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Potato Glycoalkaloids, Past Present and Future

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ABSTRACT

The steroidal glycoalkaloids are naturally occurring specialty metabolites of questionable desirability in the vegetable crop, potato. Although glycoalkaloids undoubtedly originated under selection as feeding deterrents against herbivorous pests, they no longer function as the primary feeding deterrent. Moreover, due to their potential toxicity, guidelines persist as to the maximal allowable concentrations for newly developed cultivars. The origins of the glycoalkaloids lie in the ancient relatives of the modern potato, which continue to be used in breeding programs because of the wealth of genetic diversity for performance, nutrition and disease resistance. In recent years, the genes encoding the enzymatic steps responsible for glycoalkaloid synthesis have begun to be elucidated. This in turn has presented the possibility of manipulating these genes to control glycoalkaloid accumulation and increase the availability of diverse biological resources for the development of new and improved cultivars with enhanced agronomic, processing and nutritional characteristics. This article will discuss the origin and diversity of glycoalkaloids in the potato, why they are a concern and what is being done about them, and how the advancement of biological information and technologies will impact potato glycoalkaloids in the future.

Keywords: biosynthesis, genetic manipulation, *Solanaceae*, specialty metabolites
Abbreviations: CPB, Colorado potato beetle; **EST**, expressed sequence tag; **ET**, expressed transcript; **SGA**, steroidal glycoalkaloid; **SGT**, steroidal alkaloid glycosyl transferase; **TA**, tentative assembly; **TGA**, total glycoalkaloids

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INTRODUCTION

Potatoes (*Solanum tuberosum*) are the number one vegetable crop in the world and after the three major cereals, the world's fourth largest food crop (excluding sugar cane) (FAO Statistical yearbook 2005-2006, Production of Selected Agricultural Commodities (2004) http://www.fao.org/statistics/yearbook/vol_1_1/site_en.asp?page=production).

Potatoes are members of the *Solanaceae* family that also includes regionally important vegetable crops *S. lycopersicon* (tomatoes), *Capsicum* spp. (bell peppers, chilies), *Physalis* spp. (tomatillos, strawberry tomato), and *S. melongena* (eggplant). A common thread within the *Solanaceae* is the production of a vast array of alkaloids that have been long exploited for their medicinal and pharmacological effects such as the tropane alkaloids atropine, scopolamine (Muller 1998) and nicotine in tobacco (Charlton 2004). The cultivated potato accumulates alkaloids, although to a lesser extent than the wild potato relatives. These wild relatives are an important source of biodiversity for pest and disease resistance as well as other desirable agronomic and nutritional traits. In this review the diversity of potato glycoalkaloids will be examined and their possible biological roles and potential impact on human health. Why glycoalkaloids remain a concern and what is being done by traditional and molecular methods will be discussed. Finally, how new information and new information systems will impact the nature and content of glycoalkaloids in future potato varieties.

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Invited Mini-Review

THE PAST

The steroidal alkaloids of *S. tuberosum* and its wild relatives

The major alkaloids to accumulate in the cultivated potato are solanidanes (**Fig. 1**). The tri-glycosylated derivatives of solanidine; α-chaconine and α-solanine, containing β-solatriose and β-chacotriose glycosyl moieties (**Fig. 2**), respectively (Maga 1980), are the two most abundant alkaloids to accumulate in the potato. Another important group of alkaloids not originally found in *S. tuberosum*, but that have been introduced through crosses with *S. chacoense* (Sagredo *et al.* 2006), are the leptines. Both leptines of *S. chacoense* accumulate as triglycosylated derivatives with β-solatriose and β-chacotriose moieties and are believed to contribute to resistance against the Colorado potato beetle (CPB) defoliation (Lawson *et al.* 1997). The dihydro derivative of solanidine has also been observed in potato after crosses with *S. brevidens* (Laurila *et al.* 1996).

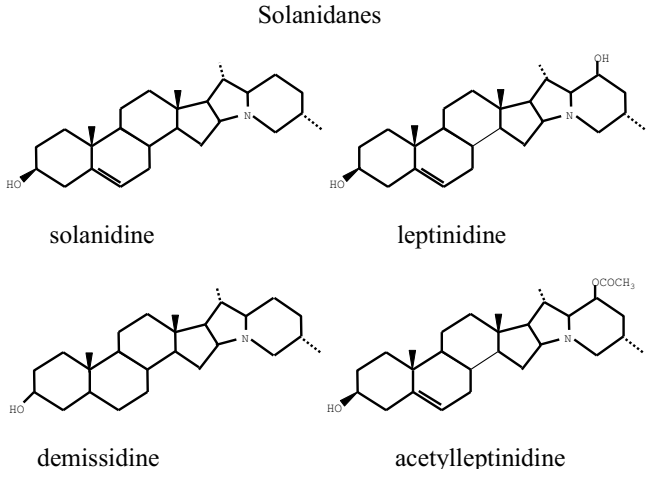

Fig. 1 Solanidanes of the potato. The most common solanidane of the cultivated potato is solanidine. Hydrogenation of the double bond produces the dihydro derivative demissidine found in many of the wild potato relatives. The hydroxyl and acetoxy derivatives (leptinidine and acetylepinidine, respectively) serve as aglycones for the leptines.

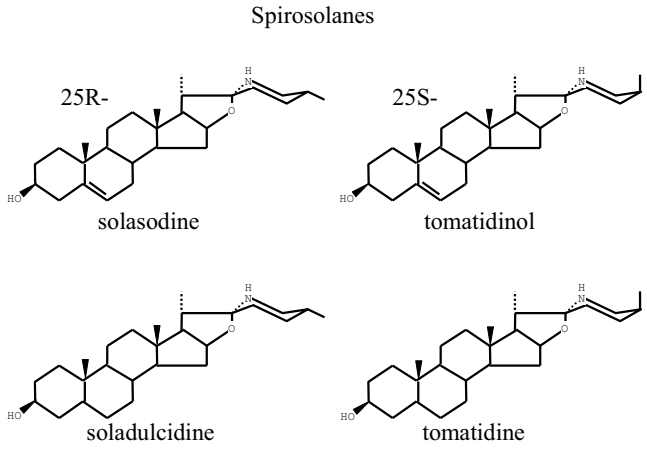

Fig. 3 Spirosolanes of the potato. The structure of 25R and 25S spirosolanes (solasodine and tomatidinol) and their dihydro derivatives soladulcidine and tomatidine.

The closely related spirosolane enantiomers (**Fig. 3**) 25R-(solasodine) introduced into cultivated potatoes through introgression of *S. berthaultii* (Yencho *et al.* 1998), or 25S-(tomatidinol) naturally and introduced in cultivated potatoes through introgression of *S. demissum* (Sinden and Sanford 1981), are also produced in some cultivars, notably in the leaves of cv. 'Kennebec' (Shih and Kuc 1974). Both spirosolane aglycones are typically found as both triose derivatives when present (Gregory 1984). In the wild relatives of the cultivated potato, these and additional alkaloids occur, including the corresponding dihydro derivatives of solanidine, solasodine and tomatidinol; demissidine, soladulcidine and tomatidine, respectively. These dihydro derivatives are most commonly glycosylated by the tetraose moieties β-lycotetraose and commertetraose (Deahl *et al.* 1993). Al-

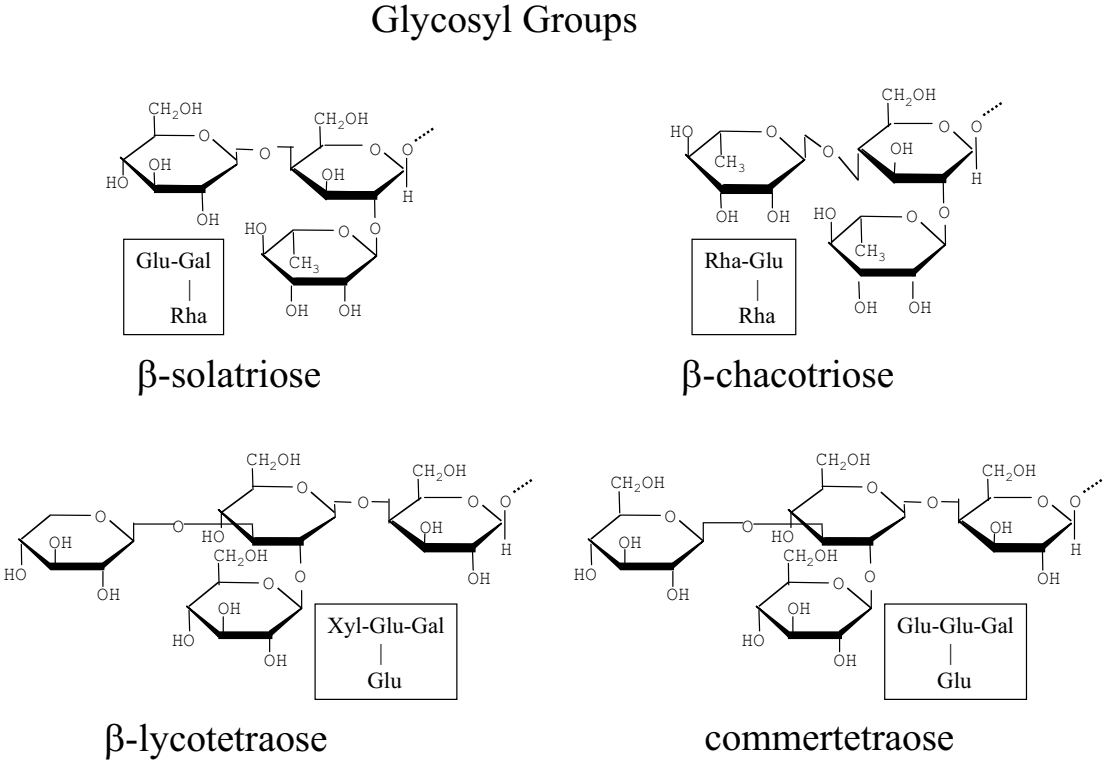

Fig. 2 Glycosyl groups of the potato steroidal glycoalkaloids. β-solatriose and β-chacotriose are the trisaccharide moieties of the common potato SGAs, α-solanine and α-chaconine, respectively. β-lycotetraose and commertetraose are tetrasaccharide moieties.

Table 1 The common steroidal alkaloid aglycones of *Solanum* sp.: associated glycosyl moieties and the names of the described glycosylated products.

Aglycone	Saccharide	Compound	Reference
Solanidine	Commertetraose	dehydrocommersonine	Carputo *et al.* 2003
	Chacotriose	α-solanine	Deahl *et al.* 1993
	Solatriose	α-chaconine	Deahl *et al.* 1993
	Lycotetraose	dehydrodemisine	Carputo *et al.* 2003
Demissidine	Commertetraose	commersonine	Deahl *et al.* 1993
	Chacotriose		
	Solatriose		
	Lycotetraose	demissine	Deahl *et al.* 1993
Solasodine	Commertetraose		
	Chacotriose	α-solasonine	Yencho *et al.* 1998
	Solatriose	α-solamargine	Yencho *et al.* 1998
	Lycotetraose		
Soladulcidine	Commertetraose		
	Chacotriose	soladulcine A	Lee *et al.* 1994
	Solatriose	β- soladulcine	Schreiber 1958
	Lycotetraose	soladulcine B	Lee *et al.* 1994
Tomatidinol	Commertetraose		
	Chacotriose	α-solamarine	Deahl *et al.* 1993
	Solatriose	β-solamarine	Deahl *et al.* 1993
	Lycotetraose	dehydrotomatine	Carputo *et al.* 2003
Tomatidine	Commertetraose	sisunine	Osman *et al.* 1986
	Chacotriose		
	Solatriose		
	Lycotetraose	tomatine	Deahl *et al.* 1993
Leptinidine	Commertetraose		
	Chacotriose	leptinine I	Lawson *et al.* 1997
	Solatriose	leptinine II	Lawson *et al.* 1997
	Lycotetraose		
Acetylleptinidine	Commertetraose		
	Chacotriose	leptinidine I	Lawson *et al.* 1997
	Solatriose	leptinidine II	Lawson *et al.* 1997
	Lycotetraose		

though uncommon, minor amounts of the delta-5 unsaturated aglycones have been reported linked to tetraose moieties (Carputo *et al.* 2003). **Table 1** lists the common aglycones and the known glycosylated products along with select references.

Feeding deterrents, pest resistance and disease resistance

It is presumed that the glycoalkaloids of the potato can trace their evolutionary origin to pest resistance. Using artificial diets, feeding studies using high levels of steroidal glycoalkaloids (SGAs) demonstrated feeding deterrent effects on the potato aphids (Güntner *et al.* 1997). Lines of potato that are resistant to leaf hoppers have higher SGA levels than lines that are sensitive (Sanford *et al.* 1992). SGAs are feeding deterrents to snails (Smith *et al.* 2001) and exhibit the ability to inhibit trypanosome growth (Chataing *et al.* 1998).

However, SGAs have little effect on the CPB (Kowalski *et al.* 1999). This may in part be due to the reduced sensitivity of the CPB acetylcholinesterase to SGAs inhibition (Wierenga and Hollingworth 1992). Leptines rather than total glycoalkaloid (TGA) levels appear to be responsible for CPB resistance (Ronning *et al.* 1999; Rangarajan *et al.* 2000; Lorenzen *et al.* 2001). A combination of breeding for reduced SGAs in cultivated potatoes and a long history of association of CPB and potatoes may have led to a loss of sensitivity of the CPB to these compounds. Tuber glycoalkaloid content does not appear to be involved in late blight resistance (Sarquís *et al.* 2000). Investigations of the relationship of SGAs to disease indicate little affect of SGA content on susceptibility of potatoes to the late blight fungus, *Phytophthora infestans*, despite possessing antifungal activity *in vitro* (Fewell and Roddick 1993).

Glycoalkaloids and human health

The potential for adverse human health effects of potato SGAs has been clearly documented (Mensinga *et al.* 2005). The physiological affects of SGAs include membrane disruption (Roddick *et al.* 2001), cholinesterase inhibition (McGehee *et al.* 2000) and liposome disruption (Roddick and Rijenberg 1987). Glycoalkaloids have been shown to be teratogenic (Crawford and Myhr 1995; Gaffield and Keeler 1996) and to have potential anticancer activities (Lavie *et al.* 2001; Lee *et al.* 2004). However, the typical effective concentrations of SGAs in many of the physiological and biochemical studies are higher than the SGA levels found in normal potatoes. The potential pharmaceutical activity of SGAs as anticancer compounds and extensive toxicological tests of SGAs are reviewed in Friedman (2006).

THE PRESENT

Current guidelines for potato glycoalkaloids

The levels of SGAs or the TGA content for existing cultivars of potatoes is currently set at 20 mg/100 g fresh weight of the potato. This level is taken as a threshold above which the TGA content should not exceed (Valkonen *et al.* 1996). Potato lines that conform to this standard are achieved by carefully monitoring TGA levels by spectrophotometric or chromatographic methods during the breeding process and removing selections that exceed the desired limits.

Although standard varieties are released to producers with acceptable levels of SGAs, occasionally environmental, physical and storage conditions can cause unexpected increases in SGAs levels that result in potential food safety affects (Friedman 2006). Environmental factors known to cause an increase in alkaloid content include exposure of tubers to light (Dale *et al.* 1993; Percival 1999), temperature during growth (Dimenstein *et al.* 1997), storage (Fitzpatrick *et al.* 1977; Griffiths *et al.* 1998), length of storage

in the dark (Love *et al.* 1994), and mechanical injury either during harvest or storage (Sinden 1972; Olsson 1986; Mondy *et al.* 1987). Other environmental conditions such as water-logging and drought can also have cultivar specific impacts on SGA accumulation (Papathanasiou *et al.* 1999).

The increase in glycoalkaloids, in response to abiotic and biotic stress, is a combination of the genotype of each variety (Sarquís *et al.* 2000) and unknown factors that contribute to rapid and unwanted accumulation. These varietal differences can in part be attributed to levels of gene expression in the isoprenoid and SGA biosynthetic pathways (Krits *et al.* 2007). Wound-induced accumulation of SGAs in tubers is correlated with dramatic increases in the steady state levels of the glycosyltransferase mRNA transcripts for the enzymes involved in the conversion of solanidine to α-chaconine and α-solanine (McCue *et al.* 2007a).

Manipulation of glycoalkaloids

Since its introduction from South America to the world, farmers have been manipulating potato glycoalkaloids along with the many other traits resulting in the potato varieties we grow today. The bitter potato SGAs have potential for combating pests and diseases. A thorough and more complete understanding of the diversity of SGAs and their biological activities is necessary to determine the optimal SGA content. Understanding the biosynthesis and underlying genetics will provide the tools for traditional and molecular breeding strategies to exploit the full potential of these compounds.

Standard breeding

The crossing of cultivated varieties of potatoes with wild potato species can have the unwanted affect of increasing the TGA level as well as affecting which alkaloid species are produced. In crosses between the cultivated potato *S. tuberosum* and the wild species *S. commersonii*, it was found that the TGA content was the trait that showed the greatest variation among the progeny (Esposito *et al.* 2002).

Genetic engineering

Effects of genetic engineering on the levels of TGAs in potatoes have been reported both directly from manipulations of the SGA biosynthetic pathway and indirectly from the alteration of biochemically related and unrelated pathways. TGA levels have been included in metabolomic analyses to establish substantial equivalence for genetically modified crops to assess indirect consequences of genetic manipulation. Potatoes transformed with a gene encoding an endochitinase gene from a mycoparasitic fungus were shown to have TGA levels unchanged from the control transgenic plants (Esposito *et al.* 2002). Potatoes transformed with the *Cry*IIIa gene to confer resistance to the CPB had minimal changes in TGA content (Perlak *et al.* 1993). Manipulation of flavonoid biosynthesis to increase antioxidant capacity of potatoes resulted in a 2-fold variation in TGA content compared to non-transformed controls (Stobiecki *et al.* 2003). Manipulation of the cholesterol biosynthetic pathway by over expression of the soybean derived sterol methyl transferase I gene product in potato reduced the levels of glycoalkaloids (Arnqvist *et al.* 2003). An early report (McCue *et al.* 2003) of reduction of TGAs due to expression of an antisense construct for the *Sgt1* of the SGA biosynthetic pathway was later revealed to be attributable to somaclonal variation (McCue *et al.* 2005).

Only recently have there been reports on the effect of

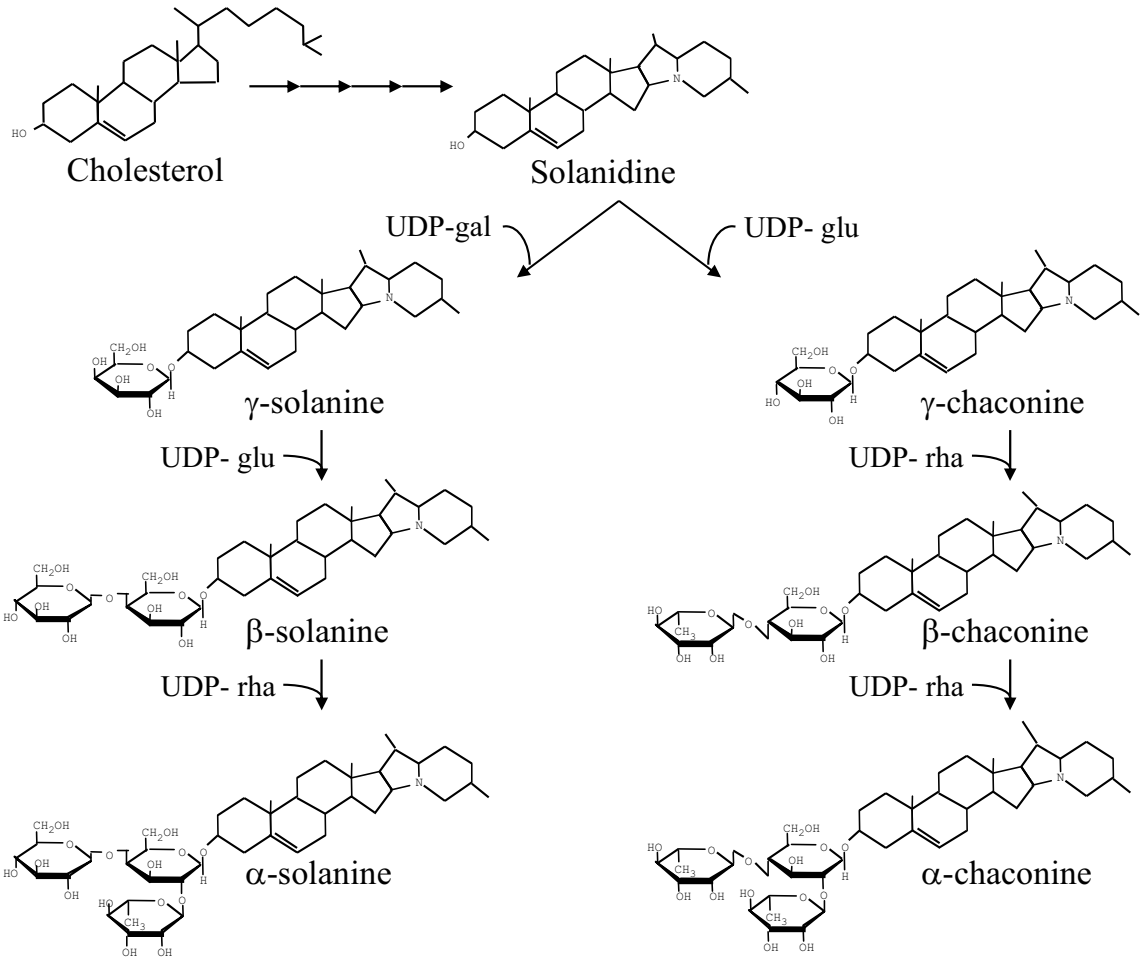

Fig. 4 Biosynthetic pathway of the most abundant SGAs of the cultivated potato α-solanine and α-chaconine from the spirosolane aglycone solanidine.

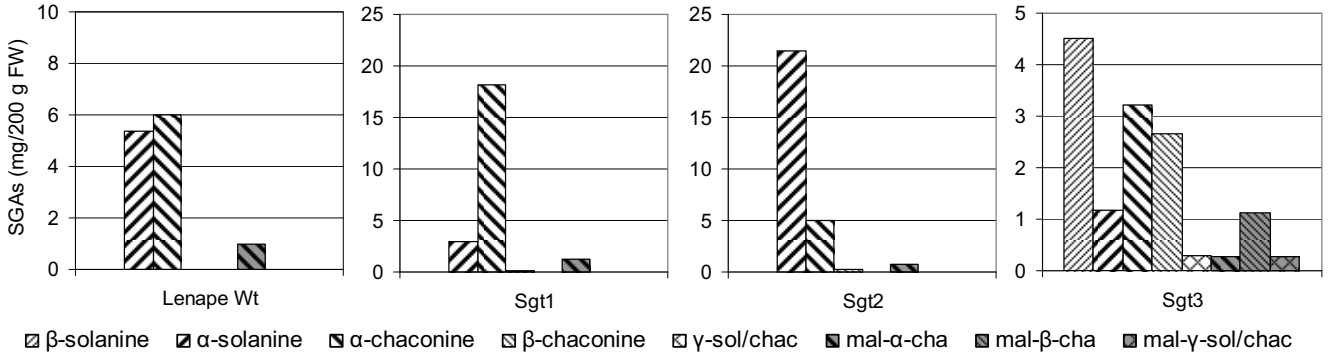

Fig. 5. Glycoalkaloid accumulation in antisense *Sgt* potato lines. Levels of triglycosylated SGAs, their intermediates, and malonyl derivatives in freeze-dried tuber slices from glasshouse grown plants. Alkaloids were extracted and assayed by LC-MS on a Thermo Finnigan LCQ-DECA. Ion trap, MS and data-dependent MS/MS on base peak ion as described (McCue *et al.* 2007b). Values for the 6 anlaytes for which pure standards are not available were estimated using the average of the relative response ratios for authentic α-solanine and α-chaconine to the reserpine internal standard. Values are for a single tuber from an effective antisense transgenic line for the genes indicated and are representative of results obtained for additional independent transgenic lines.

directly manipulating the enzymes involved in the direct biosynthesis of the potato SGAs. Manipulation of the SGA biosynthetic pathway have been performed in B5141-6 the cultivar formerly known as Lenape (Akeley *et al.* 1968). Lenape is a round white potato excellent for chipping. However, one of the parents of this cultivar is *Solanum chacoense*, and *S. chacoense* accumulates excessive levels of the steroidal glycoalkaloids solanine and chaconine (Sinden *et al.* 1984). This makes Lenape an excellent test system for the suppression of SGA levels via genetic manipulation. The biosynthesis of α-solanine and α-chaconine and the sequential formation of the β-chacotriose and β-solatriose glycosyl sidechains are shown in **Fig. 4**. The sequential glycosylation of solanidine is carried out by a family of related steroidal alkaloid glycosyl transferase (*Sgt*) genes. Manipulation of enzymes responsible for the glycosylation of solanidine and glycosylated intermediates in the biosynthesis of α-solanine and α-chaconine had dramatic effects on the ratios of the two end products, but had limited effect on lowering TGAs. In transgenic Lenape tubers expressing an antisense *Sgt1* gene, the solanidine galactosyltransferase, a reduction in the accumulation of α-solanine was observed that was compensated for by an increase in the accumulation of α-chaconine. In transgenic Désirée tubers transformed with the antisense *Sgt1* gene the compensation was less significant resulting in slightly lower TGA levels (McCue *et al.* 2005). Antisense inhibition of *Sgt2*, the solanidine glucosyltransferase, in transgenic tubers of both Lenape and Désirée resulted in significant reductions in α-solanine accumulation. Again this reduction was compensated for by increased levels of α-chaconine (McCue *et al.* 2006) and the TGA level remained high. Blockage of the 2-O-rhamnoyslation of the di-glycosides by antisense inhibition of *Sgt3*, the β-solanine/β-chaconine rhamnosyltransferase, in transgenic tubers resulted in the accumulation of the di-glycoside intermediates (McCue *et al.* 2007b). **Fig. 5** shows the relative accumulation of α-solanine, α-chaconine and biosynthetic intermediates in the tubers of representative transgenic Lenape plants for each of the three antisense constructs as compared to the wild type control tuber.

There are many factors that affect the TGA levels in potatoes, beginning with the genetics of the variety, its ancestors and the gene dosage or expression. Not enough is known about how many alleles are active in any particular cultivar. There is also no information on whether there are particular alleles associated with high or low TGA content. Additional studies are needed on SGA biosynthetic gene expression in both tubers and other parts of the plant and on other genes that may be involved in the control of SGA accumulation in response to biotic and abiotic stimuli.

THE FUTURE

Modification of SGAs in potato

Breeders continue to manipulate potato glycoalkaloids along with the many other metabolites that have potential for combating pests and diseases. With a basic understanding of the diversity of SGAs and their biological activities it is time to further explore their biosynthetic pathways. The development of new tools to further elucidate the biochemical pathways and underlying genetics will provide the means for more efficient traditional and molecular breeding options to optimize and exploit the diversity of these compounds.

Transcriptome

The following is a summary of the information available from the Harvard University Computational Biology and Functional Genomics Laboratory on Gene Index Projects. The gene transcript information, or transcriptome, for potato includes 231,299 expressed sequence tags (ESTs) and 2819 expressed transcripts (ETs) for a total of 61,372 unique sequences (including tentative consensus sequences and singletons). This compares to a total of 619,908 ESTs and 79,223 ETs for a total of 81,826 unique sequences for the genetically minimal model plant *Arabidopsis*; and 7,223,257 ESTs and 234,976 ETs resulting in 1,083,935 unique sequences in the human database.

The low coverage of transcription data for potato prevents comprehensive analysis of gene expression. Analysis of expressed sequences for the *Sgt* gene family in The Institute for Genomic Research (TIGR) database reveals representation of these genes from only three cultivars ('Bintje', 'Kennebec' and 'Shepody') in addition to the cultivar from which they were originally described ('Lemhi Russet') in the Tentative Assembly (TA) sequences. The TA sequences of each family member contain multiple ESTs and represent each of the three described genes (*Sgt1*, *Sgt2* and *Sgt3*), including the allelic variation at *Sgt2* (including both *Sgt2.1* and *Sgt2.2*). The TA for *Sgt3* contains the most individual ESTs. Conserved single nucleotide polymorphisms (SNPs) in the ESTs suggest at least two active alleles of *Sgt3* in each of the three cultivars. The representation of the *Sgt* family members, the associated TAs and cultivar representation is shown in **Table 2**. For each *Sgt* gene sequence a BLAST search of the TIGR database identified a unique TA as the primary match as well as the other family member TAs with lower scores (and higher smallest sum probabilities). Secondary matches included additional unique ESTs, and for the case of *Sgt2*, two additional TAs of 2 and 3 ESTs. These additional TAs and ESTs may represent additional alleles or read errors in the sequencing runs. Re-

Table 2 Cultivar representation and EST numbers in the Tentative Assemblies of the TIGR database for the *Sgt* gene family members.

Glycosyltransferase	Tentative Assembly	Cultivated Variety[#]	Number of ESTs
Sgt1	TA29189-4113	Bintje	4+1*
solanidine galactosyltransferase		Kennebec	9
		Shepody	3
Sgt2.1	TA25432-4113	Bintje	2+2*
solanidine glucosyltransferase		Kennebec	7
		Shepody	2
Sgt2.2	TA25434-4113	Bintje	1
solanidine glucosyltransferase		Kennebec	3
		Shepody	3
Sgt3	TA26281-4113	Bintje	5+4*
β-solanine/chaconine rhamnosyltransferase		Kennebec	14
		Shepody	6

[#] Excludes full length cDNAs described from cv. 'Lemhi Russet'.
* 'Bintje' or 'Kennebec'

gardless of the source of singleton ESTs and under-populated TAs, additional EST sequencing for the cultivars represented in the database as well as additional cultivars would greatly increase the value of the transcriptome database.

Genome

Genome sequencing efforts are currently underway for potato and several related species. The database of potato genomic sequence information currently accounts for approximately 10% of the genome. Genomic sequence for potato will be compared to its close relative the tomato that currently has 20% of its genome sequenced. By way of comparison there are complete genome sequences for a growing number of eukaryotic organisms including *Arabidopsis* and humans. New technologies and platforms for generating sequence information are becoming available. These will allow the genes and expression profiles of cultivars to be compared and assist in the identification of the genetic basis underlying key traits.

Metabolome

New advances in analytical techniques allow for the rapid analysis of a large array of plant constituents. This type of analysis is known as metabolomics. These advances allow the rapid and precise identification of plants with SGA profiles altered as desired, while allowing facile screening for those plants that possess undesirable modifications. The future for potato glycoalkaloids will rely on the rapid metabolomic screening of new and improved potato cultivars with refined glycoalkaloid profiles.

CONCLUSION

The modifications of SGA content either by traditional breeding and/or molecular breeding hold great promise for potato improvement. Regulation of SGA biosynthesis to prevent unwanted accumulation in response to environmental and mechanical stimuli will help to ensure food safety. Altered SGA profiles produced by introducing new SGAs from other *Solanum* species may eventually play a role in human nutrition. Manipulation of SGA levels in specific parts of the potato plant should also be used to increase pest resistance. Engineering the biosynthesis of specific glycoalkaloids in the foliage to optimize pest resistance while regulating their accumulation in the edible tubers to ensure consumer food safety should eventually be combined to produce new and improved potatoes.

ACKNOWLEDGEMENT

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