Patents on Plant Transcription Factors

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Received: July 1, 2008; Accepted: July 25, 2008; Revised: August 15, 2008

Abstract: Transcription factors are clue elements in the regulation of signal transduction pathways in living organisms. These proteins are able to recognize and bind specific sequences in the promoter regions of their targets and subsequently activate or repress entire metabolic or developmental processes. About 1500 TFs were informatically identified in plants, analysis mainly based in the presence of DNA-binding domains in the translated sequences. However, only a few of these 1500 were functionally characterized and clearly classified as TFs. Among these, several seem to be powerful biotechnological tools in order to improve agronomic crops via the obtaining of transgenic plants or as molecular markers. Such TFs have become the objects of patents presentations in the whole world. The assigned uses present a variety of purposes including the improvement in yield, abiotic and biotic stresses tolerances as well as a combination of them. Some examples are commented in the present overview. Most of these TFs confer to transgenic plants complex phenotypes due to a combination of different regulated pathways. In this sense, the use of inducible promoters instead of constitutive ones seems in some cases to be useful to limit the changed phenotype to the desired one, avoiding lateral effects. None of these TFs was converted up to now in a market product since time-consuming experiments and regulation permits are required to arrive to such point. Moreover, a considerable money investment must be done, not justified in all cases. However, it is likely that these molecules will become in the near future the first choice for breeders since it was demonstrated that TFs are very efficient conferring desired traits to transgenic plants. Additionally, for the public perception the over or ectopic expression of a plant gene should be more accepted than the use of molecules from other species.

Keywords: Plant transcription factor, stress tolerance, complex phenotypes, transgenic plants, plant improvement, plant domestication.

INTRODUCTION

Plant Development and the Adaptive Response to Environmental Stresses

Development in multicellular organisms results from growth and differentiation and is determined by a specific program of gene expression. In plants, environmental factors have a great influence on development via different signal transduction pathways that amplify the original stimuli and ultimately result in the activation or repression of certain genes Fig. (**1**). External factors influencing plant development and production include not only climatic ones as drought, wind, extreme temperatures, salinity of soils but also pathogens infections or herbivores attack and contamination of soils caused by human activity. Animals acquired during evolution the ability of movement to avoid adverse conditions but plants are sessile organisms unable to displace to adequate environments. However, they evolved to trigger different and complex defence mechanisms which allow them to survive in adverse conditions for variable periods of time. The ability of a given species to survive to adverse conditions depends on each species and the extent of the adverse condition, and it is related to a series of molecular, physiological and biochemical responses that plants can activate. These responses involve the activation and repression of certain genes following a fine regulation program that is ultimately written in the linear DNA sequence. Such activation and repression of genes generate the synthesis of specialized proteins, enzymes and metabolites that together constitute the defence response.

The response regulatory network turned out to be very complex. Stress tolerance and resistance seem to be controlled mostly at the transcriptional level [1], which depends largely on proteins generally called transcription factors, which are able to enhance or reduce the rate of transcription by facilitating the assembly of the transcription initiation complex. Transcription factors (also called *trans*-acting elements) specifically interact with DNA sequences (*cis*-acting elements) situated in the proximal promoter region of the target gene or with distal response elements [2]. Although transcription is the most important point of regulation, post-transcriptional silencing via different mechanisms also takes place in plants [3].

It has been estimated that *Arabidopsis* and rice have between 1300 and 1500 transcription factor encoding genes [4, 5]. Some of them have been identified as stress responsive; their expression is regulated by one or more types of stress [6]. Each of these stress-related transcription factor family exhibits a distinctive DNA binding domain, such as NAC, ERF/AP2, Zn-finger, DOF, Myb, WRKY, b-Zip and HD-Zip [7]. One example of a transcription factor family responsive to stress is the one described about WRKY family. In rice, this family is composed by 103 genes; among them, 54 exhibited differential expression levels between normal and abiotic stress conditions or phytohormones

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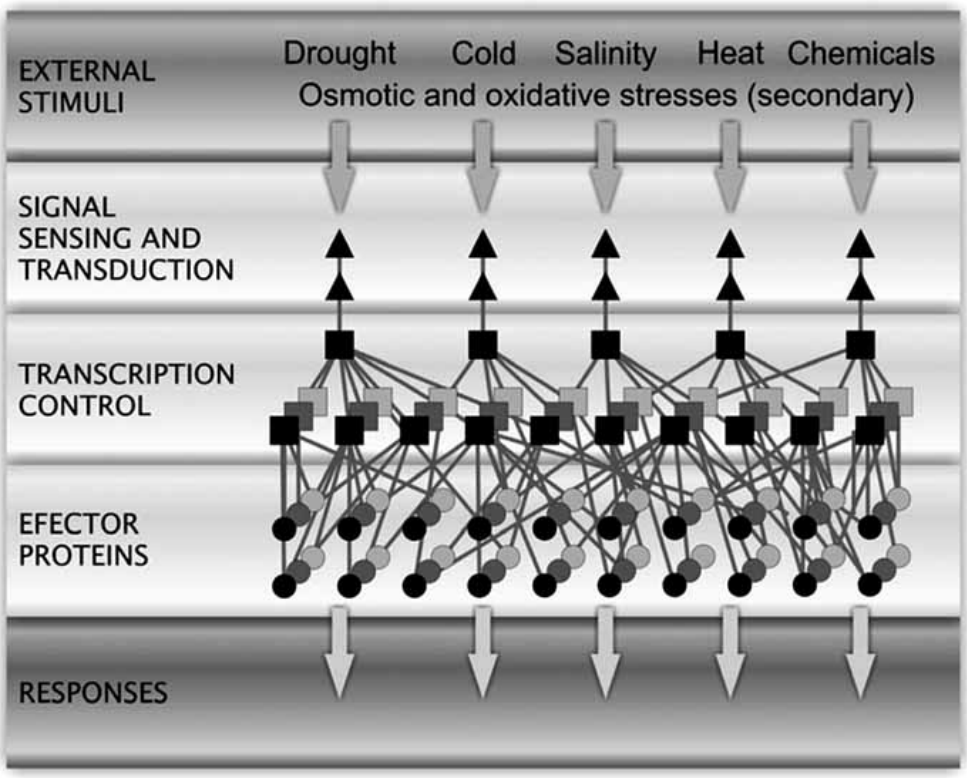

Fig. (1). Signal transduction pathways in response to abiotic stresses. The transduction network triggered by environmental stimuli is extremely complex and involves different stages from signal sensing to the final response.

treatments [8]. Several experiments of transcriptome analysis have revealed that a large number of these transcription factors are induced or repressed by various environmental stresses [9]. Moreover, the transcriptome comparison of plants under alternative stress treatments and even those including the combination of different stresses shed light on the functional basis of multiple stress tolerance [10, 11]. The Arabidopsis leaf transcriptome in response to feeding by diamond back moth larvae was recently analyzed. Among the 1,409 transcription factors represented on the array, 173 were differentially expressed in at least one time point, being 118 up-regulated and 53 down-regulated, while two displayed a mixed expression [12]. Among the down-regulated, basic helix loop helix (bHLH) and homeodomain binding (HB) proteins of the HD-ZIP II class form the dominant group. Transcription factors that were up-regulated by diamond back moth feeding predominantly belong to AP2-EREBP, MYB, and NAC type. Another case in which transcriptomic analysis helped to identify transcription factors involved in the stress response is represented by the study performed with *Arabidopsis thaliana* roots subjected to toxicity by aluminum. Among the responsive transcription factors, the most predominant families identified were AP2/EREBP, MYB and bHLH. The authors of this research proposed that the results of the performed screening contributed to the identification of candidate genes for the generation of aluminium-tolerant transgenic plants [13]. Although transcriptome and additional analyses indicate that the expression of a certain transcription factor is regulated by one or more external conditions, this does not imply that the TF is able to confer tolerance or resistance to these conditions. It must be considered that TFs compose numerous gene families and on the other hand they could be involved in the response but not necessarily conferring tolerance. A series of functional genomics experiments must be performed in order to test and demonstrate such effect. Functional genomics experiments include obtaining transgenic plants in which the tested TF is ectopically or over-expressed and a deep analysis of these plants in different environmental conditions.

From Fundamental to Applied Research on Plant TFs

Most of the knowledge about plant TFs, their structure and functions in plant development and adaptation arises from research done with mutant and transgenic plants. A significant part of this knowledge is of public access, published in peer reviewed articles in specialized journals with a great impact in the scientific community. Most of this knowledge was acquired by public institutions supported by public grants around the world and also by biotechnological companies. However, the publication of the findings inhibits the protection of the intellectual property (IP) and, in general, if the intellectual property is not protected; the use of this knowledge to improve agronomic crops is aborted. The cause of this abortion is that the investment in further experiments and requirements of regulatory institutions in the different countries is very high and could only be supported by great companies. Nevertheless, these companies generally do not invest in further development of a biotechnological tool if the IP is not protected.

These facts led public institutions and researchers as well as private companies to apply for patents even if the required research is not completely performed. This implies the economic risk of dealing with all the expenses associated with patent applications even though a high uncertainty as if the given patented biotechnological tool (in this case, a TF) will become a market product. This last conclusion clearly arises from a simple comparison between plant TFs patents (a considerable number, see Table. (**1**) and plant TFs introduced in the market as engineered crops (none until now).

In other words, TFs display complex responses and the identification of a TF, able to alter defence responses would contribute to obtain a potential biotechnological tool, but this "potential" requires a lot of work and investment to become a "real" biotechnological tool in order to obtain agronomic crops with enhanced tolerance to certain stresses. Physiological studies combined with molecular research will aid the achievement of a better comprehension of the system as a whole. Besides, regarding the use of transgenic crops, it is of great importance to understand which additional mechanisms the transgene may unchain, so as to guarantee the quality of the product. Proper research will enable humanity to satisfy the increasing food demand by the development of highly productive and safe crops.

An Overview on Plant Transcription Factors Patents

Currently, the market offers a limited variety of genetically engineered crops in which one or two genes among a reduced set have been introduced in different plants of commercial interest. These genes code for enzymes, toxins and other proteins which lack gene expression regulatory capabilities and exhibit their major impact at the metabolic level. Thus, although they represent extremely valuable biotechnological tools, they generally fail to efficiently provide transgenic plants with, for example, drought or cold tolerance since such responses involve complex signal transduction pathways including the regulation of numerous genes. Because of this, the ability of TFs to alter transcriptional networks turns them into promising candidates for bioengineering crops Fig. (**2**).

Plant transcription factors are generally patented as biotechnological tools in order to improve agronomic crops from different points of view, see Fig. (**3**) and Table (**1**). This improvement is considered as an increase in yield due to metabolic changes making that more photosynthates migrate to the seeds in normal environmental conditions or to a better behaviour under environmental stresses. In both cases, the desired result is the same: better crops yields. However, patents protecting TFs as biotechnological tools to confer stress tolerance are significantly more than those claiming improved production in normal environmental conditions, both in the US and in Europe, see Fig. (**3**). The reasons for this could be essentially two and also the combination of both. On one hand the knowledge from which the patent arises is more limited in the case of yield improvement and on the other hand, environmental stress, especially drought stress is the main cause of enormous loss in crop production around the world. Hence, great efforts in research were performed in this field, abiotic stress tolerance [14].

Table 1. Examples of Transcription Factors Patented in Order to Improve Agronomic Crops

Gene name	Gene origin	Improvement	Patent number	Reference	Date
CBF1	*Arabidopsis thaliana*	Abiotic stress	US5891859	[15]	1999
DREB1a	*Arabidopsis thaliana*	Abiotic stress	US20026495742	[16]	2002
OsDREB1b	*Oryza sativa*	Abiotic stress	US20060230471	[17]	2006
OsDREB1a	*Oryza sativa*	Abiotic stress	US20067138277	[18]	2006
Athb-12	*Arabidopsis thaliana*	Abiotic stress	US5981729	[19]	1999
HOS 10 (MYB 8)	*Arabidopsis*	Abiotic stress	WO04092326	[20]	2004
StEREBP	*Solanum tuberosum*	Abiotic stress	KR040050633	[21]	2004
Hahb-4	*Helianthus annuus*	Abiotic stress	US20070180584	[22]	2007
APZ (121)	*Arabidopsis thaliana*	Biotic stress	US 6664446	[23]	2003
OsWRKY45	*Oryza sativa*	Biotic stress	EP1889909	[24]	2008
ERF TF	*Triticum aestivum*	Biotic stress	CN101033252	[25]	2007
LFY	*Arabidopsis thaliana*	Development	US5844119	[26]	1998
OBP3	*Arabidopsis thaliana*	Development	US20077265264	[27]	2007
RISBZ1, 4 and 5	*Oryza sativa*	Development	US20040072159	[28]	2004
ZmELF3	*Zea mays*	Development	WO07103956	[29]	2007
Hahb-10	*Helianthus annuus*	Development	US20070234439	[30]	2007

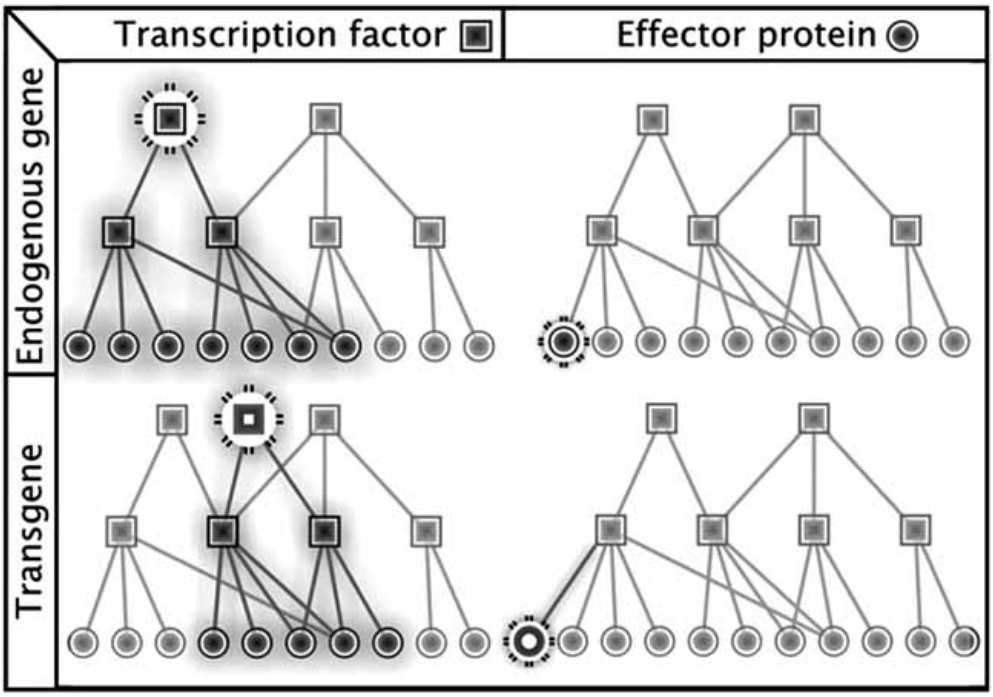

Fig. (2). Effect of the gene introduced in the genetically engineered crop. Schematic representation of the disruption generated in the signaling network by the introduction of a transgene either from the same species (endogenous gene) or from a different species (heterologous gene).

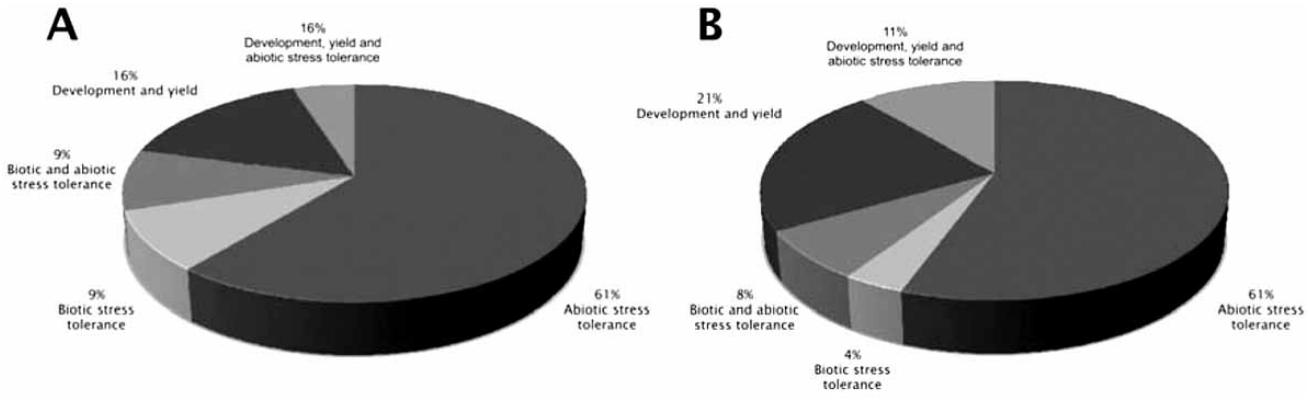

Fig. (3). Classification of patented genes according to claimed uses. In Fig. (3A), 44 patents on TFs were retrieved from the website Patent Storm (www.patentstorm.us). In Fig. (3B), 32 patents on TFs were retrieved from the website of the European Patent Office (www.epo.org)

Although crop improvement is the most ubiquous aim presented in TFs patents, there are other uses for TFs, like the conversion in a transcriptional repressor that have been object of a patent presentation [31]. In this example, the usefulness of the invention could be applicable in a wide variety of fields, other than crop improvement, such as in the repression of the expression of cancerous genes and regulation of the expression of genes encoding pigment-metabolic enzymes [31].

Patents on TFs Related to Development and Yield

We present here several examples of patents on diverse TFs belonging to different families related to plant development and the available compiled information in Table **1**.

Weigel presented in 1998 a patent protecting the TF LEAFY as a tool to genetically modify tobacco and aspen plants in order to modulate flower meristem development, generating plants flowering earlier than non transformed ones [26]. This is a typical case in which basic research led to an applied one since Weigel's group is one of the pioneers in the research of flower development and publishes its findings in prestigious journals [32-34].

A group of b-Zip TFs was protected in 2004 as tools to improve and regulate the expression of rice storage proteins. These TFs (RISBZ1, RISBZ4, and RISBZ5) were isolated from a rice seed cDNA library and it was demonstrated that they activate the synthesis of such storage proteins [35].

A Dof TF, OBP3, was patented in 2007 as a tool to increase the size of the transgenic plant in which it is inserted in a given construct [27].

HAHB10 is a sunflower HD-Zip TF patented to be used as an accelerator of the flowering process shortening the life cycle of a plant without losses in yield [30, 26]. Additionally, this TF confers tolerance to treatments with paraquat, a common herbicide. The exact molecular mechanism of action of this TF is still unknown; however experimental evidences indicating that the ability of shade avoidance is enhanced in transgenic plants transformed with this gene were presented [36].

These four examples of TFs involved in plant development pathways in which the over or ectopic expression confers to the plant a desired trait that results in an augmented yield.

Patents on TFs Related to the Abiotic Stress Response

This is the field in which the greatest number of patents on TFs is applied for; some of them also exhibit additional claims like better development or yield. There are patents protecting TFs as tools to confer tolerance to one type of abiotic stress whereas others protect to combined abiotic stresses. It is important to note that before the first TF patent was presented, several molecules from plants and other organisms were tested to improve stress tolerance. Numerous patents are available claiming methods to achieve this goal Fig. (**3)** and Table **1**.

Arabidopsis thaliana DREB1A is one of the examples of TFs from a non agricultural crop that is a object of a patent for conferring drought, cold and salt tolerance in a wide range of species [16, 37]. This case is also an example of multiple patents protecting tools based on the same original finding, i.e., constructs, plants, cells, all of them bearing the DREB1A gene. One of the patents protects the gene itself and the other one, the constructs and plants bearing them. These findings were corroborated and published in specialized journals articles [28, 38, 39]. It is important to note that when we designed Fig. (**3**), in which the percentage of different uses assigned to plant TFs are graphed proportionally, we took in account only once each gene.

A different picture is presented by the patent of an *Arabidopsis thaliana* gene encoding a HD-Zip TF [19]. In this case the gene was protected as a potential tool to confer drought tolerance in transgenic plants. However, a few years later, a research group different from that of the inventors, published a paper in which they stated that this gene is a developmental regulator in response to drought stress, diminishing developmental rate in transgenic plants and that it does not confer drought tolerance [40].

A sunflower HD-Zip protein was also protected as a tool to confer drought tolerance when its expression in transgenic plants is directed by a constitutive or inducible promoter [22]. In this case, the same authors/inventors published after the patent application, experimental results corroborating and deeply characterizing these claims [41-43]. Later, the authors found that the same gene confers tolerance to herbivory attack and wounding by a different signal transduction pathway in which jasmonic acid is involved [44].

CBF1 was protected by Thomashow, *et al.* [15] as a tool to confer combined cold and dehydration tolerance to transgenic plants. The whole scientific works it with a deep analysis of the action mechanism was published later [45].

The use of a zinc finger transcription factor, ZPT2-3, to generate plants with increased drought tolerance was protected in 2006 [46]. In this case, the authors were investigating the function of ZPT2-3, petunia transformants over-expressing this gene under the control of the CaMV 35S promoter. They observed a strong tolerance against desiccation stress treatment in these plants is accompanied by growth and morphological abnormalities. These undesired effects were reported also in other cases in which TFs generate abiotic stress tolerance, especially in those in which constitutive high expression occurs like when the 35S CaMV promoter is used. This fact is not so surprising taking in account that TFs are normally expressed in very low concentrations and such a high level of expression imply metabolic expenses as well as complex phenotypes due to the different transduction signals regulated. In subsequent works it was demonstrated that the adverse effects could be abolished in transgenic plants transformed using inducible promoters that direct expression of the TF only if it is necessary, avoiding metabolic expenses and concomitant effects [43].

Patents on TFs Related to Biotic Stress Response

Patents on TFs as biotechnological tools to confer tolerance to biotic stress are not as much as those devoted to abiotic stress and also more recent. This fact is mainly due to the accompanying research (TFs involved in biotic stress response are described later in the scientific literature than those involved in abiotic stress) and also to the great negative impact presented by abiotic stress in agriculture that clearly generated a vast research in this area.

In the field of biotic stress, disease tolerance is the more desired effect in a transgenic plant, especially in those in which bacterial or fungal infections generate devastation of the culture. TFs from different families demonstrated to be involved in disease tolerance and were used to obtain transgenic genotypes in order to test such tolerance. An example of this type of TF is APZ, isolated from *Arabidopsis*, that enhances tolerance to fungal diseases, especially those caused by *Fusarium*, *Erysiphe*, *Sclerotinia* and *Botrytis* and the use of this TF was protected in 2003 by Heard, *et al.* from Monsanto [23].

Patents on TFs Related to Other Uses

Other uses were also found for TFs that in different ways may contribute to improve agronomic plant characteristics. An example of this is the barley SUSIBA2, WRKY TF, capable of activating several promoters of genes encoding enzymes involved in the synthesis or deposition of starch in response to sugar levels in plants. As a result, the degree of branching in starch and its concentration in transgenic plants can be modulated providing a mean to produce an oligosaccharide with desired biophysical properties. This TF acts on promoters which comprise at least one SURE element and\or W box element to which it binds [47].

As it is commented above, other uses unrelated to improve a certain process in plants are also the subject of plant TFs patents presentations [31].

Promoters and Other Transcription Control Sequences Used to Express Plant TFs

Each plant gene has its own promoter, usually located upstream the coding sequences, presenting *cis*-acting elements responsible for tissue/organ specific expression as well as for induction/repression by external factors. Most recognition mechanisms are conserved in the whole plant kingdom, but significant differences have been observed between mono and dicot plants. Additional *cis*-acting elements could be located far away from the transcription initiation site, at positions 5'- or 3'-flanking and even within introns or other intergenic regions.

Biotechnology contributes to the improvement of crops by introducing a single gene conferring a desired phenotype. To succeed in this process, it is necessary to identify the gene able to confer the desired characteristic (in this overview, the adequate TF) and a promoter region directing the expression of this gene in the adequate time and place. Constitutive promoters are sequences that direct gene expression at a high level in the whole plant during all developmental stages. Examples of this kind of promoters are the 35S CaMV (described below) and the ubiquitin promoter [48, 49].

There are some typical promoters used for both, monocot and dicot plants. They have widely used for fundamental research as well as biotechnological tools, but their use sometimes leads to unnecessary metabolic expenses for the transformed plant. Additionally, in some cases, expression of the transgene in the whole plant is undesired since the gene function is needed only in a given stage and/or tissue/organ and not in others. Two main reasons justify that, on one side for the public perception of a transgenic crop is better to have a transgene non-expressed in the fruit or in the plant product; on the other side, metabolic energy costs, when occur, could significantly be diminished with the use of non constitutive promoters. For example, seeds or fruits could remain unchanged from the metabolic and proteomic point of view being tolerant to drought if the expression of the transgene occurs in roots and leaves that are not the final market products.

However, it is important to highlight that one of the most widely used promoters in transgenic crops is the viral 35S CaMV promoter [48]. It is a well characterized promoter which directs strong and almost constitutive expression; features that have been extensively exploited in plant research. In order to further increase the expression of the transgene, two related constructions have been developed: the first comprising among other elements a duplicated 35S CaMV promoter and the second involving the 35S CaMV enhancer [50].

There are other non coding DNA elements in addition to the promoter which have proved extremely valuable for transgenic crop engineering. Among them the Kozack consensus sequence [51] and the NOS terminator [52] are worth mentioning.

As it is discussed below, no transcription factors are up to now part of commercial products but fundamental research in order to attribute a function to these molecules was carried out with these chimerical promoters. Bt corn and herbicide tolerance would have not been possible without them. It is also important to note that although many authors reported that constitutive promoters directing transcription factors expression caused undesirable accompanying effects in transgenic plants, this is not always the case. In few examples the overexpression of a TF has produced the intended positive stress tolerance without unwanted side effects, both in laboratory and field experiments [46,53,54]. The seed specific sunflower transcription factor HSFA9 conferred drought tolerance when is ectopically expressed in tobacco under the control of a constitutive promoter [54]. Similar results, avoiding undesirable yield penalties while salt and drought stress tolerances were achieved in transgenic rice, were obtained with the overexpression of a SNAC (Stress NAC) transcription factor [53]. This research is particularly interesting because the authors performed also field tests besides the typical laboratory ones.

In the same sense, aiming to achieve stress tolerance without penalties using a plant TF, there is one patent claiming that modified transcription factors could be useful for reaching this objective as an alternative to the use of inducible transcription control sequences [55].

On the other hand, tissue/organ specific promoters have been described but in some cases, expression directed by them is not strong enough to reach the desired acquired phenotype in the transformed plant. The use of artificial constructions, combining specific *cis*-acting elements or entire weak promoters with enhancers, was proposed and this kind of constructs is the object of additional patents, meriting a separate overview. Patents claiming the use of inducible or tissue specific promoters could be exemplified by the stress-inducible rd29A promoter which minimized the negative effects on the plant growth in tobacco and the root specific promoter driving the expression of a LRR receptor-like kinase [56-57].

Functional TFs Discovered after Crop Domestication

The participation of TFs in crop improvement is not as novel as the picture which arises from analyzing TFs patents. Doebley, *et al.* [58] covered in detail in a review the strong evidences demonstrating that TFs played a major role in the origin of agriculture trough the domestication of various crop plants.

Good examples of TFs used to improve crops in agriculture are Tb1 from maize and qSH1 from rice [59]. The first one, belonging to TCP family represses the out-growth of lateral branches. An allele that altered the regulation of Tb1 was selected during the domestication, increasing its expression in primary auxiliary meristems. A survey of maize revealed an alteration in the regulatory region of this gene leading to a dramatic shift in the architecture of the most extensively grown crop today in North America [59]. A second example is given by the rice qsh1. Grain shattering is the key trait undesired in rice plants, it prevents seeds from dropping off the panicles and allows efficient harvesting of the grain. A quantitative trait

locus (QTL) was isolated in a cross between a shattering-type cultivar and a non-shattering-type. This QTL resulted to encode a BEL1-type TF, a homedomain containing protein. A single nucleotide polymorphism in the regulatory sequence of this TF is responsible for this trait. The non-shattering cultivar does not express qsh1 in the developing abscission layer at the base of the seed. The selection was performed for loss of expression in this location [59-60]. These are good examples of how a single TF could change an important phenotypic characteristic of a plant. In both cases, genetic engineering was absolutely absent. However, TFs took a significant role in domestication by classic techniques.

A Long Way from a Patent to a Market Product

The first commercially successful genetically engineered agricultural crops were launched twelve years ago [61]. The first products were based in large part on simple monogenic traits, such as herbicide tolerance or insect resistance, which did not require manipulations of complex molecular pathways in the transgenic plant.

A second generation of transgenic products for more challenging traits related to yield which is under complex polygenic control is expected since that. The availability of the complete genome sequences of *Arabidopsis thaliana* and *Oryza sativa* and other genomic tools (mutants, microarrays, etc.) offer a great opportunity to identify regulatory genes and networks that control these important traits.

Because transcription factors naturally act as master regulators of cellular processes, they are expected to be excellent candidates for modifying complex traits in crop plants. However, complex processes are essentially complex and the TFs known and characterized participate in more than one such process [59].

TFs seem to be useful candidate tools for agricultural biotechnology products. However, from the discovery of the gene function or ability to a market product, there is a long way to run. Fig. (**4**) schematically shows the time cost of each step in this way but does not take in account the costs of producing a genetically engineered crop. Numerous challenges must be faced to produce a commercially viable end product [62] and a period of 10-12 years from gene discovery. One of the more time consuming steps is the securing approvals from regulatory authorities.

In this sense, most patents on plant transcription factors are based in experimental data arisen from "proofs of concept", which have been performed only with model (non-crop) plants under controlled laboratory conditions.

There are only very few examples of TFs tested with crop plants grown under field conditions, being these tests essential to go from gene discovery to practical application [63]. Among them, the TF NF-YB1 was tested first in *Arabidopsis* and showed to work in drought conditions (when constantly active, the plants showed to did not wilt as much as wild type plants and maintained higher photosynthetic rates). The equivalent gene in maize switched on permanently in genetically modified plants, produced as much as 50% more than unmodified plants in simulated drought conditions that typically reduced maize yield by more than 50% [64].

As commented above, the overexpression of a stress responsive gene (SNAC I) in rice enhanced drought tolerance yielding about 30 % more seeds than untransformed plants under stress condition at the reproductive stage. These plants lose water more slowly by closing stomatal pores and are more sensitive to abscisic acid [53].

A recent review informed that most of the "premature" patents based in the proofs of concept have not resisted field testing, at least for drought stress resistance [65]. This situation would make more difficult reaching useful applications that are protected by patents. Perhaps only large companies, governments or even trans-national organizations

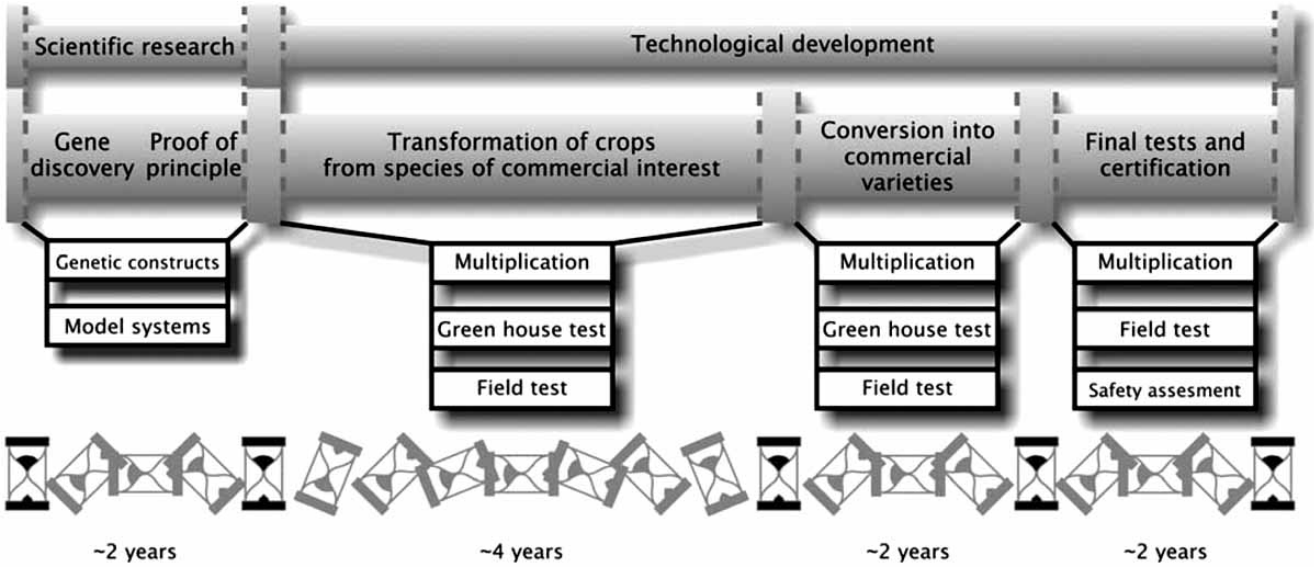

Fig. (4). Research and development pipeline.
Schematic representation of the whole process necessary to arrive from gene discovery (first step) to a genetically modified crop converted into a market product (last step).

could cope with such a long term effort. Premature patents even if found useful at a later stage could give benefits only for the few remaining years of legal protection (counting on approximately 20 years in total from patenting. Because of this, perhaps large emerging economnies and even companies could finally opt for not patenting.

The advantage of a plant TF in relation to the first generation of transgenics is essentially that these molecules are modifying native molecular pathways while nonplant molecules used for herbicide tolerance, insect resistance or virus resistance are exogenous. The disadvantage is mainly that TFs generate complex phenotypes that must be analyzed, fact that can be abolished by the use of adequate promoters as discussed above. It is a challenge to prove that a transgenic plant engineered with an enhanced trait poses no new environmental or health risks when compared to the plant from which it derives.

Scientists, regulators and people in general must understand that with an expected human population of 9 billion by the middle of the present century it is necessary to accelerate the rate of improvement in crop productivity. In this sense, plants TFs are the best and safest candidates for engineering. However, up to now no market products are available engineered using these molecules.

ACKNOWLEDGEMENTS

The work of the research group is supported by ANPCyT (PAV 137/2/2, PICT 2005 38103, PICTO 08-13204), CONICET (PIP 6383), UNL and CABBIO. ALA and JVC are Fellows of CONICET, RLC is a researcher of the same Institution.

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