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Review article

Crosstalk and specificity in signalling Are we crosstalking ourselves into general confusion?

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Abstract

The numerous examples of "crosstalk" between signal transduction pathways reported in the biochemical literature seem to imply a general common response of cells to different stimuli, even when these stimuli act initially on different cascades. This contradicts our knowledge of the specificity of action of extracellular signals in different cell types. This discrepancy is explained by the restricted occurrence of crosstalks in any cell type and by several categories of cell specificity mechanisms, for instance, the specific qualitative and quantitative expression of the various subtypes of signal transduction proteins, the combinatorial control of the cascades with specific sets of regulatory factors and the compartmentation of signal transduction cascades or their elements. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Signal transduction pathways; Crosstalk; Specificity; Compartmentation; Combinatorial; Isoforms; Kinetics; Cell models

1. Introduction

Until a few years ago, signalling pathways were described as linear sequences of interactions with a signal activating its receptor (e.g., noradrenaline and its β receptor), the receptor eliciting the generation of signal molecules (e.g., cyclic AMP), protein allosteric modulation (e.g., cyclic-AMP-activating protein kinase A) and/or posttranslation modifications (e.g., protein phosphorylation) and their ultimate effects (e.g., on gene transcription). Little mention was given to interaction between such signal transduction cascades. When we proposed in 1980 that most possible interactions between all steps of the different pathways would be found in at least one cell type at one point in its history, and that regulations were more accurately described as a network, this prediction was met with scepticism [1]. These concepts have evolved and we now know that separate cascades interact, which is often referred to as crosstalk.[1] When put together, such findings suggest that each cascade modulates all the others at several different levels. Considering the multiple theoretical kinetic consequences of even a simple reciprocal cross-signalling between two signal transduction pathways [2], the possible implications in terms of cell behaviour are staggering. In Fig. 1, we summarize experimentally demonstrated cross-signallings between four cascades as reported in the literature over the last 2 years. The result is a "horror graph". With four cascades of five steps, the number of possible positive and negative interactions is 760. This does not take into account the multiplicity of different isoforms of proteins at the different levels of the cascades, the multiplicity of effects of each intermediate in each cascade, the stimulation by a cascade of the secretion of extracellular signals, or feedback or feedforward controls within cascades. In fact, so many interactions are now described (everything does everything to everything) that it is difficult to reconcile this concept with the known specificity of action of signals in each cell.

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[1] The word crosstalk might be considered as a premature misnomer. Talk supposes a vocabulary, a grammar, a variety of meanings and a back-and-forth exchange. No relation between signal transduction cascades has been shown yet to have such properties. Until proven otherwise, cells and cascades signal and may exchange signals but they do not talk. At this stage, the word "cross-signalling" is perhaps more suitable. However, as discussed later, new properties of regulations at the level of transcription begin to fit the concept of "talk".

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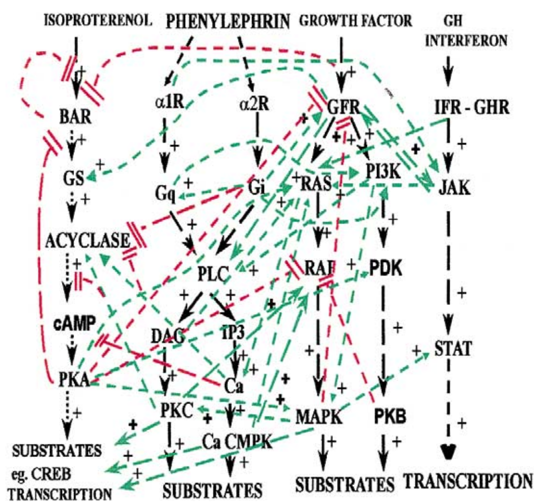

Fig. 1. Cross-signalling between five signal transduction cascades as reported in the literature for 2 years. In black, the "textbook" representation of the linear cascades. In colour, the cross-signallings: in red, negative controls (i.e., inhibitions); in green, positive controls, i.e., stimulations.

The regulation of each cell is therefore probably less and more complicated than we thought. Less than suggested by the literature, because many reported cross-signallings either do not occur or are restricted to a few cell types and circumstances, and because mechanisms already described may account for cell specificity. It is also more complicated because, as the function of more than half of the genes is still unknown, it is probable that many possible cross-signallings remain to be discovered.

2. Many reported cross-signallings may not occur in cells or may occur only at specific times in some cell types

2.1. Interactions may be artefacts of the experimental system used

Protein interactions are difficult to study at low concentrations, which may prevail in normal cells. For instance, coimmunoprecipitations depend on the affinity and specificity of the antibodies used, on the dissociation rate of the interaction and on the concentrations of the targets to be demonstrated in Western blots. To overcome such difficulties, overexpression of one or several proteins in transfected systems, sometimes by factors of over 100, has become general. At these levels, weak nonphysiological interactions, as well as interactions precluded by compartmentalization, may well occur. A factor of 100 nullified the specificity conferred by membrane localization. Even mild overexpression may saturate a stochiometric binding site and allow spilling of the protein and new nonphysiological interactions. A similar caveat applies to in vitro acellular and to double hybrid systems. Present-day journal referees are therefore correct to require a comparison of the level of expression in experimental systems and in the corresponding physiological model. Artificial systems may also miss components that would confer specificity. Conversely, weak interactions that may occur in cells may well be lost in diluted cell extracts.

2.2. Interactions may not occur because the proteins involved are not expressed in the same cells or in the same cell compartment

Interaction of proteins implies that these proteins are expressed in the same cells. Evidence in favour of this assumption may be invalid for several reasons. One type of evidence relies on the demonstration by PCR of the existence of the mRNA corresponding to the protein in the cell. With enough cycles of the PCR reaction, every mRNA resulting from illegitimate transcription might be demonstrated in every tissue. On the other hand, tissue distribution studies (for proteins or mRNA) do not give any indication of which cells in a tissue contain the protein studied. Cell distribution should therefore be proved by in situ hybridization or better by immunohistochemical evidence.

2.3. Interactions may only occur in some cell types or in experimental cells, or at some time

Many potential interactions may not take place because the participant proteins are not expressed. Differentiation implies a partly specific program of protein expression for each cell type. Moreover, the same cell type in different species may exhibit different patterns of protein expression. This may explain why activation of the same pathway in two different cell types, or in the same cell type in different species or different cell lines, may lead to the opposite results. Receptors and signal transduction proteins are differentially expressed during embryogenesis, growth and even in different physiological conditions. In fact, as signals during embryogenesis act through a few cascades, embryogenic development could not occur if these cascades were not interpreted differently by the target cells at different stages [3]. The demonstration of an interaction therefore strictly applies to the system studied and extrapolations of data obtained in one system to others should therefore be validated.

3. How to reconcile apparent general cross-signalling and signal specificity

Even if we eliminate as irrelevant some possible interactions, many are still valid. How can we then reconcile the apparent general cross-signalling and signal specificity? A clear indication of this specificity is given by the numerous examples of opposite results of the same cascade in different

cells. The effects of cyclic AMP on cell proliferation were first described as inhibitory, as they are in fibroblasts and in most cells of mesodermal origin, but were later shown to be stimulatory in some epithelial cells such as dog and human thyrocytes and pituitary somatotrophs, but not in pig thyroid cells nor in human thyroid cancers [4].

3.1. Possible cross-signallings may be restricted by the spatial compartmentation of proteins that could interact

The numerous proteins whose main function is to anchor signal transduction proteins to definite structures show the importance of such localizations. The paradigmatic example is the STE MAP kinase pathway in yeast in which the same enzymes localized by the scaffold proteins STE in different modules regulate very different physiological outcomes of different stimuli [5].

3.2. Signal specificity in a cell type depends on the qualitative pattern of expression of proteins of the same families

At each step of signal transduction cascades, the acting protein may in fact be one or several analogous proteins: isoenzymes, i.e., different enzymes catalyzing the same reaction, or isoforms, i.e., proteins of the same family having different but related roles. They may be encoded by different genes, and/or result from different mRNA splicing or posttranslational processing (e.g., the more than 40 cyclic nucleotide phosphodiesterases). Each of these proteins may present different (sometimes opposite) and overlapping regulatory properties, localizations and controls in expression at the transcriptional, translational and post-translational level. They may respond to different cross-signallings [6]. The same Ca^{2+} signal will enhance cAMP accumulation in nervous cells or decrease it in other cells depending on the type of adenylate cyclase present. The presence or absence of one or another motif of protein–protein interaction [7] or signalling domain in an alternative form of a protein will allow, or not, such interaction or according to the protein recognition code, channel a pathway in a given direction. The presence of one or another protein phosphorylation motif may confer positive or negative regulation by protein kinase A [8]. Thus, of all the possible control points, only the few permitted by the presence of particular analogous proteins operate in any given cell.

3.3. Qualitative difference of protein expression confers specificity by a combinatorial type of regulation

In this type of regulation, a signal can be compared to a letter in a word: it has no meaning per se, only the combination of several letters has a meaning and the same letter used in a different word or combination may have a different or opposite meaning (Fig. 2a). Such regulations

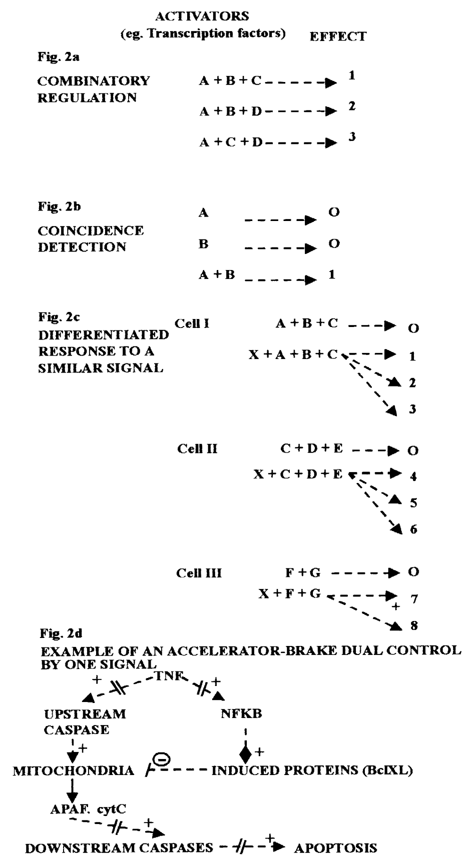

Fig. 2. Examples of combinatorial regulations. (a) Combinatory regulation: each combination of three factors out of four brings a different result (A, B, C, D could be transcription factors acting on one promoter). (b) Coincidence detection: the effect only occurs if A and B act simultaneously (e.g., the Hebbian synapse in neurophysiology). (c) Effect of a "switch" transcription factor: a common cascade induced transcription factor X complements the cells specific combination of differentiation transcription factors existing in each cell type and, thus, has different effects on the promoters corresponding to these factors in each cell. (d) Example of a signal transduction cascade exerting both a positive and a negative control (acceleration–brake cascade). (- - - - ▶ $^{+}$) Activation; (- - - - - - - $^{-}$) inhibition; (- - - -◆ $^{+}$) induction; (- - -//- -) several steps omitted in the graph.

have been demonstrated, for example, for gene expression and for odour discrimination by the olfactory system [9]. They explain how a few factors combine differently to specify many different instructions. Such concepts have mainly been demonstrated, proposed and validated in the transcription field but may well also apply to the enzymatic cascades.

The simplest case is that of coincidence detection, whereby two factors acting in parallel are necessary for an effect (Fig. 3b). The concept has been introduced in neurobiology for cases where a downstream neuron is only activated if stimulated simultaneously by two different upstream neurons (hebbian synapse). It is a general feature

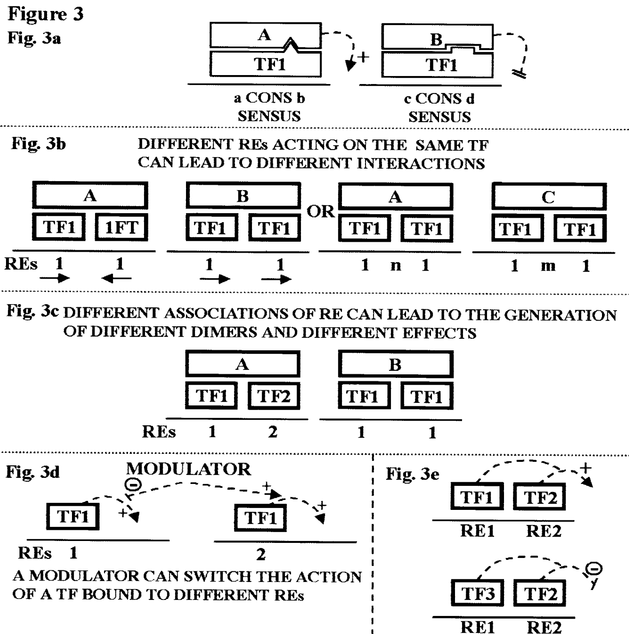

Fig. 3. Examples of the variation of effects of different combination of factors involved in a hormone nuclear receptor complex. TF1 and TF2 are different transcription factors or nuclear receptors. A and B are different coactivators or corepressors that regulate the transcription machinery. RE1 and RE2 are different responsive elements binding the TFy. (a) Variations of sequences outside the consensus sequence of the regulatory element. Consensus is common, but adjacent sequences (a and b, c and d) differ. They specify the coactivator A or corepressor B bound to TF1. (b) Variations of the orientation of REs (double RE1 is head on or repetitive) or of the number of nucleotides (*m*, *n*) between the REs. (c) Combination of different REs and their transcription factors may lead to binding of different coactivators and corepressors and, thus, different effects. (d) The nature of the RE may modify the action of a modulator on the same transcription factor. (e) Combination of different transcription factors on the same REs may lead to opposite results.

of signal transduction. For transcription, a classical example is the c-*fos* promoter in which inactivation of any of the several regulatory elements (REs), which bind the different transcription factors impairs induction by various stimuli [10].

Another simple example of combinatorial logic is the nonspecific transcription factor (the "switch") complementing existing cell-specific transcription factors. Many different signals and cascades operate in their target cells by inducing the same one or several rather ubiquitous transcription factors, i.e., early immediate genes [11] such as c-*fos*. Such a common response to cascades having very different effects is by definition general and nonspecific. Cell specificity of the cascade for induction of one gene is given by the other transcription factors present, which are cell specific (Fig. 2c). Induction of nonspecific transcription factor egr1 in gonadotrophs cells by GnRH (gonadotropin-releasing hormone) leads to the subsequent induction of *LH*β gene [12]. This concept of one general transcription factor, which complements at a given time a whole defined preexisting set of transcription factors to activate or inhibit a corresponding set of genes, would account for synexpression, i.e., the expression with a similar pattern of a set of genes in a cell type in response to a stimulus [13]. It explains how a promiscuous signalling cascade can achieve unique transcriptional effects in a given cell type. This concept applies also to the first steps of signal transduction cascades, e.g., at the level of small G proteins (Rap1) or of the activation of transcription factors (CREB).

In the case of nuclear receptor signalling pathways, numerous possibilities of combinatorial combinations in transcription factor complexes have been well studied and discussed [14–16]. In the simplest scheme, a given RE in the promoter or enhancer of genes will specify the receptor that binds to it and the consequent effects of this interaction on the recruitment of coactivators or corepressors and on the transcription of the gene downstream. However, at each of at least six levels, differences in the actors involved may exist, each one possibly determining a qualitative change, i.e., a binary switch from activation to repression or the reverse. These levels are the RE, the nuclear receptor or the transcription factor binding to the RE, the hormone binding to the receptor, the phosphorylation of the receptor, the other transcription factors on the promoter, the coactivator or corepressor and their modulators and adaptors (e.g., the tethering glucocorticoid receptor inhibiting by direct interaction AP1 transcription factors). The physical basis of such regulation is the multifaceted nuclear receptor whose different domains and functional surfaces binding to different agents in the multiprotein transcription complex signal to each other and to their partners, selecting either a coactivator or a corepressor. For instance, the same transcription factor (e.g., YY1) may have opposite effects depending on the RE on which it is bound [17]. REs with the same consensus sequence, but different adjacent sequences may impart opposite instructions to the same transcription factors (Fig. 3a). The same RE may signal to two different transcription factors with opposite results. Combination in the same promoter of the same REs, in sequence or head on in a palindrome, or of the same REs in the same position but linked by a different number of nucleotides can also lead to opposite results (Fig. 3b). Combination in one promoter of several similar REs as a response unit and of their corresponding transcription factors may greatly multiply their effect [18]. Association of different REs can lead to the generation of different dimers and, thus, different effects (Fig. 3c). In a promoter, the presence on a double RE (e.g., AP1) of different transcription factors (e.g., Jun–Jun vs. Jun–Fos heterodimers) confers to the cortisol nuclear receptor acting on the promoter opposite effects on *pdfg* gene (Fig. 3e). The nuclear receptor itself, depending on its binding of the hormone or not, or even of the type of hormone, will also act in opposite ways. Finally, modulators acting on the RE/nuclear receptor/hormone complex may invert the transcriptional outcome and conversely the nature of the RE might switch the effect of a modulator on the action of a

given transcription factor (Fig. 3d). Thus, each different combination of factors in the multimeric complex with two different possibilities for each factor (a binary switch), including the absence of a factor, will lead to a specific result (induction or repression). This is still a simplified view of the functional transcription initiation complex: Other factors regulating the outcome, but not discussed here, are the methylation of the promoter and the state of the chromatin (histone acetylation and phosphorylation, polycomb group protein binding, etc.). The various possibilities and combinations of factors in the regulatory complex can be represented in a logical matrix (Fig. 4a,b). The advantage of such a representation is that it does not require or imply a precise knowledge of the biochemical interactions but only of their general effect. For a complex of n factor with two possibilities for each factor, the number of possible combinations is 2^n. In this framework, the various combinations define a vocabulary and cross-signalling comes near to becoming crosstalk. The nature of the REs and their necessary transcription factors reflects the genetic background; the opening of the gene (methylation, chromatin), the presence of the receptor and transcription factors depend on the differentiation of the cell, and the presence of the hormone and the phosphorylation of the receptor reflect the state of this cell, i.e., the physiological context. Similar regulations operate on enhancers and silencers [19]. Such a complex combinatorial logic may apply at other levels of the signal transduction cascades and could explain the numerous variations of final effects of these cascades at different moments in different cells. Similarly, at the level of one protein, multiple possible phosphorylation sites may have distinct meanings, each with a binary choice (phosphorylated or not).

Figure 4

Fig. 4a
COMBINATORIAL EFFECTS OF CASCADES ON GENE TRANSCRIPTION

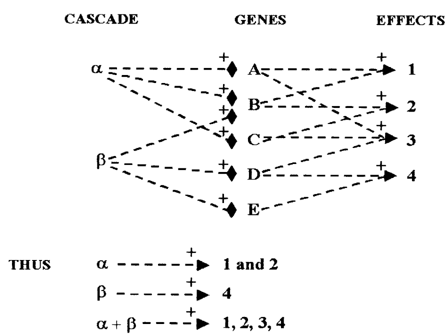

Fig. 4b
Combinatorial effects of two factors for each position of a trimeric transcription complex.

A or B	C or D	E or F	Effect
A	C	E	0
A	C	F	+
A	D	E	0
A	D	F	0
B	C	E	+
B	C	F	+
B	D	E	0
B	D	E	+

A or B could represent the RE
C or D, the other transcription factor in the promoter
E or F, the presence or absence of hormone on the receptor.

Fig. 4. (a) Combinatorial effects of signal transduction cascades inducing partially overlapping sets of genes themselves with combinatorial effects. Cascades α and β lead to the induction (- - - -◆$^+$) of set A, B, C genes for α and set B, D, E for β. Effect 1 results from the induction of both genes A and B, effect 2 of both genes B and C, effect 3 of the three genes A, C and D and effect 4 of both genes D and E. The result is that cascade α has effects 1 and 2, cascade β has effect 4 and both cascades α and β are necessary for effect 3. (b) Combinatorial effects of two factors for each position of a trimeric transcription complex: matrix analysis. For each position, there are two possibilities, each combination implies a specific results. The same formal analysis could be made for any system in which several sets of binary possibilities can be combined, each combination leading to a specific result. The sets can be different REs, transcription factors, presence or absence of hormones, coactivators or corepressors, modulators in transcription complexes. The same type of analysis could be made for other multiprotein complexes for which the presence or absence of each element would be represented by the binary choices A or B, C or D, E or F. Similarly, in protein phosphorylation, the various couples would represent the phosphorylatin or absence of phosphorylation of each of three sites. Such an analysis implies no assumption on the molecular substratum of the combinatorial effects.

3.4. Another mechanism of specificity by qualitative difference of protein expression is provided by the modulators

Modulators are proteins, not involved in the signal transduction cascades themselves, but which modulate positively or negatively the proteins of these cascades. Modulators can be pseudosubstrates or competitors, e.g., natural antagonists for extracellular signals (e.g., Agouti for MSH, Argos for EGF), soluble receptors competing with the real receptor for extracellular signals (e.g., soluble TNF receptor and TNF receptor), inhibitors for signal transduction kinases (e.g., PKI, the protein kinase inhibitor, which inhibits cyclic-AMP-dependent protein kinase, the inhibitors of the cyclin-dependent protein kinases, CDK: p21, p27, p15, p16, ...), inhibitors of transcription factors (such as Bin1 for cMyc, Graucho for LLT1/TCF). They may reverse the activation of signal transduction intermediates, such as the RGS (regulators of G protein signalling), which activate the hydrolysis of GTP by the GTP-binding proteins and, thus, inactivate them, or the phosphatases, which reverse the protein phoshorylations catalyzed by the kinases. They may stabilize an inactive conformation of a protein (as Syn1A does for the CFTR chloride channel). They may tag signal transduction proteins for ubiquitination and subsequent proteolysis (as Cbl does for the EGF receptor). Such regulations by proteolysis and the ubiquitous E3 ligases, which recognize and tag their target proteins, become increasingly important (see an example in the precisely timed degradation of the cyclins). Modulators may also

enhance the activation of a cascade. They may modulate by localizing signal transduction proteins: either sequestrating them (as 14.3.3 proteins do for forkhead associated proteins) or bringing them together as adaptors (as STE5 does in yeast for the proteins of the MAP kinase module) [5], or localizing them at the site where they may be active (as Ras bringing Raf to the membrane). Some modulators may even change the receptivity of a protein from one signal to another, i.e., its signal specificity, e.g., RAMP proteins switch the specificity of the cGRP receptor to one or the other hormone, RAMP1 to CGRP, RAMP2 to adrenomodulin [20].

3.5. The specificity of response to a cascade may depend on the lifetime of the stimulus

A signal may be short or long, immediate or delayed, continuous or oscillatory. The multiple qualitative differences in effect that such modalities confer have been well studied in the case of Ca^{2+}, for which even oscillation frequency qualitatively regulates transcription [21,22]. EGF, which stimulates MAP kinase shortly in PC12 cells, also causes proliferation, while NGF, which stimulates it much longer, causes differentiation [23].

3.6. Specificity of response to a cascade depends on quantitative differences of expression

Many cascades activate two or more different branches that may have parallel, synergistic or opposite effects. When the effects are opposite, quantitative differences in the activation of the two branches may lead to opposite results. Such differences may reflect differences in the expression of the involved proteins. TNF activates both a caspase and a NFKB cascade (Fig. 3d). In the first, activation of a first caspase leads to mitochondrial release of downstream caspase activators and to the final effect apoptosis. The NFKB cascade, on the other hand, induces antiapoptotic proteins (e.g., BclxL), which block mitochondrial activation and, thus, the apoptotic process [24]. Depending on the strength of each branch of the cascade, one outcome or the other will prevail.

4. Conclusions

Networks do indeed exist with their multiple cross-regulations. These often relate to other functional modules and are different from one cell type to another, reflecting the diversity of function and constrains of the cells [25]. Their value may lie in their robust nature: In ecology, more complex regulatory webs are also the more robust [26]. Networks and their robustness [27], as well as redundancies, explain why null genotypes for so many genes have little or no phenotype. In 2001 Space Odyssey, it takes many disconnections to finally neutralize the computer Hal. Moreover, signal transduction cascades, just as metabolic pathways, may have to be controlled at multiple steps for efficiency [28]. Conversely, networks may allow fine tuning in regulation, which, when applied to many cells, may become very important for the organism. Finally, some cross-signallings may have no role and be irrelevant innocuous relics of evolutionary history.

The significance of a signal on a given cell depends on the network into which it is inserted. The response of a cell to a signal depends on the timing and strength of the signal, on the cooperativity of the response, on the cell environment, on the cell population, on the subcellular localization of the signal transduction proteins, on the nature of their isoforms present at each level, on the positive and negative feedbacks and feedforward controls, on the and/and (synergic) or either/or controls, etc., i.e., *in fine* on the nature, quantitative importance and localization of its constituent proteins, its proteomics.

Thus, regulatory schemes can be presented and interpreted in the following two ways.

(1) As maps of all the possible interactions like the conventional metabolic pathways maps.

(2) As the regulating scheme applied to one cell type at a given time in its history. In this case, the cell type, species, history, environment and experimental condition should be defined. For physiological relevance, the choice of the right model is paramount. The validity of the scheme in "real cells", physiological or pathological, should be assessed. This increasingly recognized need explains the expanding literature on gene knockouts and especially on cell-specific and inducible gene knockouts. Reasoning about the behaviour of a given cell type should only be applied to the second type of scheme. We should realize that showing convincingly that a given control does not operate in a given cell is as important as the converse: well-realized negative experiments are important, if not easily publishable.

To evaluate the real complexity of cell regulatory networks, it would therefore be logical to concentrate our efforts on defining these circuits in one or a few model cell types and to try to relate in these models a complete knowledge of the nature of the proteins expressed (i.e., their proteomics) and of their connections, with their behaviour in response to various stimuli. That type of knowledge could then be studied by theoretical modelling. This is the approach pioneered by Gilman [29].

Acknowledgments

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