|  |  |  |
| --- | --- | --- |
| **Title/**  **context & main pathway** | **subjects** | **highlights on molecules, proteins and personalities** |
| **Prologue**  History Personalities | an account of how the term “signal transduction” entered biomedical research and how stimulus-response coupling, hormones, neurotransmitters, growth factors and their receptors were brought to light | -Alfred Gilman  -Martin Rodbell,  -Thomas Henry Huxley  -Steve Grand  -Charles Edouard Brown-Séquard  -Henry Hallett Dale  -Otto Loewi  -George Oliver  -Edward Sharpey-Schäfer  -Ernest Henry Starling  -William Maddock Baylis  -CONRO, a self-reconfigurable robot  -Paul Ehrlich  -John Newport Langley  -Francis Peyton Rous  -Rita Levi-Montalcini  -Stanley Cohen  -Alexis Carrel  -Howard Temin  -Renato Dulbecco |
| **2) an introduction to signal transduction**  Context:  Adrenaline mediated activation of glycogen phosphorylase in striated muscle, glycogenolysis  Pathway:  - beta-adrenoceptor, nucleotide exchange GPCR, Gs, activation of adenylyl cyclase, production cAMP, activation protein kinase A and glycogen phosphorylase in striated muscle | -signaling pathways serve to create symbolic representations of the cellular environment  -first messengers, description of hormones, growth and differentiation factors, cytokines, inflammatory mediators, vasoactive agents, neurotransmitters  -signaling in context, the signal itself is ambiguous but context, cell type and cell condition, determine the outcome  -receptor – ligand concept, classic pharmacology, different receptor types, receptor tyrosine kinase (RTK), receptor serine/threonine kinase, cytokine receptor, ligand-gated ion-channel, nuclear receptor, adhesion molecule, receptor guanylyl cyclase  -signaling mechanisms, the sequence of receptor – transducer – effector –second messenger, immediate (early) and late response  -adrenaline to glycogen phosphorylase, pioneer studies in signal transduction, detailed transcription of the pathway as operated in muscle, G-protein coupled receptors (GPCR), beta-adrenergic, protein kinase A (PKA), glycogenolysis, cAMP, adenylyl cyclase, glycogen phosphorylase kinase, glycogen phosphorylase, glycogen  -Nobel laureates associated with the adrenaline to glycogen phosphorylase pathway  -wired allostery, signal integration and thoughtful decisions  -post translational modifications, a broad overview, phosphorylation, ubiquitinylation, methylation, acetylation, crotonylation, myristoylation, farnesylation,  -feedback mechanisms, modelling of EGFR-mediated activation of MAPKinases, MAP kinases, EGF receptor | -Aph(2’)-Ib, aminoglycoside-2 phosphotransferase, enterococcus gallinarum, (ancient) protein kinase fold, molecular structure, conserved residues, C-helix, alphC-helix  -Docking site, substrate binding motifs in MAPKinase (MAP kinase, ERK), D-motif and DEF-motif, examples of substrates, sequence of the transcription factor ELK1  -Edmond Fischer, Edwin Krebs, Nobel Laureates 1992, protein phosphorylation, glycogen phosphorylase  -Eicosanoids, molecular composition, prostaglandin, prostacyclin, thromboxane, leukotriene, anandamide  -GNAI1, Gi-subunit of heterotrimeric G-protein (Galphai), molecular structure, conserved residues, GTP-binding pocket, GRAS and alpha-helical segment, GTP-binding protein  -H3F3A, Histone-3.3, post-translational modifications, acetylation, crotonylation, methylation and phosphorylation  -Histidine kinase (EnvZ), osmolarity sensor, interaction with OmpR, two component signaling  -HRAS (Harvey-Ras), monomeric G-protein, molecular structure, topology of conserved residues, mechanism of nucleotide exchange and GTP-hydrolysis, GTPase cycle, switch regions, farnesylation  -Cellular communication, modes of, endocrine, paracrine, juxtacrine, synaptic and autocrine  -Pharmacology, agonist, antagonist, inverse agonist, receptor-ligand interaction, affinity, dose-response curve, receptor number and signal sensitivity  -Phosphoenolpyruvate-dependent phosphotransferase system in bacteria  -Phosphorylation, change protein activity, change of subcellular localization, change in interactivity, potential phosphate donors, ATP favourite but not exclusive  -Phospho-amino acids, prevalent phosphate acceptors in proteins, characteristics of phospho-ester, phospho-ramidate and phospho-anhydride bond  -Phosphoryl transferase, phosphorylation, protein kinase, catalytic mechanism, role of conserved residues,  -PRKACA (PKA), protein kinase A, catalytic subunit, serine/threonine kinase, molecular structure, conserved residues, N-lobe, C-lobe, signature sequences, C-helix, catalytic mechanism  -Protein kinases, classification, serine/threonine, tyrosine and dual-specificity protein kinases, their mode of regulation  -Protein phosphatases, PPP, PPM, PTP, CTD, classification, serine/threonine, tyrosine and dual specificity phosphatases, molecular structure, catalytic mechanisms  -PYGM, glycogen phosphorylase, muscle, molecular structure, dimer, hydrolysis of glycogen and phosphorylation of glucose (glucose-1-phosphate), allosteric regulation, phosphorylation by glycogen phosphorylase kinase on ser-14, conformational change, tense to relaxed state  -RASA1 (RasGap), RAS GTPase activating protein, RAS-GAP domain, molecular structure, catalytic mechanism of hydrolysis of GTP  -Receptors, classification, ligands, overview of different types  -SOS1, RAS guanine nucleotide exchange factor, GEF, Cdc25 domain, molecular structure, H-helix, mechanism of GDP removal  -Two component signaling and environmental sensors in bacteria |
| **3) regulation of muscle contraction by adrenoceptors**  contexts:  -cardiac muscle contraction  -vascular smooth muscle contraction  pathways:  - action potential, depolarization, Ca2+-release though voltage-dependent L-type Ca2+ channel, giving rise to Ca2+-induced-Ca2+-release via the ryanodine receptor (RYR2), and control of contraction in cardiac muscle  - alpha-adrenoceptor, GPCR, nucleotide exchange Gq, phospholipase C, signaling through the IP3-receptor (ITPR1) and vascular smooth muscle contraction  - beta-adrenoceptor, GPCR, nucleotide exchange Gs, activation of adenyl cyclase, protein kinase A and modulation of contraction in cardiac muscle  - beta-adrenoceptor, GPCR, nucleotide exchange Gs, and pathway switching through ADRBK1, GRK6 and arrestin in cardiac muscle  - beta-adrenoceptor signaling and operating feedback mechanisms in cardiac muscle | -catecholamines (adrenaline, nor-adrenaline, dopamine), molecular composition  -central and autonomic-peripheral nervous system, anatomy and neurotransmitters involved,  -adrenoceptors, adrenergic receptors, history, classification  -agonist, inverse agonist, biased agonist and antagonist, mode of action, examples  -muscle contraction, cardiac and smooth muscle, anatomy, myosin-actin cross-bridge cycle  -GPCR, G-protein effectors, adenylyl cyclase and phospholipase C, second messengers cAMP and diacyglycerol/IP3  -nor-adrenaline-mediated control of cardiac-muscle contraction: ADRB1, GPCR, (1AR), GNAS (Gs, GalphaS), ACDY5, cAMP, PRKACA (PKA), CACNA1C (voltage sensitive Ca2+ channel), RYR2, TNNC1, TTNI3 (troponin), myosin-actin cross-bridge cycle, PLN (phospholamban), ATP2A2 (SERCA2, Ca2+-pump), KCNQ1 (K+-channel), ATP2B2 (Ca2+-pump)  -adrenaline-mediated control of vascular smooth muscle contraction, ADRA1A (1ADR), GNAQ (Gq, Galphaq), PLCB (PLC), PIP2, diacyglycerol (DAG), IP3 (inositol-3,4,5-trisphosphate), ITPR1 (IP3-receptor), RYR2 (ryanodine receptor), Ca2+ , CALM (calmodulin), MYLK (smooth muscle myosin light chain kinase), MYL12B (regulatory subunit), MYH11 (myosin-11), crossbridge cycle myosin-actin  -G-protein receptor kinases (GRK), among which ADRBK1 and GRK6  -arrestins and arrestin-dependent signaling (among others, SRC, RAF, MAPK, AKT1, NFKB)  -feedback mechanisms, modeling of nor-adrenaline mediated molecular events | -ADCY, adenylyl cyclase (adenylate), structure, catalytic mechanism, different topologies in different species, production of cAMP, family members, mode of activation and inhibition.  -ADRA, ADRB, alpha-adrenoceptor, beta-adrenoceptor, drenergic receptor, GPCR, ligand binding site, conformational changes in transmembrane helix bundle, energy landscape, coupling to heterotrimeric G-proteins or G-protein receptor kinases (GRK)  -Adrenalin, composition, its agonists, inverse agonists, biased agonist and neutral antagonists  -ARRB, arrestin proteins, structure, family members  -GRK6, G-protein receptor kinase, structure, function, family members, mechanism of attachment to GPCR, RGS-box  -Heterotrimeric G-proteins (GTP-binding protein) mechanism of nucleotide exchange, guanine-exchange function (GEF) of seven-membrane-spanning receptors (GPCR)  -ITPR1, IP3 receptor, electron cryomicroscopy-determined structure, molecular detail of the IP3-binding site  -PLC, phospholipase C, domain architecture, molecular structure PLCB3, PLCD1 and PLC staph aureus, TIM barrel, X/Y-linker, catalytic mechanism, production of diacylglycerol and inositol-1,4,5-trisphosphate (IP3), family members, family tree, control of PLCB3 by GNAQ (Gq, Galphaq) |
| **4) signaling pathway operated by acetylcholine**  Contexts:  -skeletal muscle contraction  -cardiac muscle contraction (myocytes)  -cardiac rhythmicity (myocyte pacemaker cells)  -bronchial smooth muscle contraction  -bronchial smooth muscle relaxation (salbutamol)  vascular smooth muscle relaxation (NO)  Pathways:  muscarinic (CHRM2) acetylcholine receptor, GPCR, nucleotide exchange Gi, inhibition of adenylyl cyclase and protein kinase A and control of rhythmicity (pacemaker) and force in cardiac muscle  muscarinic (CHRM3) acetylcholine, GPCR, nucleotide exchange Gq, activation of PLC, release of Ca2+, stimulation of nitric oxide synthase (NOS) in vascular smooth muscle  muscarinic (CHRM3) acetylcholine receptor, GPCR, nucleotide exchange Cq and G12, activation of phospholipase C and ARHGEF1, contraction of bronchial smooth muscle  nicotinic (CHRN) acetylcholine receptor, GPCR, depolarization, opening of voltage-dependent Na+-channel (SCN4A), Ca2+-induced-Ca2+-release at the neuromuscular junction  nitric oxide, activation of soluble guanylyl cyclase (GUCY1), cGMP, activation of protein kinase G (PRKG1), low frequency Ca2+-oscillations, relaxation of vascular smooth muscle  ANP, receptor guanylyl cyclase (NPR1), activation of phosphodiesterase (PDE2A), pathway cross-talk and inhibition of aldosterone secretion in adrenal glomerulosa cells  salbutamol (beta-adrenoceptor agonist), GPCR, nucleotide exchange Gs, activation adenylylcyclase, cAMP, EPAC1 and protein kinase A, relaxation of bronchial smooth muscle | -acetylcholine, history, composition, synthesis and breakdown  -synapse, active zone, vesicle docking, membrane fusion machinery  -muscarinic and nicotinic receptors  -nicotinic receptor (type IV), ligand-gated ion channel, neuromuscular junction, membrane depolarization and skeletal muscle contraction  -muscarinic receptor (M2) and vagal (parasympathetic) control of cardiac force and rhythmicity  -cyclic nucleotide phosphodiesterase (PDE) and pathway control  -muscarinic receptor (M3), GPCR, bronchial smooth muscle contraction, mucus production, salbutamol and asthma  -nitric oxide, history, NO-synthase, smooth muscle relaxation,  -guanylyl cyclases, cGMP, protein kinase G (PRKG, PKG)  -PDE5A, cGMP-specific 3’,5’-cyclic phosphodiesterase-5A, in corpus cavernosum, inhibition by sildenafil (Viagra) and penile erection  -examples of ionotropic and metabotropic receptors for neurotransmitters | -ACh, acetylcholine, composition, synthesis, breakdown, agonists and antagonists  -CHRN, nicotinic acetylcholine receptors, ligand-gated ion channel, topology, molecular structure, subunits, control of pore permeability (gating), detail ligand binding pocket, aromatic cage, comparison with AChBP, snail protein  -CHRM, muscarinic acetylcholine receptors, molecular structure, transmembrane helix bundle, bitopic ligand binding site  -GUCY, guanylyl cyclase (soluble), guanylate, family tree of guanylyl cyclases, molecular structure, - and -subunit, catalytic mechanism  -Inward rectifier K+-channel (Kcnj6) (GIRK2) complexed with G-protein G(Gbetagamma),  -NOS, nitric oxide synthase, molecular structure, prosthetic groups, catalytic mechanism  -PDE, cyclic nucleotide phosphodiesterase, structure, cyclic-nucleotide binding (cAMP versus cGMP), (cyclic-AMP, cyclic-GMP) regulation of activity  -PDE5A, cGMP-specific 3’,5’-cyclic phosphodiesterase-5A, target of sildenafil (Viagra), molecular structure with inhibitor  -PRKG1, protein kinase G (PKG), molecular structure, regulation by cGMP  -RGS box family, regulator of G-protein signaling |
| **5) sensory signal processing; visual transduction and olfaction**  Contexts:  -vision and retinal photoreceptors  -smell and olfactory epithelium  Pathways:  visual transduction, rhodopsin, GPCR, transducin, guanylyl cyclase, phosphodiesterase and arrestin  olfaction, odorant receptors, GPCR, Galpha-olf, adenylyl cyclase and Ca2+/calmodulin-gated chloride channel | -eye, development, anatomy, retina, cell types  -rods and cones, discs, rhodopsin, absorption spectra, colour vision, 11-cis-retinal, all-trans-retinal, vitamin A  -retinal metabolism, retinal-pigment epithelium  -rhodopsin (RHO), metarhodopsin, structure, conformational change of helical bundle, binding of Gt (transducin, Galphat), binding of GRK1  -effectors, inhibition of guanylyl cyclase GUCY2D, guanylate cyclase, activation phosphodiesterase PDE6, cGMP-sensitive cation channel (CNGA1), cyclic GMP  -signal attenuation, GRK1, arrestin (SAG) and transducin GAP-complex (PDE6G, GBB5, RGS9)  -light, darkness, adaptation  -drosophila compound eye, norpA (PLC), InaC (PRKC), InaD (scaffold) and Trp-channels  -chemosensory organs mouse, fly and human, olfactory bulb, olfactory epithelium  -odorant receptors, GPCR, Golf (GNAL, Galphaolf), adenylyl cyclase (ACDY3), adenylate, cyclic-nucleotide gated channel (CNG), Ca2+/calmodulin-gated chloride channel (ANO2), calcium  -excursion on G-protein coupled receptors (GPCR) | -G-protein coupled receptor, GPCR, 7TM-receptor, excursion: classification, topology of transmembrane helical bundle, Ballesteros-Weinstein generic numbering of highly conserved residues, contact network of ligand and of G(Galpha), ligand binding pockets across the category A (rhodopsin-type) receptors, structure comparison between category A and B (secretin type)  -Metarhodopsin II, light receptor, molecular structure, interaction with effectors, Gt (transducin,GNAT), interaction with GRK1, G-protein coupled receptor kinase  -Retinal, chromophore, 11-cis retinal-lysine, all-trans-retinal, photo-isomerization, vitamin A, metabolic pathway, retinal pigment epithelium  -Rhodopsin, opsin + 11-cis-retinal, GPCR, different members (OPN1SW, OPN1MW, OPN1LW, RHO), molecular structure of RHO, residues that determine differences in absorption spectra, light receptor  -Transducin GAP complex, molecular structure of GNAT1, PDE6G, RGS9, domain architecture, membrane recruitment via RGS9BP (R9AP), anchoring protein, acceleration of GTP-hydrolysis of transducin, GTPase activating protein |
| **6) intracellular calcium**  Contexts:  -muscle contraction  -neurotransmitter release, exocytosis  -cell migration  Pathway:  action potential, depolarization, opening of voltage-dependent L-type Ca2+ channel its role in synaptotagmin and SNARE-mediated membrane fusion and exocytosis  calcium-employing pathways, mechanisms that mobilise and respond to Ca2+  inmuscle contraction, exocytosis and cell migration  chemokine (PDGF)(RTK), activation of phospholipase C, inducation of Ca2+ oscillations and migration of cells | -calcium-storing organelles and Ca2+-transporter  -Ca2+-coordination geometry, Ca2+-binding proteins and Ca2+-chelators (EDTA, EGTA),calcium  -Ca2+-binding domains (EF-hand, C2-domain, P- and C-domain, Calx--motif (Calx-beta), gelsolin-repeat)  -calmodulin-binding proteins as effectors  -Ca2+ indicators (from aquorin to genetically-encoded indicators)  -Ca2+ permeable channels (ITPR, RYR, TPCN, KNCA, TRP, THEM16A, CACNA1, ORAI1)  -store replenishment through ORAI1 (calcium-release operated calcium channel), the Ca2+-sensor STIM1 and the Ca2+-ATPase (ATP2A1)  -Ca2+ blips, puffs, spikes and waves, calcium  -vesicle fusion with membrane, exocytosis, secretion, SNARE complex, synaptotagmin, voltage-gated Ca2+-channel (CACNA1C)  -cell migration, protrusion, retraction, actin cytoskeleton (arcs and stress fibres)  -chemokine receptor-mediated localized Ca2+-oscillations (calcium), activation of smooth muscle myosin light chain kinase, MYLK (MLCK) and activation of WAVE/SCAR/WASP-mediated actin-filament nucleation  -Michel Abercrombie, a pioneer in cell migration | -Ca2+-binding domains or motifs, molecular structure of: EF-hand, C2-domain, Calx- motif (Calx-beta) and gelsolin repeat, calcium  -Ca2+-permeable channels, members, membrane topology, calcium  -Ca2+, measurements, indicators, genetically encoded, blip, puff, spike, waves  -CALM, calmodulin, molecular structure, change in conformation upon binding of four Ca2+ ions, interaction with Camk2a, Mylk2 and Kcnn2, calcium  -CAMK, Ca2+/calmodulin protein kinase, molecular structure of hub, linker and kinase domain, schematic representation of the assembly into a multiprotein complex, control of kinase activity by Ca2+-oscillations, calcium  -GCaMP3, genetically encoded Ca2+-indicator, GFP (green fluorescent protein) bound to Ca2+/calmodulin, molecular structure, calcium  -ITPR, IP3-receptor, cryo-electron microscopy structure determination, control of Ca2+ conductivity, molecular structure of IP3-binding site, calcium  -Metal coordination geometry, Ca2+-binding proteins and metal chelators (EDTA, EGTA), calcium  -Michel Abercrombie, a pioneer in cell migration  -RYR, ryanodine receptor, cryo-electron microscopy structure determination, molecular composition of cytoplasmic vestibule and control of Ca2+- conductivity, calcium |
| **7) Bringing the signal into the nucleus; regulation of gene expression**  Context:  -gluconeogenesis  Pathway:  glucagon, GPCR, activation of Gs, adenylyl cyclase, protein kinase A, leading to phosphorylation of CREB and induction of the gluconeogenesis programme | -estimated number of human genes and the central dogma of molecular biology  -starvation and the processes that control gluconeogenesis, role of glucagon and glucocorticoid  -signaling by the glucacon receptor, adenylyl cyclase, cAMP and regulation of activity of protein kinase A  -AKAP, anchoring of protein kinase A to subcellular compartments and scaffolding of signaling complexes, example of AMPA-receptor, DLG1 and AKAP79  -CREB, transcription factor, is a nuclear target of protein kinase A  -gene transcription and transcription factors, from Jacob & Monod until today, histone acetylation and methylation, pre-initiation transcription complex  -CREB recruits co-activators, CREBBP, PE300 and CRTC2  -CREB1, FOXO1, PPAR and the glucocorticoid receptor NR4A1 drive the gluconeogenic programme  -insulin disables the gluconeogenic programme (cytoplasmic sequestration of CRTC2 and FOXO1, phosphorylation and dissociation of CREBBP)  -trancription initiation complex | -human genome, estimated number of genes and gene products  -A-kinase anchor protein-79, AKAP79, schematic representation of scaffolding role in signaling complex assembly (ADCY8, PPP3CB, PPP3CA, PRKACA, PRKARIIA, DLG1), role in control of phosphorylation of the AMPA-type glutamate receptor (GRIA1)  -bZIP, basic leucine-zipper protein, list of members of the protein family  -CREB1, cAMP-response element binding protein, structural compositioin of bZIP domain bound to cAMP-response element (CRE), phosphorylation sites in KID domain and interaction with CREBBP (CREB binding protein)  -CRTC2, CREB-regulated transcription co-activator  -genome, transcription, human genes, mRNA, rRNA, tRNA, snRNA, snoRNA, aRNA, lncRNA, miRNA, siRNA, piRNA, eRNA  -GCGR, glucagon receptor, bound to glucagon, predicted structure  -Histone-3, methylation- and acetylation-signatures of a repressed and activated enhancer, promotor and coding region  -master transcription factor, cell fate, embryonic stem cell, OCT4, MYOD, NANOG, GAT4  -PIC, transcription pre-initiation complex, schematic representation of proteins  -PRKACA, catalytic subunit of protein kinase A (PKA), domain architecture, molecular structure, conserved residues, position of N-tail with myristate and of C-tail, co- and post-translational phosphorylation and phosphosite sequence logo of substrates  -PRKARIA, regulatory subunit of protein kinase A (PKA), domain architecture, molecular structure with or without cAMP (cyclic-AMP), function of pseudosubstrate (in RRGAI), dimerization through dimerization domain and interactions with CNBA (cyclic-nucleotide binding domain-A)  - transcription regulation, Chaques Monod, Francois Jacob, nucleosome, enhancer, promoter, coding region, transcription factors, mediator, TF-complexes, SWI, cohesin, RNA polymerase-II |
| **8) nuclear receptors**  Contexts:  -sperm motility and capacitation  -mammary gland development  -memory consolidation and cortisol (and dealing with pregnancy)  -endocrine disruption  Pathways:  nuclear receptor-mediated regulation of gene transcription, ligand-mediated structural change, recruitment of co-activators NCOA1, NCOA2 and others  nuclear receptor, transcription transrepression and transactivation, association with RELA, NFKB, JUN, FOS and CREB | -steroid hormones, everything from domestic animals, the Chinese pharmacopoeia of 725 AD, to 19th and 20th century personalities in the discovery of steroids  -steroids accumulate in the nucleus, bound to nuclear receptors  -regulation of transcription by steroids discovered in giant chromosomes of insect salivary glands  -superfamily of nuclear receptors and recognition of specific promoter enhancer sites (inverted or direct repeat DNA-sequences)  -ligand-mediated activation or repression of gene transcription, histone acetylation or de-acetylation  - chaperone (or heat-shock) proteins and the loading of receptors with their ligand  -cooperation with other transcription factors (transrepression or transactivation)  -non-genomic action of nuclear receptors (activation of SRC, interfering with integrin binding, gating of the AMPA-type glutamate receptor)  -paracrine signaling between oestrogen and progesterone-receptor-bearing epithelial cells and mammary-gland stem cells  -sperm capacitance and motility induced by progesterone in a non-genomic fashion (effect on the CATSPER Ca2+-channel)  -glucocorticoid-mediated synapse strengthening and memory  -endocrine disruption in a plastic world (bisphenol A) | -ESR1, estrogen receptor, molecular structure of ligand binding domain with agonist (DES), detail of coordinating amino acids of the ligand binding pocket, position of NCOA2 co-activator, molecular structure of dimer of DNA binding domain, comprising two C4-type Zn2+-fingers  -ESR2, estrogen receptor, molecular structure of ligand-binding domain in the presence of by agonist (DES) and antagonist (tamoxifen), interaction with NCOA2  -Ludwig Fraenkel, rabbits, pigs, and the search for progesterone  -Nuclear receptors, domain architecture, classification, ligands, molecular composition of some ligands  -RARA, retinoic acid receptor alpha, molecular structure of ligand-binding domain in presence of agonist (BMS493 or AM580, antagonist (BMS614) , interaction with NCOR1 or NCOA1  -VDR/RXRA, vitamin-D3 and retinoic-acid receptor, dimer bound to DNA, cryo-electron microscopy structure determination, crystal structure modelled, associated ligands 1,25-dihyroxy vitamin D3 and 9-cis retinoic acid  -non-genomic action of nuclear receptors |
| **9) protein kinase C in oncogenic transformation and cell polarity**  Contexts:  -oncogenic transformation  -cell polarity (spindle orientation in development, migration of astrocytes and axonal outgrowth)  Pathways:  protein kinase C (atypical) activation, CDC42 and PARD6, and cell polarity  protein kinase C (classical) activation(RTK), phospholipase C, diacylglycerol and IP3, release of Ca2+, and epithelial cell-stem cell programme | -phorbol ester and the characteristics of inflammation  -the protein kinase C family (PKC), member of the group of AGC-kinases, domain architecture  -classical protein kinase C, role of Ca2+ and diacyglycerol (or phorbol ester) in activation of the kinase, displacement of the pseudosubstrate sequence by C1 and C2 domains, calcium  -atypical protein kinase C, role of AC1 and PB1 domain plus substrate in rendering atypical protein kinases catalytically competent  -protein kinase-C anchoring proteins, RACKs, STICKs and PICKs  -Protein kinase C as a potential oncogene, history, phorbol ester and signaling to AP-1 transcription complexes  -role of classical protein kinase C (PRKCA) in facilitating the cancer stem cell programme, role of, JNK1 & JUN and RAF & FOS  - atypical protein kinase C, different types of polarity cues and the localization of PARD-polarity complexes  -discovery of Par proteins in Caenorhabditis elegans (zygote)  -polarity complexes in flies and mice (CDC42, PRKCI or PRKCZ, PARD3, PARD6, GNAI3, GPSM2, INSC, NUMA and DLG1) | AP-1, activator protein-1, molecular structure of JUN and FOS bound to DNA and linked through leucine zipper, different protein combinations (JUN/JUNB, JUN/ATF7, FOS/JUN, FOS/ATP7, etc), different response elements (TRE, CRE, MARE1, MAREII and ARE)  -C1A, C1B and C2 domains, Ca2+-binding, membrane binding, role in protein kinase activation, calcium  -Phox-Bem1 domain, PB1, molecular structure of type-I, type-11 and type I/II domains, OPCA motif, lysine, heterodimer assembly and formation of homotypic array  -Polarity complexes, composition, membrane anchors (GNAI (Galphai) or CDC42), signaling complex (PARD3, PARD6, atypical PKC), adaptors (GPMS2, NUMA or INSC,GPMS2, DLG1), motor proteins (dynein complex or kinesin complex) and microtubules, par3, par6  -Phorbol ester, phorbol-12-myristate-13-acetate, PMA, TPA, molecular composition, inflammation  -PRKCI, atypical protein kinase iota, aPKC, molecular structure of kinase domain and PB1 domain, position of AGC-tail, model of activation mechanism, removal of AC1, pseudosubstrate, and PB1, role of substrate in rendering kinase fully competent, phox, bem  -Protein kinase C, PKC, classical and novel, family members, molecular structure of domains, priming of the protein kinase through phosphorylation of the AGC-tail by mTORC2 (co-translational), and through phosphorylation of the activation segment by PDK1 (3-phosphoinositide-dependent protein kinase), comparison of conserved phosphorylation sites and phosphosite sequence logo of PRKCA substrates PKCalpha) |
| **10) regulation of cell proliferation by receptor tyrosine protein kinases**  Context:  EGF-mediated activation of gene expression, cell division cycle, proliferation and oncogenic transformation  Pathway  EGF(RTK), receptor activation, recruitment of Grb2/SOS1 and activation of the Ras-RAF-MEK-MAP kinase pathway  EGF-signaling and operating feedback mechanisms | -receptor tyrosine protein kinases, classification, family  -EGF receptor (ERBB), family members, ligands, dimer combinations, intracellular adaptors and effectors  - adaptors and effector proteins of receptor tyrosine kinases, their discovery, SH2 and PTB domains, phosphotyrosine binding domain  -SH2 and PTB-containing proteins, enzymes, transcription factors, adaptors, docking proteins  -Drosophila compound eye, C elegans vulval induction, and the elucidation of the Ras-MAPKinase pathway (MAP kinase)  -EGFR (RTK), SOS, RAS, BRAF, MEK1 (MAP2K1), ERK1 (MAPK3) pathway, detail of BRAF dimer, MAP kinase pathway  -RAS and RAF oncogenes, detail of multiple regulation mechanisms that control RAF  -MAPKinase (ERK, MAP kinase) docking sites  -MAPKinase-activated kinases, family tree, MKNK (MNK), RPS6KA, MAPKAPK  -MAP kinase-mediated phosphorylation of transcription factors, example ELK4, MAPK  -MNK1 mediated regulation of protein synthesis, phosphorylation of components of the ribosome translation initiation complex  -scaffold for the RAS-MAPK pathway, yeast STE5, mammalian KSR2  -why are signaling pathways so complicated?  -MAPKinase-related proteins, subfamilies, ERK, JNK and p38 (SAPK) pathways, family tree, MAP3K, MAP2K, MAPK, signature sequence, activation segment, SEG, TEY, TGY  -other branches of EGFR signaling pathways, Ca2+/calmodulin, PI-3-kinase, STAT proteins  -transactivation, from GPCR to EGFR | AKT1, serine/threonine protein kinase (PKB), Ak-thymoma retrovirus, molecular structure, conserved residues, substrate binding site (penetrates into catalytic cleft, comparison with INSR)  -BRAF, rat fibrosarcoma (RafB1), murine sarcoma viral oncogene, domain architecture, molecular structure, conserved residues, activation mechanism, side-to-side dimerization, oncogenic mutants  -EGFR (ERBB1, HER1), epidermal growth factor receptor, extracellular and transmembrane segment, domain architecture, molecular structure, ligand-mediated conformational changes, CR-domain mediated dimerization  -EGFR, epidermal growth factor receptor, intracellular segment, role of LLRRL helix in juxta-membrane segment in membrane binding of receptor monomer and in stabilization of kinase domain in receptor dimer, allosteric regulation through asymmetric dimer formation of two kinase domains  -EGFR, epidermal growth factor receptor, kinase domain, detail of regulation of kinase activity through removal of leucine wedge (L858, L861), illustration of how oncogenic L858R mutation removes the inhibitory constraint (increase in kinase activity without need of receptor dimerization)  -ELK4, ets-domain leukemia gene, SRF-associated protein (SAP1), DNA-binding domain, SRE enhancer element, serum response element  -INSR, insulin receptor kinase domain, tyrosine protein kinase, molecular structure, conserved residues and substrate binding site (surface oriented, long tyrosine required to reach catalytic residue, comparison with AKT1)  -ERK2, extracellular-signal regulated kinase, MAP kinase-1, mitogen-activated protein kinase, molecular structure, conserved residues, activation mechanism, activation segment phosphorylation  ERK2, extrecellular-signal regulated kinase (MAPK1), substrate docking sites, linear motif, phosphosequence logo, D-motif, DEF-motif  -MAPK-related protein kinases, scheme of three tier-cascades of the ERK, p38 and JNK pathways, family tree of MAPK members, activation segment signature, MAP kinase, PEY,  -Receptor tyrosine protein kinases, RTK, classification, domain architecture  -SH2-domain, Src-homology domain, contextual peptide and selectivity of phosphotyrosine recognition, Src-homology  -SOS1, son of sevenless, domain architecture, molecular structure, function, tandem binding sites for RAS.GTP, guanine nucleotide exchange factor  -RAS, oncogene, oncogenic mutation, G12V, G13R, Q61R, A146T  -RAF, oncogenic mutations, V600E, G446V |
| **11) signal transduction to and from adhesion molecules**  Context :  -integrins, cell survival and cell proliferation  Pathways:  growth factor (RTK) activation of integrins via RHOA and RAP1  integrin, focal adhesion, talin, paxillin, recruitment of PTK2 (FAK) and SRC (NRPTK), activation of PI 3-K, AKT and cell survival  integrin, focal adhesion, talin, paxillin, recruitment of PTK2 (FAK) and SRC (NRTK), recruitment Grb/SOS1, activation RAS-MAP kinase pathway and cell proliferation  integrin, hemi-desmosome, paxillin, recruitment of PTK2 (FAK), SRC (NRTK), BCAR1, activation RAP1-MAP kinase, STAT1 and RAC-JNK1 pathways | -three modes of communication (endocrine, paracrine, juxtacrine)  -overview of adhesion molecules, members of the immunoglobulin superfamily (VCAM, ICAM, SIGLEC), junctional adhesion molecule, occludin, claudin, integrin, cadherin, selectin and cartilage link-protein  -highlight of integrin activation, role of talin and its F3 FERM-domain, 4.1, Ezrin, Radixin, Moesin.  -receptor-mediated integrin activation, RHOA, RAP1, their guanine-nucleotide exchange factors, PI 5-kinase, RASSF5 (Rap-ligand), SKAP1, APBB1IP (Riam), TLN1 (talin)  -focal adhesion complex formation, RHOA, ARHGEF18, PI 5-kinase, PI-4,5-P2, VCL (vinculin), TLN1 (talin) and ACTN1 (-actinin)  - focal adhesion signaling complex, PTK2 (focal adhesion kinase), PXN (paxillin), SRC, BCAR1 (Cas)  -focal adhesion signaling complex, PTK2 (FAK), TLN1 (talin), SOS1, PI 3-kinase, proliferation (RAS-MAPK and STAT pathway) and survival (AKT1) through control of apoptosis  -control of the cell division-cycle inhibitor CDKN1B (p27kip) through ubiquitination by the SCFSKP2 E3-ubiquitin ligase complex (SKP1, SKP2, CUL1 and E2-ubiquitin conjugation enzyme)  -Cadherin-mediated activation of PI 3-kinase (survival), microtubule-recruitment (vesicle transport, provision of mRNA and proteins) and development of the zonula adherens (actin contractile filaments). | -CD22, cluster of differentiation, adhesion, siglec-2, V-set immunoglobulin domain bound to sialic acid, molecular structure, intracellular domain ITIM motif  -CD44, cartilage link proteins, adhesion, domain architecture, family members, link-domain bound to hyaluronan (hyaluronic acid), molecular structure, cluster of differertiation  -CDH, cadherin, adhesion, domain architecture, family members, molecular structure of EC1 and EC2 domains, role of tryptophan, different types of homophilic interactions (cis/trans, involving EC1 and/or EC3)  -ITGA, ITGB (alpha and beta integrin), integrin, adhesion, domain architecture, family members, molecular structure(ITGAV, ITGB3), dimer combinations of - and -integrin, activation mechanism (switch blade), role of F3-domain of TLN1 in changing the position of the transmembrane segment of -integrin binding to TLN1.  -PTK2, focal adhesion kinase (FAK), interaction with BCAR (Cas), PXN (paxillin), domain architecture and phosphorylation sites, other interacting proteins  -SCFskp2, E3-ubiquitin ligase complex, schematic representation of molecular structure, SKP2 substrate receptor,  -SEL, selectin, adhesion, domain architecture, family members, lectin-like domain bound to fucose of SELPLG, molecular structure |
| **12) WNT signaling and the regulation of cell adhesion and differentiation**  Contexts :  -epithelial mesenchymal transition (EMT)  -stem cell niche  -cell polarity  Pathways:  Wnt pathway via AXIN-APC, beta-catenin and TCF, canonical pathway  Wnt pathway via DAAM, RAC, PLC, non canonical pathway | -dissipation of cell polarity and de-differentiation  -markers of epithelial mesenchymal transition  -Wnt family of cytokines, history of discovery (Int and Wg), integration site, wingless, epistatic analysis of drosophila mutants  --catenin (beta-catenin, CTNNB1) switches TCF from a gene transcription repressor to an activator  -different partners of -catenin (CDH1, TCF) and the role of AXIN/APC (destruction complex) in the elimination of unbound protein  -the SCFBTRC E3-ubiquitin ligase complex and ubiquitination of -catenin  -Wnt-signaling disables the AXIN/APC destruction complex (role of FZD, LRP, DVL, CSNK1G1 (casein kinase), adenomatous polyposis coli  -Wnt signaling, induction of expression of SNAI1, SNAI2 (slug), TWIST1, ZEP1 and suppression of expression of CDH1 (E-cadherin)  -Wnt signaling (WNT3 and FDZ7/LPR6) and stem cell self-renewal, the stem cell niche of the crypts in the small intestine, role of R-spondins and the LGR5 receptor in boosting the Wnt response  -Wnt expression and ephrin-B receptors (EphB)  -Wnt and planar cell polarity in Drosophila and mammalian cells (RHO, ROCK, myosin light chain, actin filament nucleation and organization)  -Adenomatous polyposis coli, colon cancer, mutations in CTNNB1, AXIN and APC | -CTNNB1, –catenin, armadillo repeats, interaction with fragment of CDH1 (E-cadherin), beta-catenin  -CTNNB1, –catenin, armadillo repeats, interaction with fragment of APC (adenomatous polyposis coli), beta-catenin  -CTNNB1, –catenin, armadillo repeats, interaction with fragment of AXIN (Xenopus axis inhibitory protein), beta-catenin  -CTNNB1, –catenin, armadillo repeats, interaction with LEF1 (lymphoid-enhancer binding factor), beta-catenin  -CTNNB1, -catenin N-terminal segment phosphorylation and ubiquitination sites, beta-catenin  -Wnt pathway, domain architecture and domain interactions, components, LRP6, DVL1, AXIN, APC, GSK3B, CSNK2A2 (casein kinase), CTNN1B, CDH1  -T-cell factor (TCF), domain architecture and domain interactions of TCF7 (TCF1) and TCF7L1 (TCF4) and their association with transcriptional repressor and activator complexes, transcription  -stem cell niche small intestine, epithelium, villus, crypt of Lieberkühn, enterocyte, Paneth cell, goblet cells, crypt base columnar cell (Lgr5+ stem cell).  -Fzd8, Frizzled-8, receptor extracellular segment bound to wnt-8 (xWnt8), molecular structure, frizzled, wnt  -LEF1, lymphoid enhancer factor, C-terminal segment (HMG-BT) bound to DNA  - T-cell factor (TCF), family members, gene structure and domain architecture, |
| **13) activation of the innate immune system: the toll-like receptor-4 and signaling through ubiquitination**  Context:  -Innate immunity (activation of the dendritic cell)  Pathway:  Toll-like receptor-4, LPS, ubiquitin-mediated signaling via MYD88, IRAK1, IRAK4, TRAF6, MAP3K7 (Tak1), IKBKB leading to activation of NFKB  Toll-like receptor-4, LPS, ubiquitin-mediated signaling via MYD88, MAP3K7 (Tak1), MAP2K3 (MEK3), MAPK8 (Jnk1) and activation of ATF2/JUN  Toll-like receptor, LPS, ubiquitin-mediated signaling via TICAM2 (Tram), TICAM1 (Trif), TRAF3, IKBKE, TBK1 and activation of IRF3 | -sensing the microbial universe by pattern-recognition receptors, PRR, of dendritic cells  -toll and toll-like receptors (TLR), discovery in drosophila mutants, types and ligand  -composition of bacterial cell walls, Gram-positive, negative and mycobacteria, lipopolysaccharides acting as a shield and a pathogen-associated molecular-pattern, PAM, which acts as a ligand for the TLR4 receptor on dendritic cells  -LPS-mediated receptor dimerization and assembly of large signaling complexes through assembly of DD-domain carrying proteins (MYD88, IRAK4 and IRAK1), lipopolysaccharide  -signaling complex formation through K63-connected ubiquitin chains, role of the TRAF6 E3-ubiquitin ligase complex, binding of TAB2 associated with MAP3K7 (Tak1), and of IKBKG (Nemo) associated with IKBKB (IKK) and CHUK (IKK), ubiquitinylation  -phosphorylation of NFKBIA (inhibitor of B), recognition by the SCFBTRC E3-ubiquitin ligase complex, K48-ubiquitination, destruction by the proteasome, nuclear localization of NFKB (NFkappaB) and induction of gene transcription  -MAPK14 (p38a) and MAPK8 (JNK1) activation through MAP3K7 (Tak1), activation of JUN/ATF2 (AP-1 complex) and induction of gene transcription  -TLR4-mediated signaling complex assembly comprising TICAM2 (Tram), TICAM1 (Trif) and the E3-ubiquitin ligase TRAF3. Ubiquitin-chain formation, binding of TANK, activation of IKBKE and TBK1, leading to phosphorylation of IRF3 followed by nuclear translocation and induction of gene transcription  -feedback mechanisms, holding the inflammatory response in check.  -excursion on ubiquitinylation and sumoylation | -apoptosis, CASP, caspase, cysteine-aspartate proteinase  -CBL, casitas B-lineage proto-oncogene, E3-ligase, UBE2L3, E2-conjugating enzyme, ubiquitin, substrate complex, molecular structure, casitas B-lineage lymphoma  -E3-ubiquitin ligase classes, RING single component (TRAF6, CBL), RING multicomponent (SCF), HECT (HECT, SMURF) and RING-between-RING (RNF31)  -Enhanceosome of the interferon- gene (IFNB1, interferon-beta), atomic model of IRF3, IRF7, NFKB, JUN and ATF2 bound to their enhancer elements, transcription  -Nuclear factor kappa B (NFKB), reticuloendotheliosis (REL), NFkappaB family members, domain architecture and proteolytic processing  Inhibitor of kappa B (NFKBI), iB, ankyrin repeat proteins  -TANK-binding kinase (TBK1), activation, molecular structure of protein kinase (kinase- + ULD- + SDD-domain), conserved residues and phosphorylation of the activation segment, role of TANK binding to the K63-ubiquitin chain in bringing inactive protein kinases together and phosphorylation of the activation segment *in trans*.  -TLR4, Toll-like receptor-4, molecular structure, leucine-rich repeats, toll-interleukin receptor domain (TIR), death-domain (DD) and interaction with cellular adaptors and effectors  -TLR4, toll-like receptor-4, receptor dimer-mediated assembly of large signaling complexes through sequential re-enforcing DD domain interactions of MYD88 (adaptor), IRAK4 and IRAK1 (kinases), molecular structure and assembly mechanism  -Proteasome, model of capture of phosphorylated CTNNB1 (beta-catenin) by PSMD4 and RAD23A, molecular structure of RAD23A, XPC, ubiquitin binding domain (UBA) and ubiquitin like domain (UBL)  -ubiquitinylation, excursion, enzymatic process, E1-ubiquitin activation, E2-ubiquitin conjugation and E3-ubiquitin ligation, isopeptide bond, peptide bond (linear linkage), different linkages, M1, K11, K48, K63 |
| **14) chemokines and traffic of white blood cells**  Context:  Inflammation and recruitment of leukocytes (diapedesis), chemotaxis  pathways:  TNF-receptor ubiquitin-mediated signaling via TRADD, TRAF2, BIRC2 and RIPK1 and leading to activation of NFB  TNF-receptor and linear (methionine-1) ubiquitinylation through RNF31 (HOIP), SHARPIN and RBCK1 (HOIL)  chemokine receptor (CXCR2), nucleotide exchange Gi, dissociation G and activation of phospholipase-C2, activation of integrins  chemokine receptor, activation of phospholipase A2, phospholipase C, phospholipase D and phosphatidylinositol 3-kinase plus production of eicosanoids (leukotrienes, prostaglandins)  chemokine receptor, nucleotide exchange G13 and Gi, leading to activation of ARHGEF1 and TIAM1 and giving rise to cell migration | -first evidence of extravasation in the tongue of a frog, the account of Augustus Waller (1864)  -bacterial infection (S erysipelas) in the treatment from “new growth” and the discovery of tumor necrosis factors  -inflammatory mediators and their sources  -TNF receptor (TNFRSF1A), trimerization, assembly of signaling complex through death domains (DD), binding of TRADD, TRAF2, RIPK1  -K63-ubiquitin chain attachment to RIPK1 by the E3-ubiquitin ligase complex BIRC2/UB2D3, binding of IKBKG (Nemo) and TAB2 associated with MAP3K7 (Tak1), IKBKB (IKK) and CHUK (IKK)  -phosphorylation of NFKBIA (inhibitor B), recognition by CSFBTRC followed by its destruction, translocation of NFKB to the nucleus  -LUBAC, linear ubiquitin chain assembly, by E3-ubiquitin ligase RNF31, re-enforces the signaling complex, ubiquitinylation  -role of the E3-ubiquitin ligase PELI3 in preventing the apoptotic pathway  -chemokine-receptor mediated activation of phospholipase A2 (PLA2G6), phospholipase C (PLCB2 or PLCG1), phospholipase C (PKD1) and PI 3-kinase (PIK3CA), enzyme products and their biological effects  -CXCL1 (Gro), CXCR2 (IL8RB) and activation of PLCB2, formation of diacylglycerol, activation of RASGRP2 (guanine nucleotide exchange factor), loading of GTP on RAP1A, leading to membrane recruitment of RASSF5, APBB1IP, and talin-mediated activation of integrins, binding to ICAM1 and arresting the cell on the surface of vascular endothelium  -chemokine mediated migration of leukocytes, role of RHOA and RAC1 | -Chemokine receptors, downstream enzymes, effectors, their products and biological effects  -Chemokines, classification, topology of cysteine bonds  -CXCL8, interleukin-8 (IL-8), bound to fragment of CXCR1 (IL8RA), receptor, molecular structure  -leukocyte extravasation, a three-step process, circulation, attachment/rolling and arrest/diapedesis, chemotaxis  LUBAC complex, role of linear ubiquitin-chains, M1, in the stabilization of signaling complexes, complex of RNF31 (HOIP), RBCK1 (HOIL), SHARPIN, ubiquitinylation  -Protrusion and retraction, mode of cell migration, proteins involved, domain architecture and domain interactions (PI 3-kinase-(PIK3CG), TIAM, RAC1, GNA13, ARHGEF1, RHOA, ROCK1)  -TAK1-binding protein 2 (TAB2), adaptor, binding to K63-ubiquitin dimer, structural aspect, TGF-beta-activated kinase binding protein, MAP3K7-binding protein,  -RNF31, RING-finger protein 31 (HOIP), domain architecture, linear ubiquitin chain formation (M1-G76), RING-between-RING segment of E3-ubiquitin ligase, schematic representation of association with SHARPIN, RBCK1 (Hoil), OTULIN, CYLD and ubiquitin-chains, ubiquitinylation  -TNFRSF, members of the tumor necrosis factor receptor superfamily, domain architecture and ligands, TNF, LTA (TNFbeta), FASLG (CD95L), TNFSF10 (TRAIL), TNFSF11 (RANKL) and FAS (CD95), TNFRSF10A (DR4), TNFRSF10C (DCR1), TNFRSF11A (RANK),  -TNFRSF1A, TNF-receptor-1, domain architecture, molecular structure, schematic representation of receptor associated adaptors and effectors (TRADD, TRAF2, BIRC2, RIPK1) or the inhibitor (BAG4) |
| **15) activating the adaptive immune system; role of non-receptor tyrosine kinases**  Context:  Adaptive immunity, T-cell activation, T-cell receptor (TCR) engaged by antigen bound to MHCII  Pathways:  T-cell receptor (TCR), ZAP70 (NRTK), LAT, PLC, Calineurin (PPP3CA) and activation of NFAT in adaptive immunity  T-cell receptor (TCR), ZAP70 (NRTK), LAT, PLC, novel protein kinase C, activation of CARD11 and creation of a MALT1/TRAF6 signaling complex in adaptive immunity  IFN (interferon), activation of JAK1 and TYK2 (NRTK), transcription activation through STAT and IRF9  IFN (interferon) signaling and modulation by protein tyrosine phosphatases (PTP), SOCS1 and PIAS2 | -overview of members of non-receptor protein tyrosine kinases  -T-cell receptor (TCR), antigen presenting dendritic cell, MHC classII, CD4, CD28, CD80  -activation of ZAP70 by LCK, phosphorylation of LAT, recruitment of various effectors, among which phospholipase C (PLCG1, phospholipase Cgamma)  -production of diacylglycerol and IP3, liberation of Ca2+ from intracellular stores, activation of Ca2+/calmodulin-sensitive calcineurin (phosphatase), dephosphorylation of NFAT, nuclear translocation, DNA-binding and gene expression, calcium  -activation of atypical protein kinase- (PRKCQ, PKCtheta), phosphorylation of CARD11 (Carma1), filamentous assembly of BCL10 (CARD domains), binding of MALT1 and TRAF6 leading to ubiquitin-mediated assembly of a large signaling complex, comprising TAB2/MAP3K7 (Tak1), IKBKG (Nemo)/IKBKB (IKK)/CHUK(IKK), phosphorylation of inhibitor kB, nuclear translocation of transcription factor NFKB/RELA, DNA-binding and gene expression, kappaB  -interferon (IFN) mediated dimerization of IFNAR1 and -2, activation of the non-receptor protein tyrosine kinases TYK2 and JAK1, JAK1-mediated phosphorylation of STAT1 and -2, dimerization, binding of IRF9 (ISGF3), nuclear translocation, DNA-binding, gene expression  -down regulation of the interferon pathway  -excursion on non-receptor tyrosine protein kinases | -BCL10, adaptor protein with CARD domain, cryo-electron microscopy structure determination, filamentous assembly, formation of a large adaptor structure that recruits numerous MALT1 proteins (caspase-like protease) and these, in turn, recruit TRAF6 proteins (E3-ubiquitin ligase), assembly of a big signaling complex, B-cell lymphoma  -CARD11 caspace-recruitment domain protein-11 (CARMA1), schematic representation of protein unfolding, nucleation site of BCL10 assembly through CARD-CARD interaction, caspace-recruitment domain  -CSK, C-Src kinase, non-receptor tyrosine kinase, activator kinase of SRC, domain architecture, molecular structure, membrane recruitment and activation through phosphorylated PAG1 (CBP)  -IFN, interferon, classification  -IFNAR1, IFNAR2, interferon receptors bound to interferon- (IFNalpha, IFNA), molecular structure combined with schematic representation  -MHCII, major histocompatibility complex class-II, schematic representation, binding of CD4  -Non-receptor tyrosine protein kinases (NRTK), excursion, classification, domain architecture, members acting as oncogenes  -SRC, non-receptor tyrosine kinase, domain architecture, molecular structure, activation mechanisms, role of the membrane recruitment protein PAG1 (CBP), the upstream protein tyrosine kinase CSK and the tyrosine phosphatase PTPRC (CD45), sarcoma  -STAT, signal transducer and activator of transcription, schematic representation of phosphorylation, dimerization, association of IRF9, DNA-binding and induction of gene expression  -TCR, T-cell receptor, schematic and realistic representation, proximity of CD4  -TCR-mediated activation of NFAT, domain architecture and domain interactions of proteins involved in the signaling pathway, nuclear factor of activated T-cells |
| **16) signaling through the insulin receptor: phosphoinositide 3-kinase and AKT**  Context:  Anabolic action of insulin, protein synthesis and glycogenesis  Pathways:  Insulin, receptor activation (RTK), recruitment and phosphorylation of IRS, recruitment and activation of PI 3K, recruitment and activation of AKT2 and its effect on mTORC1, GSK3B, FOXO1 and SREBP1  2)  insulin receptor activation (RTK), recruitment and phosphorylation of SH2/SORBS1/CBL, activation of RAPGEF1, recruitment to plasma membrane and fusion of GLUT4 vesicles  insulin signaling, depletion of ATP and amino-acids, inhibition of mTORC1 by 5'-AMP-sensitive kinase PRKAA2 (AMPK) via TSC2 and RHEB | -a brief history of the discovery of insulin  -insulin receptor dimer (INSR), change in relative positions of kinase domain (mechanism unknown), activation of kinases through transphosphorylation of activation segment  -recruitment of scaffold protein IRS1 and adaptor protein SH2B2 (APS) via an phosphotyrosine PTB and SH2 domain respectively, insulin receptor substrate  -recruitment of phosphatidylinositol 3-kinases (PIK3C) and production of phosphatidylinositol-3,4,5-phosphate,  -recruitment of PDK1 and AKT2 through their PH-domain. Formation of a transient kinase dimer followed by transphosphorylation (in activation segment) and activation of AKT2 (PKBbeta), phosphoinositide-dependent protein kinase  -phosphorylation and inhibition of GSK3B, activation of glycogen synthase (GYS) and phosphorylation and inhibition of TSC2 (GTPase activating protein), accumulation of the monomeric GTPase RHEB in its GTP-bound state at the lysosomal membrane, activation of the mTORC1 complex in the presence of RRAGA/B bound to GTP and RRAGC/D bound to GDP (permissive condition, only occurs in the presence of sufficient amino-acids in the lysosome), tuberous sclerosis, tuberin, ras-related GTP-binding protein  -mTORC1 phosphorylation and activation of RPS6KB1 and phosphorylation and inhibition of 4EBP1 (removed from EIF4E, bound to the mRNA 5’cap, stimulation of protein synthesis), mammalian target of rapamycin, MTOR  -5’AMP-mediated activation or PRKAA2 (AMPK), with the help of STK11, phosphorylation and activation of TSC2, accumulation of RHEB in GDP-bound state, enhanced autophagy and reduced protein synthesis | -AGC-kinases, members, their domain architecture and common priming and activation mechanism  -AKT2 (PKBbeta), domain architecture, family members, molecular structure, hydrophobic motif, activation segment, conserved residues, activation mechanism, role of mTORC2 (priming) and of PDK1 (activation), phosphosite sequence logo of substrates, protein kinase B  -GSK3B, glycogen synthase kinase-3, surface representation of kinase domain, inhibition through phosphorylation of the N-terminal (pseudosubstrate), processive phosphorylation, role in glycogen metabolism,  -INSR, insulin receptor, extracellular segment, molecular structure, - and -chain, domain architecture, cleavage sites and disulphide bonds  -MTORC1, kinase complex, domain architecture, complex composition, MTOR (kinase), RAPTOR (interacting with RRAGA/B), DEPTOR (inhibitor), MLST8 and interaction with FKB12/rapamycin, mammalian target of rapamycin  -MTORC2, kinase complex, domain architecture, complex composition, MTOR (kinase), RICTOR (interacting with PROTOR), DEPTOR (inhibitor), MLST8, mammalian target of rapamycin  -Phosphoinositide metabolism (PI), kinases, phosphatases and interacting protein domains (ENTH, FYVE, PH, PX, WD-repeat)  -PIK3C (PI 3-kinase, PI3K, phosphatidyl inositol 3-kinase, catalytic subunits, classification, regulatory subunits, upstream receptors (TRK, GPCR/ARRB1/RALGDS, GPCR/G) and interacting proteins  -PIK3CG, PI 3-kinase-, molecular structure, binding to phospholipid membrane and phosphatidylinositol-4,5-bisphosphate, interaction with inhibitors (LY and Wortmannin)  -Ribosome, translation initiation complex, schematic representation, of components and phosphorylation processes (mRNA, EIF3, EIF4G, EIF4E, IEF2G, EIF4A/4B, tRNAmet, RPS6, RPS6KB1 (p70S6K1), MTORC1  -TSC1, domain architecture, phosphorylation sites, tuberous sclerosis, hamartin  -TSC2, domain architecture, phosphorylation sites, tuberous sclerosis, tuberin |
| **17) TGF and signaling through serine/threonine receptors**  Contexts:  -Cell cycle regulation,  -Cell fate decision during development  -Epithelial mesenchymal transition (EMT)  Pathways:  TGFbeta-receptor signaling, receptor serine/threonine protein kinase, via SMAD proteins, canonical pathway  TGFbeta-receptor, receptor serine/threonine protein kinase, signaling via PARD6, non canonical pathway | -TGF (TGFbeta, TGFB) a matrix associated cytokine, precursor form (LAP-TGFB)  -TGFBR, a family or receptors, accessory and pseudo receptors, ligands and traps, ACVR (activin), AMHR (anti-Muellerin hormone), BMPR (bone morphogenetic) and BAMBI, endoglin (ENG), FSTL (follistatin), CHRD (chordin), NOG (noggin), CER1 (Cerberus), DCN (decorin)  -contribution of Drosophila *melanogaster* (Dpp, Sax, Tkv, Mad)*,* Caenorhabditis *elegans* (Daf, Sma) and Xenopus *laevis* (Vg1) in the discovery of the signaling pathway  -type 1 and type-2 receptor, phosphorylation of GS-domain, removal of inhibitory wedge, kinase activation, role or ZFYVE9 (SARA) in bringing SMAD to the receptor  -SMAD types, receptor-regulated, common mediator and inhibitory, phosphorylation of regulated SMAD protein by type-1 receptor, association with common mediator SMAD4, translocation to the nucleus, binding to SMAD-binding element  -association of co-activators, PIN1, YAP1, EP300, CREBP, mediator complex, elongation complex, SWI/SNF  -role of master transcription factors, SPI, POU5F1, MYOD1, in making DNA accessible for SMAD proteins, cell-lineage dependent, cooperative action with other transcription factors (FOXO1, E2F4, STAT3, ATF3, JUN, RBL1) which are controlled by other cytokines (signal integration)  -phosphorylation of linker region determines duration of transcriptional activity, role of kinases CDK8, CDK9 and phosphatase PPM1A and the RNA-polymerase-associated phosphatases CTDSP1, CTDSP2 and CTDSPL, regulation of protein half-life by phosphorylation through the kinase GSK3B  -mono-ubiquitination dissociates SMAD complexes, role of TRIM33/UBE2D3, polyubiquitination (K48) causes destruction, role of NEDD4L and SMURF1  -phosphorylation of linker region in cytoplasm prevents nuclear translocation, role of MAPkinase, and promotes destruction, role of SMURF1  -holding the pathway in check, role of inhibitory SMAD proteins, SMAD6 in creating inactive SMAD complexes, SMAD7 in blocking the receptors, and causing their uptake and destruction (SMURF2/SMAD7 complex)  - bone-morphogenetic protein (BMP, member of the TGFB family) and fibroblast growth factor (FGF) in the induction of neuro-ectoderm in the Xenopus *laevis* embryo (Spemann organizer activity).  -TGF and inhibition of cell division cycle progression, SMAD mutations and cancer, role of TGF in epithelial mesenchymal transition (EMT) | -Hans Spemann, Hilde Mangold, the organizer, Xenopus Laevis, embryonic development, Nobel Prize  -SMAD, transcription factor, molecular structure, MH1 and MH2 domain, DNA-binding, schematic representation of phosphorylation and ubiquitination sites, composition of trimeric complex, sma, MAD  -TGFB (TGFTGFbeta), transforming growth factor beta, ligand, dimer, cysteine knot, precursor protein LAP-LTBP (latency associated binding protein)  TGFB, transforming growth factor beta, family of ligandsINHB (activin), AMH (anti-Muellerian hormone), BMP (bone morphogenetic), GDF (growth and differentiation), INH (inhibin) LEFTY, MSTN (myostatin), NODAL  -TGFBR (TGFreceptor, TGFbeta receptor), type-1 and -2, extracellular segment, domain architecture, molecular structure, ligand binding, dimerization  -TGFBR, overview of receptor types, pseudoreceptors and accessory receptors, their ligands and traps, ACVR (activin), AMHR, BMPR, TGFBR3, TDGF1, and BAMBI, ENG (endoglin), LAP-LTBP1, FSTL (follistatin), CHRD (chordin), NOG (noggin), CER1 (Cerberus), DCN (decorin)  -TGFBR1, kinase domain, molecular structure, GS-domain, L45 loop, conserved residues, activation mechanism  -transcription co-factors, PIN1, YAP1, CREBBP, SMARCA4, SWI/SNF  -master transcription factors, SPI1 (Pu.1), POUF5F1 (Oct4), MYOD1  -TRIM33, tripartite motif, bromo- and PHD domain, interaction with acetylated and methylated Histone-3.3, E3-ubiquitin-protein ligase, |
| **18) protein phosphatases**  Contexts:  -diabetes and obesity  -redox regulation and growth factor signaling  -inflammation  -T-cell activation  -tumor suppression  -establishment and maturation of neuronal synapse, memory consolidation  -control of MAPkinase pathway  -control of glycogen metabolism, glycogenolysis, glycogenesis  Pathways:  beta-adrenoceptor, GPCR, modulation of protein kinase A signaling by PPP serine/threonine phosphatases in muscle glycogen metabolism  growth factor signaling, RTK, through MAP kinase and modulation by DUSP dual specificity phosphatases  growth factor signaling, RTK, through MAP kinase and modulation by SH2-domain phosphatases  growth factor signaling, RTK, through PI 3-kinase and modulation by PTEN dual specificity phosphatase  insulin signaling, RTK, through IRS1 and modulation by PTPN1 tyrosine phosphatase  insulin signaling, RTK, through PI 3-K and modulation by PPP serine/threonine phosphatases  redox signaling, inactivation of tyrosine phosphatase PTPN1, and amplification of growth factor and insulin signaling  T-cell activation, NRTK, and modulation by CD45 (PTPRC) tyrosine phosphatase | -overview of the superfamily of protein phosphatases (PTP, PPP, PPM, CTD)  -domain architecture of members of the family of tyrosine phosphatases, both receptor-like (PTPR) and non-receptor (PTPN)  -tyrosine phosphatases, catalytic mechanism, catalytic pocket and phosphotyrosine specificity  -PTPN1 (PTP1B) in diabetes and obesity, inhibition of insulin signaling, dephosphorylation of receptor and IRS1, inhibitors of PTPN1 avoid insulin resistance, at the level of glucose transport in muscle and liver as well as at the level of POMC transcription in neurons of the arcuate nucleus involved in the inhibition of appetite (anorexigenic signal)  -redox regulation of PTPN1, reactive oxygen species (ROS), hydrogen peroxide, thiolate, H2O2-mediated formation of a cyclic sulphonamide that inhibits phosphatase activity leading to amplification of insulin and growth factor signaling  -SH2-domain-containing phosphatases, PTPN6 (SHP-1) and PTPN11 (SHP-2), their regulation through binding of SH2-domains to tyrosine phosphorylated proteins, the role of PTPN6 in the attenuating the inflammatory response, loss-of-function causes severe skin inflammation, the role of PTPN11 in boosting the RAS-MAPkinase pathway, gain-of-function mutations of the latter phosphatase cause the Noonan and LEOPARD syndrome and are associated with leukaemia  -receptor-like tyrosine phosphatase TPTRC (CD45), loss-of-function cause severe combined immunodeficiency (SCID), primes LCK for activity, essential for activation of ZAP70 at the T-cell receptor  -receptor-like tyrosine phosphatases PTPRF (LAR), PTPRD and PTPRS are adhesion molecules, recognize multiple ligands and the interaction between the two plays a key role in the establishment and subsequent maturation of the neuronal synapse, signaling role still undetermined  -dual specificity phosphatases, domain architecture of family members (classified as subfamily of PTP)  -DUSP1 and DUSP6 bind, dephosphorylate and inhibit MAPKinase, nuclear action of DUSP1 and cytoplasmic action of DUSP6  - puc, a Drosophila dual specificity phosphatase, controls the activity of bsk (MAPKinase) and controls epithelial cell movement and elongation in the process of dorsal closure  -PTEN, a dual specificity phosphatase, recognizes phosphatidylinositol phosphates, true tumor suppressor, loss-of-function mutations in Cowden-syndrome and in hamartomas development, controls the PI 3-kinase pathway, regulated by multiple phosphorylation sites, carries an intrinsic disordered C-tail which enables a large range of protein-protein interactions, a single ubiquitin modification causes nuclear translocation, acts in processes that conserves chromosome integrity  -serine/threonine phosphatases, domain architecture of members and of some of their regulatory subunits  -substrate recognition and subcellular localization determined by regulatory subunits  - PPP1CA, molecular structure, substrate recognition grooves and catalytic mechanism  - PPPC5, phosphatase regulated by intramolecular domain interaction  -PPP1CB associated with PPP1R12A (Mypt1), selective for myosin regulatory light chain, inhibition by okadaic acid (toxin from dinoflagellates)  -PPP1CA bound to PPP1R3A (glycogen targeting in muscle) or PPP1R3B (glycogen targeting in liver), glycogen metabolism, glycogenesis versus glycogenolysis, is discussed in relation to the action of protein kinase A (PRKACA) and glycogen synthase kinase (GSK3B)  -PPP3C (calcineurin or CnA), control by Ca2+/calmodulin and by PPP3R1 (CnB), dephosphorylation of NFAT, activation of gene transcription in T-cells. | -DUSP6 (MKP3), dual-specificity phosphatase, surface representation, conserved segments, cartoon representation, interaction with MAPK1 (ERK2)  -Overview of the superfamily of protein phosphatases PPP, PPM, PTP, CTD  -PPP1CA, serine/threonine phosphatase, molecular structure, signature sequence, catalytic pocket, catalytic mechanism, substrate interaction grooves, binding to PPP1R12A (MYPT1), regulatory subunit, determinant in substrate specificity, myosin regulatory light chain, okadaic acid, toxin from dinoflagellates, binding site  -PPP5C, serine/threonine phosphatase, molecular structure, regulation by TPR domain, TPR-repeats, binding to heat-shock protein HSP90.  -PPP3R1 (CnB), PPP3CA (CnA), calcineurin, serine/threonine phosphatase, Ca2+-sensitive, calcium, molecular structure of complex, dephosphorylation of NFAT; inhibited by the FK506 bound to the immunophilin FKBP1A, nuclear factor of activated T-cells  -PTEN, dual-specificity phosphatase, phosphatidylinositol substrate, surface representation, catalytic pocket, conserved segments, domain architecture, cartoon representation of C2- and PTP-domain, phosphorylation and ubiquitination sites, detail of mutations detected in cancer, regulation of activity by protein kinases (SRC, GSK3B, CSNK2A2 (casein kinase), phospholipid and phosphatidylinositol-lipid binding sites, intrinsic disordered C-tail, binding site for numerous proteins (hub function)  -PTPN1 (PTP1B), non-receptor tyrosine phosphatase, molecular structure, conserved segments (PTP, Q and WPD loops), catalytic pocket, phosphotyrosine specificity, catalytic mechanism, redox regulation  -PTPN6 (SHP-1), non-receptor tyrosine phosphatases, molecular structure, conserved segments, regulation by SH2-domain  -PTPN11 (SHP-2), domain architecture, mutations found in Noonan and LEOPARD syndrome, mutations found in leukaemia, consequences for phosphatase activity, SH2-domain  -PTPRF (LAR), receptor tyrosine phosphatase, surface representation of cytosolic segment, tandem phosphatase domain, conserved segments, dimerization and inhibitory wedge, leucocyte common antigen related  -Redox regulation of activity, reactive oxygen species, ROS, PTPN1 (PTP1B), thiolate, sulphenic acid, cyclic sulphonamide, superoxide, hydrogen peroxide, H202 |
| **19) cell fate determination by Notch**  Contexts:  -bristle containing sensory organ development in Drosophila wing  -cell fate decision during development  -maintenance of the stem cell niche in the intestinal crypt  Pathway:  Notch pathway employing Nicd, RBPJ, MAML1 and EP300 and leading to transcription of HES and HEY genes | -Morgan, the notched wings of Drosophila and the gene theory  -domain architecture of NOTCH2 and its ligands (JAG1, DLL1)  -description of the cleavage sites, S1 (furin), S2 (ADAM17) and S3 (-secretase complex) in the extracellular membrane-proximal segment, role of S2 and S3 in the signaling mechanism of NOTCH  -cleavage of the S3-site liberates the intracellular segment, Nicd, which translocates into the nucleus, binds the transcription factor RBPJ, an event that leads to the loss of transcriptional repressors (NCOR2, HDAC1)and recruitment of transcriptional activators such as EP300 and the mediator complex.  -target genes are HES1, HES5, HES7, HEY1, HEY2 and HEYL, transcription factors involved in the determination of cell fate  -description of Ncid destruction through phosphorylation of the PEST motif (at C-terminal) by CDK8 followed by its recognition by the E3-ubiquitin ligase SCFFBXW7, multi-ubiquitination (K48), recognition by proteasome  -endocytosis is essential for notch signaling in Drosophila, both ligand (delta) and receptor (notch), description of proteins involved in uptake of both (itch, nedd4, lap, numb, shibire (dynamin), mib1 and adaptor-protein-2 complex)  -description of imaginal discs of the 3rd instar larva and the corresponding body parts of the adult fly, focus on the wing imaginal disc  -description of the mechanoreceptor on thorax and wing, part of the bristle-containing sensory organ. Notch signaling in the sensory organ precursor (SOP) gives rise to two cell types (pIIa and pIIb), each with distinct fates (socket and shaft versus sheath, neuron and glia cell)  -description of intestinal stem cell compartment, expression of NOTCH1 in the cycling crypt-base columnar cells (Lgr5+ stem cells) and expression of DLL4 in the adjacent Paneth cells, NOTCH1-mediated expression of HES1 leads to suppression of ATOH1 (a transcription factor instrumental in the differentiation towards a secretory cell type), one of the mechanisms by which NOTCH1 maintains the stem cell in a undifferentiated (self-renewable) state  -examples of cross-talk between Notch and with BMP/TGF or Wnt signaling pathways  -NOTCH mutations in lymphoblastic leukaemia | -HES1, HEY2, helix-loop-helix protein, structure of HLH segment, schematic representation of interaction with TLE4 (groucho) and SIRT1,both histone deacetylases  -NOTCH2, domain architecture, structure of EGF-like (class II) repeats, phosphorylation sites, realistic and schematic representation of the extracellular membrane proximal segment comprising the Notch regulatory region with Lin-12 repeats (LNR) and heterodimerization domain (HD) and containing the S1 (furin) S2 (ADAM), S3 (-secretase, gamma-secretase) cleavage sites  NOTCH, highlight of mutations in the extracellular segment that facilitate cleavage and are associated with lymphoblastic leukemia  -NOTCH intracellular domain, NOTCH-nicd, binding to RBPK and MAML1, structure composition of transcription complex bound to DNA containing a paired response element |