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Synthetic biology strategies for synthesizing polyhydroxyalkanoates from unrelated carbon sources

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HIGHLIGHTS

- A list of 64 new and unique PHA monomers identified since 1995 was compiled.
- An argument was made for accessing novel monomers by avoiding related feedstocks.
- Review of known and potential pathways for making monomers from unrelated sources.
- Synthetic biology and its impact on metabolic engineering of PHA was discussed.

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ABSTRACT

Discovered in the 1920s, polyhydroxyalkanoates (PHA) are a naturally occurring class of biopolyesters that have long been touted as a renewable, biodegradable plastic alternative. Demand for sustainable products and over a half century of research have led to moderate commercial success of PHA. Yet, these materials are not pervasive. Therefore, an important question to address is, "what is the barrier that prevents widespread application of these materials?" PHA can be made from an incredibly diverse class of monomers that incorporate both simple and complex organic acids. Herein, we provide an updated list of unique PHA monomers that are substrates for a PHA polymerase. Unfortunately, most unique monomers are incorporated only after feeding a structurally related feedstock to a PHA accumulating bacterium. Therefore, we put forward an argument that research must now turn to developing feedstock-independent, synthetic pathways to produce an increased diversity of PHAs capable of competing with petroleum-derived plastics.

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1. Introduction

Polyhydroxyalkanoates (PHA) are a class of renewable, biodegradable polyesters: renewable because their synthesis involves biological conversion of sugars or other biomass derived feedstocks to a polymer that accumulates inside a cell; biodegradable because native producers can depolymerize and metabolize PHA—even if the material is encountered outside the cell (Tokiwa and Calabia, 2004). PHA exist as a way for the cell to store carbon and energy when the availability of non-carbon nutrients limits growth. Since the discovery of PHA in the 1920s, it has been postulated that more than 150 unique monomers have been incorporated into a PHA polymer. Varying the monomer composition impacts the material properties of the polyester and provides handles for further functionalization in specialty applications. Therefore, one focus of PHA research has been to identify substrates for PHA polymerase, usually through feeding studies, and subsequent characterization of the resulting material. The broad specificity of PHA polymerases is both impressive in its ability to accept more than 150 hydroxy acids, and appealing from an industrial perspective. Specifically, the opportunity to capitalize on a versatile platform for generating a series of renewable, biodegradable plastics that could supplement and eventually replace petroleum derived counterparts has been the perpetual promise of PHA since the first commercial enterprises in the 1980s. In the intervening time, a number of ventures have

Abbreviations: PHA, polyhydroxyalkanoate; PHB, polyhydroxybutyrate; 3HB, 3-hydroxybutyrate; scl, short-chain-length; 3HV, 3-hydroxyvalerate; 4HV, 4-hydroxyvalerate; mcl, medium-chain-length; BTE, California bay laurel thioesterase; PKS, polyketide synthase; FAS, fatty acid synthase; ACP, acyl-carrier protein; CoA, coenzyme A

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emerged around the globe [recently reviewed here: (Chen, 2009)] and yet, PHA are not a pervasive material in daily life.

The most promising, near-term commercial applications of PHA are in the medical, biomaterials and pharmaceutical industries where premium prices are easily commanded or in other niche markets where there is a demand for biodegradability. For example, Metabolix, a US-based bioplastics company, has had commercial success in incorporating Mirel™ (PHA) into biodegradable gardening containers and premium, eco-friendly beach toys. On the other hand, the realization of PHA as a replacement for non-biodegradable, petroleum derived plastics still seems to be a ways off due to the premium (~$0.75/lb) over comparable, renewably sourced polymers and even larger premiums compared to traditional plastics (Table 1). Metabolix's Mirel™ is marketed at $2.25–$2.75/lb, whereas polypropylene, a plastic with comparable material properties, is available at $0.75/lb. Oil price volatility and increasing demand for sustainable alternatives have continued to motivate researchers to improve PHA production processes despite past obstacles to commercialization. While many non-PHA renewable plastics are being developed (Harracksingh, 2012; Sudesh and Iwata, 2008), PHA biochemistry offers flexibility to pursue a wide range of material properties from the same platform.

This review will provide a brief summary of the range of monomers that have been incorporated into PHA granules and suggest future research directions that leverage the promising field of synthetic biology to increase the viability of PHA as a petrochemical plastic alternative. Our strategy for enhancing PHA production via synthetic biology is based upon the following logic:

(1) More than 150 monomers can be incorporated into PHA, providing routes to a wide range of material properties that would be useful in high-value applications.

Table 1
Prices for a selection of common polymers derived from both traditional (petrochemical) and alternative (biological) routes. Pricing data was acquired from ICIS Chemical Business and are listed as of the date of the publication.

Material	Price ($/lb)	Date of publication
PVC	0.45	8/27/2012
PET	0.59–0.85	2/14/2011
PP	0.74	8/28/2012
LDPE	0.77	8/27/2012
PLA	0.85–1.25	8/27/2012
PS	1.00	2/14/2011
Starch-based biodegradable plastics	1.50–2.20	2/14/2011
BASF Ecoflex	2.00	2/14/2011
PLA/PBS	2.00–2.50	2/27/2012
PHA (Mirel)	2.25–2.75	2/14/2011

(2) The cost of related feedstocks that are fed to PHA accumulating organisms to make non-traditional PHA precludes the economic viability of these materials.
(3) Synthetic biology can and has been used to assemble novel metabolic pathways inside cells for producing high-value molecules relevant to chemical and polymer synthesis.
(4) If metabolic pathways that link unrelated feedstocks (*e.g.*, glucose) to high-value PHA monomers are assembled, then PHA production costs could be greatly reduced.

For these reasons, we posit that research should turn towards developing feedstock-independent, synthetic pathways for producing an increased diversity of PHA monomers which when polymerized produce materials capable of competing with traditional, petroleum-derived plastics.

2. Diversity of PHA monomers

In 1995, the review "Diversity of Bacterial Polyhydroxyalkanoic Acids," detailed the known monomer constituents of this class of polyester materials (Steinbüchel and Valentin, 1995). At the time of publication, a striking 91 unique monomers had been characterized as substrates for a PHA polymerase. Since then, it has been postulated that more than 150 unique PHA monomers have been described in the literature (Steinbüchel and Lutke-Eversloh, 2003). Confirming this claim, we have identified an additional 64 monomers that have been described in the PHA literature bringing the current total to 155 unique monomers (Figs. 1 and 2 and Supplementary materials). Of the 64 unique monomers described since the 1995 review, many are closely related to prior classes of known PHA monomers, but a handful of new functional groups were successfully incorporated. These include dimethyl substituted carbons, terminal methyl- and fluorophenoxy, thiophenoxy, oxo (keto) and acetylthioester groups (Fig. 3). Additionally, an expanded number of 4-hydroxy and methyl substituted PHA monomers have been added to the list of unique monomers.

Of the 155 unique monomers that have been incorporated into PHA, a relatively small subset has been produced from an unrelated feedstock (carbon source). Here, a related feedstock is defined as any starting material that is structurally related to the resulting monomer and especially the resulting side-chain/pendant group. In many cases feeding of exotic feedstocks will be the only feasible route to produce the desired PHA monomer. However, the costs associated with synthesizing, purifying, and feeding complex precursors to a PHA producer will significantly limit economic viability—especially in situations where traditional chemistry can be used to make similar

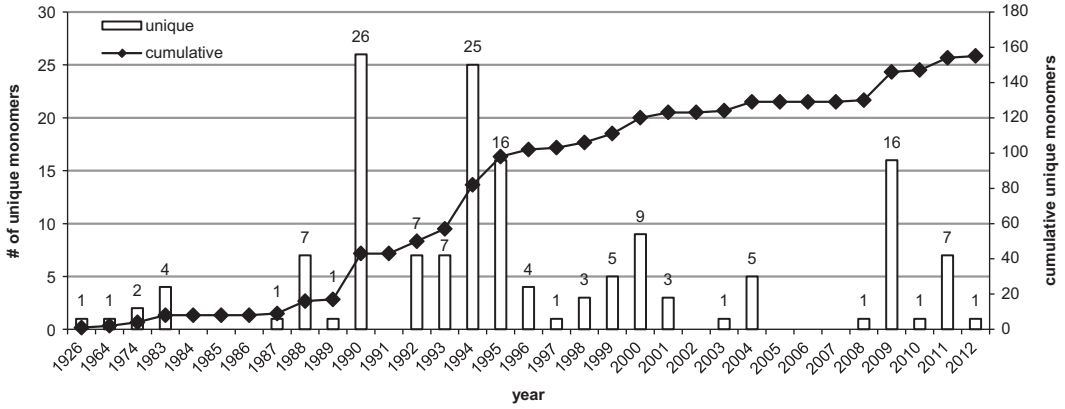

Fig. 1. Unique PHA monomers discovered since 1926. Bars indicate number of unique PHA monomers discovered in a given year while points indicate the cumulative total number of unique monomers. Note that the horizontal axis is non-linear for 1926–1983 and linear from 1983-2012. See Fig. 2 for a detailed list of monomers.

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