolated primary cells.

Thiazolidinedions

A peroxisome proliferator-activated receptor (PPAR) binding site was identified in the murine FATP1 promoter. Several reports have shown a positive regulation of mouse FATPs by ligands that activate PPAR-α, PPAR-γ, or PPAR-γ/RXR heterodimers.

TNF

Tumor necrosis factor alpha (TNFα) is a negative regulator of FATP expression and downregulates FATP mRNA and protein levels in several tissues.

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Favism

Favism is the haemolysis observed after eating Vica fava. This reaction is observed in individuals with glucose-6-phosphate dehydrogenase deficiency. This common deficiency is also responsible for haemolysis in response to the antimalarial drug primaquine and others.

►Pharmacogenetics

Fc Receptor

Immune receptors that recognize the Fc (fragment, crystallizable) of antibodies when bound to pathogen, thereby exerting effector functions such as phagocytosis or antibody-dependent cell-mediated cytoxicity.

►T Cell Receptors

Fever

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Synonyms

Pyrexia; (Hyperpyrexia)

Definition

The term *fever* specifically defines the elevation of body core temperature (T_c) that characteristically occurs in most animals in response to the invasion of their body by infectious organisms such as bacteria, viruses, and fungi. It is also a frequent reaction to nonmicrobial illnesses (e.g., autoimmune and neoplastic diseases), some host-derived substances (e.g., antigen–antibody complexes), as well as to certain synthetic products (e.g., antitumor agents, immunoadjuvants). The English word *fever* stems from the Latin word *febris;* pyrexia is a synonym derived from the Greek word *pyretos.* In humans, T_cs above 38°C are generally considered clinical fevers. Hyperpyrexia is a medical emergency defined as a T_c over 41.1°C.

Our knowledge of the underlying mechanism of fever derives largely from research using animals. Thus, generally in such studies, a fever-producing substance (►exogenous pyrogen) is administered as a bolus to conscious rodents. In most cases, this material is an extract of the outer wall of gram-negative bacteria (*bacterial endotoxic lipopolysaccharide*, LPS); a multiphasic rise in T_c is consequently generated that, due to its causative agent, is prototypic ►endotoxic fever. Importantly, however, this T_c rise is but one among an array of systemic, nonspecific, highly coordinated reactions typifying gram-negative bacteremia, all directed to combating the deleterious effects of the pathogenic compound. They are termed collectively the *acute-phase reaction* (APR), a pathognomonic collection of behavioral (Table 1) and physiological (Table 2) responses. Fever is the most manifest among these signs and, therefore, it is the hallmark of infection. Indeed, since the early 1900s, the measurement of body temperature has become a clinically routine practice in the detection of infectious disease.

Basic Mechanisms

The Febrile Course

T_c does not rise immediately following the entry into the body of an infectious pathogen. Rather, there is an interval, from minutes to days, during which the various host-generated reactions that eventuate in the development of fever (and the other components of the APR) take place. This period is called the *latent* or *prodromal* period. Its duration depends on the nature of the invading microorganisms and/or its products, its route of entry, its amount, the site of its localization, certain physiological variables of the afflicted host, and other factors. It is succeeded by the *phase of rising* T_c or *febrigenesis*. The height, duration, and other characteristics of the ensuing fever are also largely dependent on the amount and type of the pathogen. They can, however, be influenced by various endogenous (e.g., state of hydration) and exogenous (e.g., climatic) factors; to wit, dehydration and high ambient temperature (T_a) exacerbate fever. The upper limit of fever in humans is ~40.5°C. When T_c reaches its maximum, it remains there for a period of time, termed the *stable* or *plateau phase* or *fastigium*. Its magnitude and duration are also related to the dose (severity of the infection) and type of the pathogen, and can also be modified by extraneous factors. Finally, the fever breaks (*crisis*) and T_c begins to decrease toward its normal level. This phase is variously called *the phase of falling* T_c, *febrilysis*, or *defervescence*.

Functionally, the onset of fever is mediated by an increase in metabolic heat production (*thermogenesis*) and cutaneous vasoconstriction (to reduce heat loss from the skin), and by cessation of sweating, if present. The

Fever. Table 1 "Sickness behaviors" typically elicited by infectious pathogens or their products

Hyperalgesisa, later hypoalgesia
Lethargy, somnolence
Anorexia, adipsia
Weakness, malaise
Decreased locomotor activity
Inability to concentrate
Loss of interest in usual activities, listlessness
Disappearance of body-care activities
Withdrawal

Fever. Table 2 Some characteristic physiological responses to infectious pathogens or their products (the "acute-phase reaction")

Fever ↑
Slow-wave sleep ↑
Pituitary hormones↑↓ ACTH↑, PRL↑, GH↑, AVP↑, αMSH↑, βEndo↑, SRIF↑ LH↓, TSH↓
Plasma Fe↓, Zn↓, Cu↑
Erythropoiesis↓ (anemia)
Circulating neutrophils↑
Sympathetic nervous activity ↑
Acute-phase proteins↑↓ CRP↑, complement↑, PLA_2↑, serum amyloid A↑, fibrinogen↑, α_1-acid glycoprotein↑, IL-1Ra↑, ceruloplasmin↑, α_1-antichymotrypsin↑, LBP↑ albumin↓, haptoglobin↓, IGF-1↓, transferrin↓, α_2-HS glycoprotein↓
Bone substance ↓
Muscle proteolysis↑
Pancreatic insulin↑, glucagon↑
Lipogenesis↑
Gluconeogenesis↓

F

increased heat production is achieved by the most visible sign of fever production, shivering (*chills*); in neonates and cold-acclimated rodents, in which shivering thermogenesis is normally replaced by brown adipose tissue (BAT) nonshivering thermogenesis, the latter substitutes for shivering in the production of fever. In a thermally neutral environment (~22–24°C for humans), the contribution of increased thermogenesis to the T_c rise is usually relatively brief; a greater role is played by the reduction in blood flow to the skin effected by cutaneous vasoconstriction. This is manifested by a cold and pale skin, provoking subjective sensations of cold that prompt the afflicted subject to actively (i.e., behaviorally) seek warmer surroundings. The thermoeffector responses evoked are thus analogous to those caused by acute cold exposure; but, since they occur in a warmer environment, the consequently narrower gradient between skin (T_{sk}) and ambient (T_a) temperatures results in less heat flowing from the skin to the environment and more, therefore, being retained in the body; hence, T_c rises. Fever developing in the cold, however, requires more intense heat production, whereas a decrease in heat loss (i.e., more generalized cutaneous vasoconstriction) may be sufficient in the heat. During the plateau phase of fever, the cutaneous vasculature resumes its normal, relatively constricted state (inappropriate as compared to an expected dilated state at a T_c comparably elevated passively by heat exposure, but thereby helping to maintain T_c at its febrile level). Since the blood perfusing the skin is now warmer, T_{sk} rises and the skin condition changes to warm and pink; consequently, the earlier sensation of cold disappears. When the fever drive eventually abates, the effector mechanisms evoked resemble those of heat-exposed subjects, viz., T_c falls in conjunction with cutaneous vasodilation and drenching sweating, and the defervescing subject seeks a cooler environment.

It should be apparent from the preceding that the T_c rise of fever is not the unavoidable consequence of the *passive* gain of heat in excess of the capability of *active thermolytic* (heat-dissipating) *effectors* to disperse it; this characterizes ►hyperthermia. Fever is, rather, the deliberate result of the *regulated* operation of *active thermogenic* (heat-producing) *effectors;* it thus develops as the result of an upward shift of the thermoregulatory ►set point, that is, it represents the regulated adjustment of T_c to a higher than the basal level rather than an uncontrolled side effect of disease; fever is indeed characterized by the active defense of the new, higher T_c. Hyperthermia, thus, is dependent on the T_a, whereas fever can develop at any T_a. A characteristic thermoregulatory behavior that derives from this difference is that febrile subjects prefer warm thermal environments to facilitate heat storage, as already mentioned, whereas hyperthermic subjects choose cool ones to enhance heat loss. Fever is therefore clearly distinct from hyperthermia, and the two terms should not be used interchangeably.

Various circulatory and respiratory adjustments that serve to support the increased metabolic demands of the heat-producing tissues accompany the febrile rise. These include increases in heart rate, increased blood flow to the thermogenic organs (viz., skeletal muscle, BAT), and associated adjustments and redistributions of the cardiac output. Hyperventilation also occurs transiently, resulting in a fall in P_{aCO2} and a rise in pH_a; P_{aO2} is generally unaffected. Other changes involve endocrine, enzymatic, and cellular effectors involved in the provision and utilization of energy; these are analogous to those that sustain the increased heat production on cold exposure.

Pathogenesis of the Febrile Response

Fever arises as the result of a complex, phased sequence of interactions among soluble factors and cells that is initiated in the periphery by the presence of the pathogens or their products and is eventually transmitted to the brain, which modulates the febrile response [2]. The process is driven in the periphery and in the brain via mediators that provide propyretic (e.g., ►pyrogenic cytokines, prostaglandin (PG)E_2) and antipyretic (e.g., arginine vasopressin, nitric oxide) signals at different points along the fever pathway and whose sequence is time-dependent. ►Endogenous antipyresis is an essential, autoregulatory feedback that serves to prevent an exaggerated fever from occurring during systemic infectious challenges [3]. However, the precise interplay of mediators, their sequence, and their site of action along the route to the brain and/or within it are still incompletely defined.

Many different substances are capable of causing fever; some common pyrogenic stimuli are listed in Table 3. These materials, however, are not the factors that directly induce fever and its nonthermal correlates. Rather, they induce in the host certain immunoregulatory mediators that entrain the APR. Thus, extraneous organisms or their products that have penetrated the body are immediately recognized through their unique molecular patterns (pathogen-associated molecular patterns, PAMPs) by specialized receptors on the host's immune cells. These receptors, called Toll-like receptors (TLRs), occur, predominantly, on mononuclear phagocytes (e.g., circulating and resident macrophages). Their activation transduces the pathogenic microbial signal into intracellular molecular processes that eventuate in the concatenated production of the factors that mediate the APR. LPS acts via the TLR4 receptor; other PAMPs activate other TLRs, but it would appear that the cascades of mediators thus produced are similar.

These propyretic factors belong to the class of immunomodulatory polypeptides called ►cytokines. Most prominent among these are interleukins (IL)-1β

Fever. Table 3 Some common pathogenic stimuli that induce fever ("exogenous pyrogens")

A. Microbial
• *Viruses* (whole organisms; hemagglutinin; dsRNA)
• *Bacteria*
• Gram-positive (whole organisms; peptidoglycans [*e.g.*, muramyl dipeptide]; lipoteichoic acids; exotoxins; enterotoxins; erythrogenic toxins; group B polysaccharides)
• Gram-negative (whole organisms; peptidoglycans; lipopolysaccharides [lipid A])
• *Mycobacteria* (whole organisms; peptidoglycans; polysaccharides; lipoarabinomannan)
• *Fungi* (whole yeasts; capsular polysaccharides; proteins)
B. Nonmicrobial
• *Antigens (e.g.*, bovine or human serum albumin, bovine gamma globulin, ovalbumin, penicillin)
• *Inflammatory agents* (*e.g.,* asbestos, silicia, UV radiation, turpentine)
• *Plant lectins* (*e.g.*, concanavalin A, phytohemagglutinin)
• *Drugs* (*e.g.*, polynucleotides [e.g., polyriboinosinic:polyribocytidylic acid], antitumor agents [e.g., bleomycin], plant alkaloids [*e.g.*, colchicine], synthetic immunoadjuvants [*e.g.*, muramyl peptides]
• *Host-derived* (*e.g.*, antigen-antibody complexes, activated complement fragments, inflammatory bile acids, urate crystals, certain androgenic steroid metabolites [*e.g.*, etiocholanolone], certain lymphocyte products)

and -6, tumor necrosis factor (TNF)-α, and interferons (IFN)-α and -γ. Following the administration of LPS, TNF-α normally appears in the bloodstream first, followed by IL-1β, and finally by IL-6; IFNs do not occur or occur very late – they are induced predominantly in response to viruses and their products. Their functional levels are modulated by the coincident release of their own antagonists, viz., specific target cell-surface antagonists (e.g., IL-1 receptor antagonist), soluble blood-borne receptors (e.g., soluble TNF receptor type II), and/or inhibitors of their synthesis (e.g., glucocorticoids) or their actions (e.g., arginine vasopressin in the POA).

How precisely circulating cytokines trigger the neural circuits that modulate the febrile response is still uncertain. Several possible mechanisms have been proposed: (i) active transport across the blood–brain barrier (BBB), which is otherwise impermeable to proteins; (ii) passage through "leaky portals" in the BBB, the so-called circumventricular organs, especially the *organum vasculosum laminae terminalis* (OVLT) which is located on the midline of the preoptic area (POA) of the anterior hypothalamus, the brain region controlling T_c; (iii) interaction with endothelial cells in the blood–brain interface, causing the abluminal release of additional cytokines and/or of a further factor, PGE_2, which is considered to be the final, central fever mediator [5]; and (iv) activation of sensory nerves, particularly hepatic vagal and trigeminal afferents. However, because under certain experimental conditions, for example, the i.v. injection of LPS, fever develops before cytokines are detectable in the blood, it has been suggested that, alternatively, circulating LPS could directly trigger endothelial cells in the cerebral microvasculature or in the OVLT, that is, independently of circulating cytokines, via the circulating receptor for LPS, soluble CD14, which can act on these cells (endothelial cells do not express the membrane-bound LPS receptor), engendering PGE_2. However, again, the synthesis of the enzyme that is thus specifically induced to catalyze the formation of PGE_2 from its substrate, arachidonic acid, cyclooxygenase (COX)-2, significantly lags the onset of fever. Indeed, experimental manipulations that inhibit either the actions of TNF-α or IL-1β or the production of PGE_2 attenuate the late, but not the early, phases of the febrile response, indicating that cytokines and PGE_2 are more likely involved in the maintenance than in the initiation of fever [2]. Moreover, recent evidence has indicated that the LPS-stimulated secretion of cytokines and PGE_2 by cerebral endothelial cells is polarized luminally, that is, toward the blood, and that the thus activated cells are not localized to the POA region, but nonselectively across the brain. Hence, an alternative, rapid, signaling pathway to the POA must operate in this model. Very recently, evidence was adduced that the fever-triggering factor is PGE_2, very rapidly elaborated not in the POA, but by hepatic macrophages (Kupffer cells, Kc). Two disparate views have been advanced as to what obtains. One holds that the Kc are activated by LPS acting via the TLR4 system, inducing within 30 min COX-2-dependent PGE_2 (COX-2 is constitutively expressed in Kc) which is released into the circulation, coupled to a carrier, albumin, and transported to the brain into which it, as a lipophilic molecule, freely diffuses [5]. There is indeed good evidence that COX-2 is upregulated in the liver and that PGE_2 is detectable in the blood within 30–45 min post-LPS administration, but no compelling evidence exists that blood-borne PGE_2 passes into the POA. The other view argues that the Kc are activated by an immune mediator, complement component C5a, itself activated immediately on contact with LPS, causing the release (within 2 min) of PGE_2 into the liver interstitium; the released PGE_2 then activates

hepatic vagal afferents that project to the POA via noradrenergic connections in the medulla of the brain. Norepinephrine (NE) is consequently very quickly released in the POA, activating two of its receptors, α_1 and α_2. Stimulation of the first inhibits warm-sensitive neurons in the POA, thereby reducing peripheral heat loss (by inducing cutaneous vasoconstriction) and, hence, causing the first febrile rise and stimulation of the second activates after a ca. 60–90 min delay POA COX-2, inducing the production of PGE_2 and the second phase of fever. Nitric oxide, also concomitantly liberated in the POA, counteracts the release of NE, thereby limiting fever height and duration. All the steps in this sequence have been confirmed by their blockade by cognate antagonists and by vagotomy [8].

Pharmacological Interventions

Fever has been recorded and associated with disease throughout history and, prior to the discovery of infectious pathogens, was taken as an illness in its own right. Now, however, although disagreeable and debilitating, fever is generally considered to be a healing response. Indeed, although no direct link between fever and host survival has definitively been demonstrated, there remains little doubt that it is a defensive response to the invasion of the body by infectious organisms and that its heat is beneficial as an adjuvant to the various immunological functions that are coactivated with it by creating the optimal thermal environment for their precisely timed and patterned expression, particularly during the early phases of the host's responses, that is, the APR [9].

Nevertheless, the use of antipyretics, viz., nonsteroidal anti-inflammatory drugs, such as aspirin, ibuprofen, naproxen, is very popular, particularly since the reduction in T_c is also associated with the relief of the untoward symptoms of sickness behavior, thus moderating the discomfort level and consequently alleviating the anxiety of both the afflicted patients and their caregivers. It is true, however, that the increased metabolic rate associated with fever production could represent a potential strain for those whose energy reserves may be limited, such as the malnourished, elderly, neonates, cancer patients, patients with metabolic diseases, and others. Similarly, the tachycardia and polypnea associated with sustaining the increase in metabolism may put at risk patients with a diminished capacity to increase cardiac work (e.g., congestive heart failure) or to hyperventilate (e.g., chronic obstructive pulmonary disease, asthma). Patients with dysfunctional kidneys may also be imperiled. There is, therefore, merit in attenuating fever in such patients. But, in general, it may be just as well not to treat the T_c rise per se in the absence of high-risk predisposing factors or when the fever is not unduly prolonged or rises to temperatures above 41°C.

Acknowledgments

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Fibrates

Fibrates are fibric acid derivatives, including e.g. bezafibrate, gemfibrozil, fenofibrate or clofibrate. Fibrates cause a marked reduction in circulating very low density lipoproteins (VLDL) as well as a modest (10%) reduction in low density lipoproteins (LDL) and an approximately 10% increase in high density lipoproteins (HDL). Many of the effects of fibrates on blood lipids are mediated by their interaction with ►peroxisome proliferator activated receptor (PPAR), which regulates gene-transcription in a variety of organs. Fibrates bind to the α -isotype of PPAR (PPARα), which is expressed primarily in the liver and brown adipose tissue and to a lesser extend in kidney, heart and skeletal muscle. Fibrates reduce triglycerides through PPARα -mediated stimulation of fatty acid oxidation, increased lipoprotein lipase synthesis and reduced expression of apoC-III. A major side-effect of fibrates is myositis, which is rare but can be severe. Fibrates are clinically used to treat elevated levels of triglycerides.

►Peroxisome Proliferator-Activated Receptor (PPARs)
►HMG-CoA Reductase Inhibitors

Aδ-fibres

Aδ-fibres are small diameter myelinated afferent fibres. As part of the pain sensory system they are present in

nerves that innervate the skin and deep somatic and visceral structures.

►Nociception

Fibrin

Fibrin is an elastic filamentous protein elaborated from its precursor, fibrinogen, which is present in plasma at high concentration. Fibrin is formed in response to the actions of thrombin. Thrombin cleaves small peptides from the fibrinogen molecule, forming fibrin monomers that will begin to polymerize and become crosslinked.

►Fibrinolytics
►Coagulation/Thrombosis

Fibrinogen

Fibrinogen, a glycoprotein with an overall homodimeric structure (340 kDa), is synthesized by the liver and secreted into the blood, where its concentration is ~10 μM. If its N-terminal portion is removed by serine proteases (e.g., thrombin, snake venoms), the remaining part, the fibrin loses its solubility, and forms aggregate (the blood clot, the main structure of a thrombus). The homodimeric structure allows fibrinogen to cross-bridge activated integrin αIIbβ3 molecules on adjacent platelets, the crucial step in platelet aggregation.

►Fibrinolytics
►Coagulation/Thrombosis
►Antiplatelet Drugs

Fibrinolytics

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Synonyms

Fibrinolysis; Thrombolysis

Definition

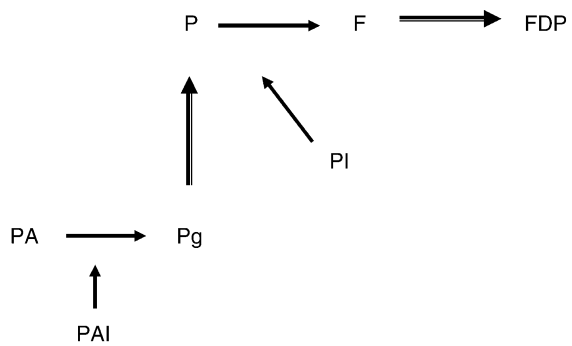
Fibrinolytic enzymes (proteases) are used to dissolve thrombus, the insoluble aggregate of ►fibrin and platelet including several additional cellular and molecular components of the blood.

Mechanism of Action

The term fibrinolysis means the degradation of fibrin (present as an insoluble protein molecule in the blood, which is useful to prevent bleeding and is dangerous if it is formed inside the blood circulation). However, the system in vivo is more complicated because fibrin exists in a compartment with several cellular and molecular components, which modulate fibrinolytic processes. In addition, the fibrinolytic enzymes are synthesized in proenzyme (zymogen) form. Thus, their activation is a prerequisite for their function. Moreover, both the fibrin degradation and the zymogene activation are controlled at multiple levels. Although there are several proteases with the capacity to digest fibrin, such as trypsin, elastase, cathepsin G, extracellular matrix metalloproteinases, in medicine, ►plasmin is considered to be the main fibrinolytic enzyme [1]. A simplified model of the ►plasminogen–plasmin system is illustrated by Fig. 1.

Fibrin Degradation

Fibrin is formed from ►fibrinogen synthesized by the liver and secreted into the circulation. The conversion of fibrinogen to fibrin is initiated by a serine protease, thrombin. Thrombin, at the same time, can activate a transglutaminase enzyme, factor XIII present in



Fibrinolytics. Figure 1 The plasminogen–plasmin system. Plasminogen activators (PA) convert plasminogen (Pg) to plasmin (P), and the latter solubilizes fibrin (F) via digestion, resulting in fibrin degradation products (FDP). Both reactions, the plasmin activity and plasminogen activation, are controlled by inhibitors, such as α_2-plasmin inhibitor (PI) and plasminogen activator inhibitor-1 (PAI-1), respectively.

the blood bound to fibrinogen. The activated factor XIII (F-XIIIa) thereafter forms crosslinks (izopeptid bonds) between fibrin molecules. In addition, F-XIIIa is able to crosslink α_2-plasmin inhibitor (α_2-PI, see later) to fibrin. Thus, at least three forms of fibrin substrate may exist for the fibrinolytic enzyme, plasmin. The rate of their digestion is different; fibrin degradation is more efficient than that of crosslinked fibrin, and the degradation of fibrin crosslinked with α_2-PI is less efficient [2]. The reactions are illustrated in Fig. 2.

Plasminogen Activation

Plasminogen, a single-chain glycoprotein (92 kDa) is synthesized by hepatocytes and secreted into the blood circulation, where its concentration is fairly stable (≈2 μM). It is converted to plasmin by plasminogen activators; all plasminogen activators cleave the Arg_{561}–Val_{562} peptide bond yielding plasmin (83 kDa), which consists of two chains held together by disulfide bridges. The conformation change in plasminogen during activation results in the appearance of active site (Ser, His, Asp) of the enzyme. Native plasminogen is not a susceptible substrate to activators, however, removal of its N-terminal portion either conformationally (e.g., binding to fibrin) or proteolytically (e.g., hydrolyzing peptide bond at Lys_{76} by plasmin) makes peptide bond Arg_{561}–Val_{562} sensitive to plasminogen activators. The latter reaction, the acceleration of plasminogen conversion to plasmin by plasmin indicates that plasminogen activation is under positive feedback control [2].

Regulation of Plasminogen Activation

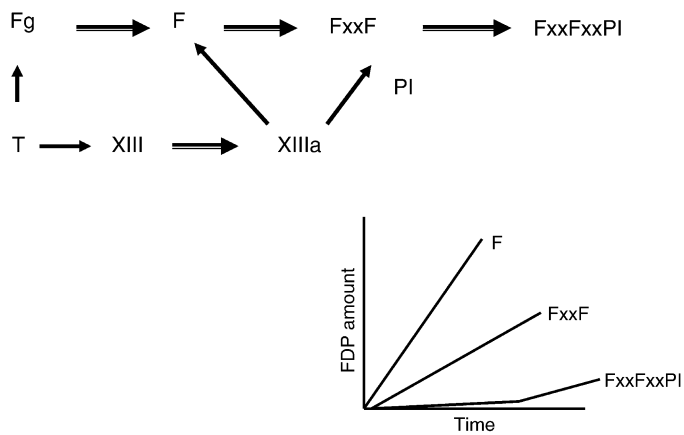
There are endogenous and exogenous plasminogen activators. Endothelial cells (and tumor cells) synthesize both urokinase-type (uPA) and tissue-type (tPA) plasminogen activators. uPA is produced in a zymogen form, and is converted to active enzyme by plasmin (and kallikrein), this reaction indicates a positive feedback control. tPA is secreted by an active enzyme conformation, which means that it is responsible, very probably, for the initiation of fibrinolysis. tPA is not an efficient enzyme (uPA is more active, approximately by an order of magnitude), however in the presence of cofactors it becomes as efficient as uPA (Fig. 3). Fibrin, the substrate of plasmin, at the same time, is a cofactor for tPA (uPA activity is not affected by fibrin). Besides fibrin, endothelial cell surface, myosin, actin, some extracellular matrix proteins, certain denatured proteins, and additional components may also serve as cofactor for tPA, but their exact in vivo role is not clear yet.

The fibrinolytic reactions are controlled by endogenous blood plasma inhibitors as well [3].

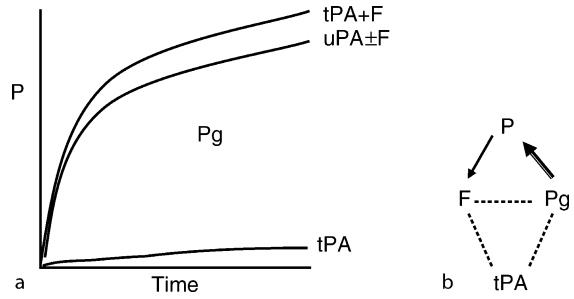
The α_2-Plasmin Inhibitor

One of the most efficient plasmin inhibitor is α_2-PI (70 kDa), which is synthesized by the liver, secreted into the blood circulation, where its concentration is ~1 μM. It rapidly forms equimolar complex with plasmin, and in this complex, the active site of the enzyme is irreversibly blocked. The complex, thereafter, is removed by the liver. It is remarkable that when plasmin is bound to its substrate (fibrin), it is protected against its primarily inhibitor, α_2-PI: the rate of inactivation decreases by ~400-fold (Fig. 4) [3].

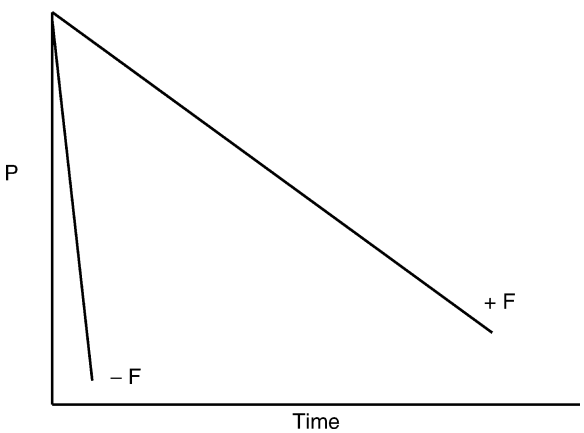
There are several additional plasmin inhibitors in the blood, e.g., α_2-macroglobulin, α_1-proteinase inhibitor, antithrombin, but their role in the control of fibrinolysis is questionable, because their action on plasmin is eliminated by fibrin.



Fibrinolytics. Figure 2 Various fibrin structures for plasmin. Fibrinogen (Fg) is converted to fibrin (F) by thrombin (T), and thrombin can also convert factor XIII (XIII) to activated factor XIII (XIIIa). The latter produces crosslinks between fibrins (FxxF) and also may crosslink fibrin with α_2-plasmin inhibitor (FxxFxxPI). The efficiency of digestion of these plasmin substrates by plasmin, resulting in the soluble fibrin degradation products (FDP), is different. The amount of FDP formed in time is expressed in arbitrary units.



Fibrinolytics. Figure 3 Plasminogen activation (a): Kinetics of plasminogen activation by uPA (urokinase-type) and tPA (tissue-type) plasminogen activators. Effect of fibrin (b): Ternary complex formation between enzyme (tPA), substrate (Pg) and cofactor (F) Abbreviations: plasmin (P), fibrin (F), plasminogen (Pg). Plasmin, formed in time, is expressed in arbitrary units.



Fibrinolytics. Figure 4 Inactivation of plasmin by α_2-plasmin inhibitor: Effect of fibrin. The inactivation rate of free plasmin is very rapid (the second order rate constant: k"≈430 × $10^4 M^{-1}s^{-1}$), while of fibrin bound plasmin is slow (the second order rate constant: k"≈1 × $10^4 M^{-1}s^{-1}$). Inactivation of plasmin in the figure is shown in arbitrary units. Abbreviations: plasmin (P), fibrin (F).

Termination of Plasminogen Activation

There are several blood plasma inhibitors for plasminogen activators as well. Among them, the most significant is the plasminogen activator inhibitor-1 (PAI-1). It is a glycoprotein (52 kDa), synthesized by endothelial cells and is present in the blood circulation (mainly in platelets) at varying concentration up to 2 nM. This inhibitor forms equimolar complexes with both tPA and uPA, where the enzymes lose their activity. The regulation of the amount of plasminogen activators and PAI-1 is not clearly known.

A Compartmental Approach to Fibrinolysis

Similarly to blood coagulation, reactions of fibrinolysis occur on the interface of fluid-and solid-phase structures, generally in transiently formed compartments. Enzymology of proteases in a water-phase is well known, but its alteration in a compartment is poorly understood. There are dramatical changes in reaction rates, in enzyme contractions and in enzyme sensitivity to inhibitors, which are not exactly described. In addition, besides fibrin and platelets there are several cellular and molecular components present in a thrombus compartment, where their influence on the basic fibrinolytic reactions is not known. To study this aspect of fibrinolysis is a task of the near future [4].

Clinical Use

Since plasmin in free form (not bound to fibrin) is extremely and rapidly inactivated by the inhibitor system (Fig. 4), plasminogen activators are used for treatment of thrombosis. Under such a condition, if plasmin is formed by the activators (especially by tPA) at the site of fibrin, the bound form can degrade fibrin because it is "protected" against the inhibitor system. In the medical practice, mainly two endogenous plasminogen activators, tPA and uPA, and one exogenous, the ►streptokinase (SK) are used [1,4].

Tissue-Type Plasminogen Activator

The ►tissue-type plasminogen activator (tPA) is a single-chain glycoprotein (sctPA) with 68 kDa molecular mass, present in blood at ~60 pM concentration (20% in free form, 80% in a complex with PAI-1). The N-terminal portion of tPA consists of a finger, an epidermal growth factor (EGF) and two kringle domains. Its C-terminal part comprises the catalytic domain, which is homogenous to that of other trypsin-like serine proteases. The sctPA can be converted by plasmin to a two-chain form (tctPA), but the biological significance of this modification in not known. tPA levels in vivo are influenced by various factors, such as hormones, exercise etc., but the exact control of its synthesis and release is not well known. tPA is also produced by engineering technique and used as fibrinolytic drug. During applications, the PAI-1 level should be overtitrated by tPA, which is not a problem, because PAI-1 concentration is low.

Urokinase-Type Plasminogen Activator

The ►urokinase-type plasminogen activator (UPA, urokinase) is a single-chain glycoprotein with 55 kDa molecular mass, produced by variety of cells, among them endothelial and tumor cells, and is present at ~70 pM in blood plasma. It consists of an EGF domain (responsible for binding to cell surface receptors), a kringle and a catalytic domain (the latter homologous to the trypsin-like proteases). Single-chain uPA (scuPA) has no catalytic activity, but following cleavage at the Lys_{158}–Ile_{159} bond by plasmin (or kallikrein), the emerged two-chain form held together by S–S bridges (tcuPA) is a potent plasminogen activator. Thus, uPA

F

can contribute mainly to amplification of fibrinolysis. The main problem in the therapeutical application of uPA is that it activates plasminogen randomly (see (SK) as well).

Streptokinase

SK is a single-chain protein (47 kDa), produced by *Streptococcus hemolyticus*. SK is not an enzyme, but forms a complex with human plasminogen, and in the complex an active site of plasminogen develops, which acts as a plasminogen activator, converting a neighboring free plasminogen to plasmin. There are two problems with SK treatments. It activates plasminogen (like uPA) efficiently but randomly, thus fibrinolytic therapy is generally efficient only, when ►α_2-plasmin inhibitor is consumed (blood concentration of plasminogen and its inhibitor is 2 μM and 1 μM, respectively), which on the other hand, may cause bleeding complication. In the future, perhaps a fibrin-dependent form of SK will be developed. If the N-terminal residues (59 amino acids) of SK are removed, the remaining portion becomes fibrin-dependent plasminogen activator in a complex with plasminogen. An additional problem with SK is that as a foreign protein it may provoke immunological complications, anaphylactic reactions, when it is used again.

There are several other sources and recombinant variations of plasminogen activators as well. To illustrate them, only a few examples are mentioned. Blood coagulation factor XIIa can activate plasminogen, although not efficiently, but perhaps it may play a role in the initiation of fibrinolysis. It needs additional works. Staphylokinase (15 kDa), synthesized by Staphylococcus aureus, somehow is similar to SK, it also interacts with human plasminogen. Recombinant derivates of tPA and uPA also exist. For example, reteplase, a tPA variant, consists of the kringle-2 and protease domains (lack of the finger and the kringle-1 domains) of the wild-type activator. Their mechanism of action and especially their possible clinical application are under investigation.

Summarizing the fibrinolytic therapy, it should be emphasized that efficient treatment needs urgent application of plasminogen activator (within a few hours) to prevent the formation of crosslinks in the fibrin structure (Fig. 2) and to find the localization of thrombus to emerge plasmin on the surface of fibrin to prevent rapid inactivation of the enzyme by the inhibitor system of fibrinolysis (Fig. 3).

►Anticoagulants
►Coagulation/Thrombosis

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Fibroblast Growth Factors

Fibroblast growth factors (FGFs) are a group of about 20 growth factors, which function through a group of receptor tyrosine kinases (FGF-R-1, -2, -3 and -4). They play multiple roles in the morphogenesis and growth of higher organisms.

►Growth Factors

Filamin

Also called filamin human actin-binding protein (ABP). A 280 kd dimeric actin-crosslinking protein that plays a key role in the anchoring of membrane proteins to the actin cytoskeleton and is responsible for the crosslinking of actin filaments into orthogonal networks in the cytoplasm. It is comprised of three functional domains: an N-terminal filamentous actin-binding domain, a C-terminal self-association domain, and a membrane glycoprotein-binding domain. As a protein involved in the remodeling of the cytoskeleton, Filamin A is central to the modulation of cell shape and migration.

►Cytoskeleton
►Transforming Growth Factor-Beta

First-order Kinetics

First order kinetics describes the most common time course of drug elimination. The amount eliminated within a time-interval is proportionate to the drug concentration in the blood.

►Pharmacokinetics

First-pass (Presystemic) Metabolism

First-pass metabolism is the elimination of an orally administed drug by the liver or sometimes the gut wall, before it reaches the systemic circulation. First-pass metabolism results in a decreased systemic bioavailability.

►Pharmacokinetics

FK506

Synonym
Tacrolimus

Definition
A secondary metabolite produced by *Streptomyces tsukubaensis*. This bacterium was initially isolated in a soil sample collected in Japan. FK506 is a macrocyclic lactone and shares structural similarity with rapamycin. Consistently, both rapamycin and FK506 bind the same immunophillin FKBP12 (FK506 binding protein of 12 kDa). However, unlike rapamycin-FKBP12 which binds and inhibits the TOR kinase, FK506-FKBP12 binds and inhibits the protein phosphatase calcineurin.
FK5096 is clinically used as immunosuppressant.

►TOR Signalling
►Immunosuppresive Agents
►Protein Phosphatases

FKBP12

Synonyms
12 kDa FK506-binding protein

Definition
FKBP12 is a member of immunophilin family that has prolyl isomerase activity and is related to the cyclophilins in function. FKBP12 binds immunosuppressant molecule FK506 (tacrolimus). The FBKP–FK506 complex inhibits calcineurin, a protein phosphatase, thus blocking signal transduction in the T-lymphocyte transduction pathway. In addition, FKBP12 binds to ryanodine receptor/Ca^{2+}-induced Ca^{2+} release channel to modulate its function.

►FK506
►Immunosuppressive Agents
►Protein Phosphatases
►Ryanodine Receptor

F

Flare

The surrounding redness caused by the vasodilatation of local blood vessels in the skin (hyperaemia). Histamine released at the site of contact acts on sensory nerve endings in the skin. Impluses travel along the axon to other peripheral branches of the same neuron to cause release of vasodilataory peptide neurotransmitters from nerve endings serving a wider area of skin than the initial contact point. Impluses reaching the CNS are interpreted as itch and pain.

►Histaminergic System

Flavin Adenine Dinucleotide (FAD)

Flavin Adenine Dinucleotide (FAD) (C_{27} H_{33} N_9 $O_{15}P_2$) is a coenzyme that acts as a hydrogen acceptor in dehydrogenation reactions in an oxidized or reduced form. FAD is one of the primary cofactors in biological redox reactions.

►Vitamins B2
►Monoamine Oxidases and their Inhibitors

Flavin Mononucleotide (FMN)

Flavin Mononucleotide (FMN) ($C_{17}H_{21}N_4O_9P$) is a phosphoric ester of riboflavin that constitutes the cofactor of various flavoproteins.

►Vitamins B2

Flp/FRT

Flp/FRT is a system analogous to the cre/loxP system. Flp is an yeast enzyme that recognizes FRT sites. If two FRT sites have a parallel orientation, the DNA segment between these sites will be deleted by the action of the Flp recombinase.

►Transgenic Animal Models

Fluorescence in situ Hybridization (FISH)

A diagnostic method using fluorescence labeled DNA probes to detect and quantify the number complementary chromosomal sequences on a cellular resolution. A related technique that also allows assessment of gene amplifications, but without precise quantification of copy numbers is the chromogenic in situ hybridization (CISH). Here, instead of a fluorescent dye an enzyme that can generate a colored precipitate in the tissue samples is coupled to the DNA probe.

Fluoride

Fluoride forms a tetrahedral ion with aluminium, AlF_4^B, which forms a complex with the GDPXαβγ form of G-proteins. In the case of G_s, the complex AlF_4^BCGDP behaves much as GTP or the more stable GTP derivatives, GTPγs or GPP(NH)p, and causes activation of adenylyl cyclase through the complex AlF_4^B-XGDPXα_sXC.

Fluoride stimulates bone formation by protein kinase activation mediated effects on osteoblasts. Fluorides have been used in the treatment of osteoporosis, but their anti-fracture effect is not undisputed.

►Heterotrimeric G-Proteins
►Adenylyl Cyclases
►Bone Metabolism

Fluoroquinolones

A fluorine atom in position 6 of the basic structure of quinolones enhances the antimicrobial activity considerably. All widely used quinolones are fluorinated in position 6 and the term "fluoroquinolones" is often used to describe these drugs. However, some new quinolones with similar antimicrobial activity are not fluorinated in position 6 (e.g. garenoxacin, PGE9262932) and therefore the term "quinolones" is more appropriate to describe this group of antimicrobial agents.

►Quinolones

FMN

►Flavin Mononucleotide
►Vitamin B2

Foam Cells

Cells in the atheroma derived from both macrophages and smooth muscle cells that have accumulated modified low-density lipoproteins. Their cytoplasm laden with lipid causes the "foamy" appearance on microscopy

►Atherosclerosis

Folate

►Folic Acid
►Dihydrofolate Reductase

Folic Acid

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Synonyms

Folate

Definition

Folic acid is sensitive to photodegradation as well as oxidative degradation and as an acid only slightly soluble in water, but in the salt form well soluble. 5,6,7,8-Tetrahydro-folic acid (H_4PteGlu) is derived from folic acid by two consecutive reductions using $NADPH_2$. H_4PteGlu and its derivatives are the biologically active vitamers. Reduced folates (H_2PteGlu or H_4PteGlu) are less stable than folic acid itself. Folate losses during food preparation are high, especially when foods are excessively heated or soaked in water. Bioavailability of natural folate from foods averages 50%, while folic acid from supplements or fortified foods is absorbed to more than 90%.

Spinach, salad, cereal germ, and bran as well as pulses are good sources of folic acid. Liver and yeast contain high amounts of this vitamin, too, but are not consumed frequently enough to be relevant for the coverage of daily requirements [1,2].

Folic acid or folate (Fig. 1) is the collective name for more than 100 derivatives of pteroyl-mono-L-glutamate. In plant and animal tissues, folic acid mostly occurs as pteroyloligo-L-glutamate ($PteGlu_n$), with up to eight glutamyl residues.

Mechanism of Action

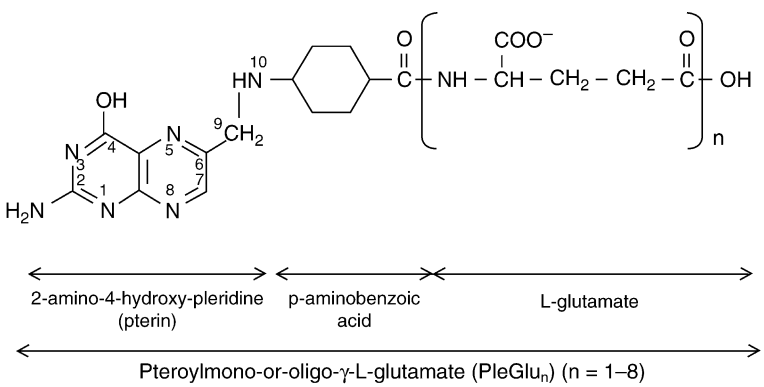
Tetrahydrofolic acid (H_4PteGlu) accepts and transfers activated one-carbon units in the form of 5-methyl-, 10-formyl-, 5-formyl-, 5,10-methenyl-, 5,10-methylene-, and 5-formiminotetrahydrofolate (Fig. 2). These activated metabolites are involved in the methylation of homocysteine to methionine, the conversion of glycine to serine, in histidine metabolism as well as in choline, purine, and pyrimidene biosynthesis.

5-Methyl-tetrahydro folic acid is furthermore, together with vitamin B12 and B6, required to regenerate homocysteine (see ►Vitamin B12, Fig. 1). Homocysteine results when methionine is used as a substrate for methyl group transfer. During the last few years, homocysteine has been acknowledged as an independent risk factor in ►atherosclerosis etiology. Folic acid supplementation can help reduce elevated homocysteine plasma levels and is therefore supposed to reduce the risk of atherosclerosis as well [2].

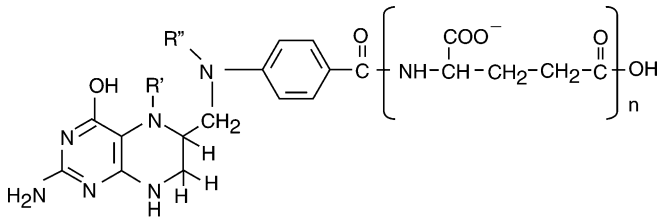
Clinical Use (Including Side Effects)

Folic acid deficiency is common even in industrial countries. High-risk groups to develop folic acid deficiency are pregnant and breastfeeding women, people who regularly take anticonvulsant drugs, oral ►contraceptives, or tuberculostatics, patients suffering from malabsorption, and chronic alcoholics. As folic acid is involved in cell proliferation, deficiency symptoms first become evident in tissues and cells with high proliferation rates, such as erythrocytes and epithelia.

It is recommended that women of childbearing age take 400 µg/d synthetic folic acid as a supplement in order to reduce the risk of neural tube defects of the embryo when they later become pregnant (periconceptional folic acid supplementation) [2]. When supplementing folic acid, it should be considered that this vitamin can mask the simultaneous presence of vitamin B12 deficiency. The typical symptom of vitamin B12 deficiency, megaloblastic (= macrocytic) anemia, will be reduced by high doses of folic acid, yet the nervous system will – in the long run – be irreversibly damaged (= ►funicular myelitis) when vitamin B12 is not provided as well.



Folic Acid. Figure 1 Structure of folic acid.



Coenzyme	R'		R"
Tetrahydro folic acid	–H		–H
5-methyl-tetrahydro folic acid	$-CH_3$		–H
5,10-methylene-tetrahydro folic acid		$-CH_{2-}$	
5,10-methenyl-tetrahydro folic acid		–CH=	
5,formyl-tetrahydro folic acid	–HCO		–H
10,formyl-tetrahydro folic acid	–H		–HCO
5-formimino-tetrahydro folic acid	–HCNH		–H

Folic Acid. Figure 2 Coenzyme forms of folic acid.

Overall, supplementation with folic acid is considered safe as the vitamin has low acute and chronic toxicity.

►Biotin
►Niacin
►Pantothenic Acid
►Vitamin B1
►Vitamin B2
►Vitamin B6
►Vitamin B12
►Vitamin C
►Dihydrofolate Reductase
►Antiplatelet Drugs
►Antineoplastic Agents

References

1. Biesalski HK, Grimm P (2005) Pocket Atlas of Nutrition. Thieme, New York
2. Rucker RB, Suttie JW, McCormick DB et al (2001) Handbook of vitamins, 3rd edn (revised and expanded). Marcel Dekker, Inc. New York, Basel

Follicle-stimulating Hormone (FSH, Follitrophin)

►Contraceptives

Force Fields/Molecular Mechanics

Force field methods, also called molecular mechanics, are empirical approaches to calculate molecular geometries and energies. The general aim of a force field calculation is to find that conformation of the 3D-dimensional structure of a molecule or complex with the minimal energy. The acting forces between the atoms are described by analytical functions with customisable parameters. Covalent as well as noncovalent forces are considered.

The basic idea of force fields is the assumption that bond length and bond angles adjusts whenever possible to standard values. Steric hindrance of nonbonded atoms can cause nonideal values of bond length and angle. The repulsive interaction is called van der Waals interaction. A force field equation to calculate the energy of the structure for a molecule contains at least the terms van der Waals interaction, bond length stretching, angle deformation and torsion angle deformations. Many force fields contain additional terms like electrostatic attraction and others. The derived force field for each term is achieved by calibration on experimental structural data, quantum-chemical calculation and, if included, charge-type calculations. There are a variety of different force fields calibrated for certain type of molecules and solutes. Among the force fields for proteins the AMBER force field is suitable for protein calculations in vacuum and water, the GROMACS force field is suitable for proteins in water and lipid environments.

►Molecular Modeling
►Bioinformatics

Forskolin

Forskolin is a diterpene derivative from the plant *Coleus forskohlii*. It activates all mammalian isozymes of adenylyl cyclase except AC9 and AC10.

Active derivatives of forskolin include: 7-deacetyl-forskolin (EC_{50} ~20μM), 6-acetyl-7-deacetyl-forskolin (EC_{50} ~40μM), 7-deacetyl-7-O-hemisuccinyl-forskolin (EC_{50} ~50μM). The last of these has been used as an immobilized affinity chromatography ligand for the purification of adenylyl cyclases from tissues.

►Adenylyl Cyclases

FoxO1a

FoxO1a (previously known as "FKHR", synonym "forkhead in rhabdomyosarcoma", gene name: FOXO1a) is a transcription factor which is regulated by phosphorylation of three serine/threonine residues. Phosphorylation of these residues by the protein kinase Akt leads to inactivation and nuclear exclusion of FoxO1a. Insulin regulates FoxO1a-dependent transactivation of gene expression through activation of Akt. FoxO1a is thought to bind to a conserved consensus sequence (T(G/A)TTT) found in the promoter region of several insulin responsive genes. The promoter of the glucose-6-phosphatase contains three of these FoxO1a binding sites.

►Insulin Receptor

Frizzled

Receptor for wingless ligands.

►Wnt Signalling
►Low-Density Lipoprotein Receptor Gene Family

Frontal Cortex

The frontal cortex consists of three main structures: (i) motoric regions (including the Broca area and ocular areas), (ii) the prefrontal cortex, and (iii) the orbital cortex. The prefrontal cortex is associated with attention, arousal, and expectation, the orbital cortex with motivation.

►Psychostimulants

FSH

Follicle-stimulating Hormone.

►Contraceptives

Functional Genomics

Functional genomics (sometimes referred to as functional proteomics) aims at determining the function of the proteome (the protein complement encoded by an organism's entire genome). It expands the scope of biological investigation from studying single genes or proteins to studying all genes or proteins at once in a systematic fashion, using large-scale experimental methodologies combined with statistical analysis of the results.

►Bioinformatics
►Gene Expression Analysis
►Microarray Technology
►Pharmacogenetics
►Proteomics

Functional Magnetic Resonance Imaging (fMRI)

Brain imaging technique that allows visualization of the brain, in order to understand which brain regions are involved in specific functions. Its functioning is based on the measurement of the regional cerebral blood flow which increases when a specific brain region is activated. Its use is similar to that of positron emission tomography (PET).

►Placebo Effect

Fungi

Fungi (Mycophyta, Mycota, Eumycetes) are chlorophyll-free plants, eukaryotic cells growing in hyphae or yeasts and causing diseases in plants, animals and humans.

►Antifungal Drugs

Fungicidal Effect

A fungicidal effect is that which kills the fungal cell.

►Antifungal Drugs

Fungistasis

Fungistasis is the inhibition of fungal growth without killing the fungal cell.

►Antifungal Drugs

Funicular Myelitis

The neurological disorder associated with severe vitamin B12 deficiency is termed funicular myelitis. Vitamin B12 deficiency leads to disturbed choline-, phospholipid-, and nucleic-acid synthesis, resulting in spinal marrow damages. Disturbed myelin synthesis finally causes irreversible neurological failure. In addition, there are psychiatric disturbances (disturbed memory, apathy).

►Vitamin B12
►Folic Acid

Furin

Furin, also known as paired basic amino-acid-cleaving enzyme (PACE), is a membrane bound subtilisin-like serine protease of the *trans* Golgi compartment. It is ubiquitously expressed and mediates processing of many protein precursors at Arg-X-Lys/Arg-Arg sites.

So far, seven mammalian precursor convertases (PCs) have been identified: furin, PC1, PC2, PC4, PC5, PACE4 and PC7.

►Somatostatin

Furin-like Protease

A furin-like protease is a recursor (prehormone, preprotein) convertase (PC).

►Endothelins
►Furin

Fyn

Fyn is a nonreceptor tyrosine kinase related to Src that is frequently found in cell junctions. The protein is N-myristoylated and palmitoylated and thereby becomes associated with caveolae-like membrane microdomains. Fyn can interact with a variety of other signaling molecules and control a diversity of biological processes such as T cell receptor signaling, regulation of brain function, and adhesion mediated signaling.

►Tyrosine Kinases
►Cadherins/Catenins

FYVE Domain

The FYVE domain is a phosphatidylinositol-3-phosphate-binding module of approximately 60 to 80 amino acids. It was named after the first four proteins, where this domain was described (Fab1p, YOTB, Vac1p and EEA1).

►Phospholipid Kinase

Fz Receptors

Frizzled (Fz) proteins comprise a family of seven-pass transmembrane receptors with a cysteine-rich extracellular domain. As a class, Fz proteins are structurally related to the superfamily of heterotrimeric ►G-protein coupled receptors (GPCRs). There are 4 *Fz* genes in *Drosophila* and 10 in humans, with close orthologs

in mice. Fz proteins participate in both Wnt/β-catenin-dependent and Wnt/non-β-catenin signaling, but individual Fz receptors may differ in their basal (minus ligand) ability to activate signaling of each type, suggesting that structural differences among the Fz proteins contribute to functional specificity. There is contradictory evidence regarding the importance of the Fz extracellular domain for this specificity, but it is clear that the carboxyl-terminal tail and intracellular loops contribute. There is evidence that other members of the seven-pass transmembrane receptor superfamily act as multimers on the cell surface. In the case of the Fz receptors there is no direct functional evidence for this, but crystallization studies have revealed a conserved dimerization interface in the extracellular cysteine-rich domain.

►Wnt Signaling