consequences of matched versus mismatched AA composition remain to be fully elucidated, Piper and colleagues have provided us with an invaluable tool to predict these imbalances.

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Should I Stay or Should I Go: A Clash of α-Cell Identity

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Understanding mechanisms for maintaining pancreatic islet cell fate and function is important for addressing the urgent challenge of restoring islet β- and α-cell function in T1DM. In this issue of *Cell Metabolism*, Chakravarthy et al. (2017) identify a genetic mechanism by which mouse β-cells are spontaneously regenerated from adult α-cells.

Type 1 diabetes is characterized by pancreatic β-cell dysfunction and inflammation, leading to immune cell destruction and loss of β-cell mass. Conversion of adult cells into functional insulin-producing β-cells is a promising alternative for regenerative treatments in diabetes. Adult glucagon-producing α-cells can reprogram and convert into insulin-secreting β-cells (reviewed by Chera and Herrera, 2016; Cigliola et al., 2016); however, the genetic or epigenetic mechanisms, including the heterogeneity and extent of this conversion, has not been elucidated yet. In this issue of *Cell Metabolism*, Chakravarthy et al. (2017) show that β-cells are spontaneously regenerated from adult α-cells following simultaneous inactivation of mouse *Aristaless-related homeobox* (*Arx*) and DNA methyltransferase 1 (*Dnmt1*), key regulators of α-cell fate (Collombat et al., 2007; Dhawan et al., 2011).

To determine whether Arx loss in vivo directly alters α-cell fate, Chakravarthy and colleagues (Chakravarthy et al., 2017) generated mice for simultaneous deletion of Arx and lineage tracing in α-cells. Arx knockout α-cells from these mice demonstrated failure to maintain their differentiated state, leading to a time-dependent adoption of alternate islet cell fates. Lineage-traced α-cells lose their adult α-cell markers as glucagon or MafB and express β-cell markers as insulin, Pdx1, or Nkx6.1, or other islet hormones as somatostatin or ghrelin and become poly-hormonal cells (Figure 1). It is important to note that none of the converted α-cells express MafA, a critical β-cell marker, and that conversion to these poly-hormonal cells occurs without reactivation of neurogenin 3, a transcription factor expressed in fetal immature pancreatic endocrine progenitor cells. Notably, regulation of islet epigenetics by DNA methylation also appears to be an important regulatory mechanism during α- and β-cell maturation. Previous studies showed that DNA methyltransferase 1 (DNMT1) expression in adult α-cells is required for maintenance of α-cell fate (Dhawan et al., 2011); however, direct testing of Dnmt1 requirement in adult α-cells in vivo was not studied. Chakravarthy and colleagues (Chakravarthy et al., 2017) found that conditional deletion of Dnmt1 in adult α-cells was insufficient to induce changes in α-cell fate (Figure 1), with knockout cells not showing any detectable insulin, Pdx1, or Nkx6.1, even a long time after Dnmt1 deletion.

Strikingly, however, by using an inducible mouse of simultaneous deletion of both Arx and Dnmt1 in α-cells, Chakravarthy and colleagues (Chakravarthy et al., 2017) demonstrated profound changes in α-cell fate. Four weeks after Arx/Dnmt1 inactivation, linage tracing analysis showed that 50% of α-cells fail to maintain

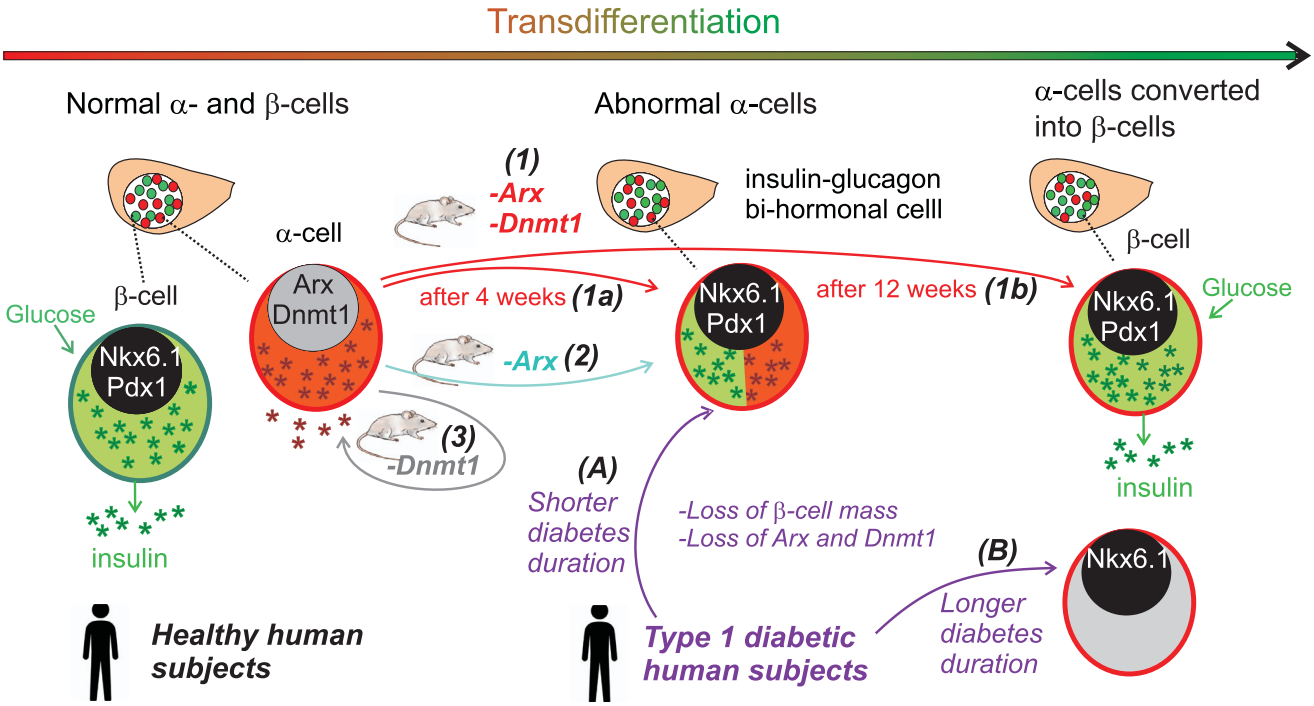

Figure 1. Changes Occurring in α-Cells following Conditional Deletion of Arx and Dnmt1 in Mice, or in Type-1 Diabetic Human Subjects
Simultaneous deletion of Arx and Dnmt1 in α-cells allows appearance of bi-hormonal insulin and glucagon abnormal cells with expression of Pdx1 and Nkx6.1 by 4 weeks (1a), with full conversion to functional insulin-secreting β-cells by 12 weeks (1b). Deletion of Arx alone induced conversion of α-cells into bi-hormonal insulin and glucagon-positive cells (2). Deletion of Dnmt1 alone is insufficient to induce changes in α-cell identity (3). Pancreata from younger type 1 diabetic human subjects with shorter diabetes duration show a marked decrease in insulin-containing β-cells accompanied by an increase in bi-hormonal insulin and glucagon-positive cells, cells that lack Arx or Dnmt1 and expressed Pdx1 and Nkx6.1 (A). Pancreata from older patients with longer diabetes duration show lack of both Dnmt1 and Arx with co-expression of NKX6.1, undetectable Pdx1, or bi-hormonal positive cells (B).

cell identity with most α-cells lacking either glucagon or MafB, or co-expressing insulin, Pdx1, or Nkx6.1. By 12 weeks, most Arx/Dnmt1 knockout α-cells show a clear switch to expression of only β-cell markers as insulin, Pdx1, and Nkx6.1, with a subset of cells also expressing MafA and *Slc2a2* (encoding for glucose transporter 2) (Figure 1), all key factors present in native β-cells. In addition, single-cell RNA-seq in converted α-cells revealed a rapid and extensive expression of genes that regulate β-cell fate and function. Converted α-cells also acquired the Na^+ current inactivation, glucose-dependent capacitance/exocytotic response to membrane depolarization, and glucose-dependent increase in intracellular [Ca^{2+}] and insulin secretion, all features that make them morphologically and functionally indistinguishable of native β-cells. It is important to note that α- to β-cell conversion did not occur through reactivation of neurogenin 3 in Arx/Dnmt1 null mice (Figure 1). Together, these results demonstrate a complete, and direct, conversion of α-cells into fully functional β-cells, with genome-scale evidence for the range, trajectory, and extent of these changes following *Arx* and *Dnmt1* deletion.

The results shown by Chakravarthy and colleagues using Arx knockout mice differ from those previously reported by Courtney and colleagues (Courtney et al., 2013). While Chakravarthy and colleagues demonstrated a time-dependent cell fate change to a population of cells mainly comprised by poly-hormonal cells in Arx knockout mice, Courtney and colleagues showed islet hyperplasia, a large increase in insulin-positive cells through reactivation of neurogenin 3 without the presence of any poly-hormonal cells. This discrepancy could be attributed to the different mouse models used, conditional versus constitutive Arx deletion, but also to the fact that it was impossible to distinguish between ductal and α-cell progeny in the latter model. Mouse models of near-complete β-cell ablation also demonstrated reprogramming of α-cells into β-cells, with appearance of bi-hormonal insulin/glucagon-positive cells (reviewed by Chera and Herrera, 2016); however, the underlying mechanisms of these changes were not clearly defined. It is important to note that even though converted α-cells from Arx/Dnmt1 knockout mice show very similar morphological and physiological characteristics as native β-cells, the heterogeneity of gene expression patterns, which is also reflected in differences in hormone secretion, suggests that other critical factors might also be important for a more complete and homogeneous adult α- to β-cell conversion. The mechanisms by which deletion of Dnmt1 contributes to a rapid loss of α-cell identity, but only in the absence of Arx, remains to be elucidated. However, epigenetic DNA methylation mechanisms are also sensitive to the cellular metabolic status, and one can speculate that metabolic changes in diabetes may lead to dysregulation of DNA methylation, and DNA damage, along with altered cell identity.

Impaired glucagon response to hypoglycemia in type 1 diabetic individuals

suggests altered α-cell fate and function (Cryer, 2012). Similar to previous reports (Piran et al., 2014; Yoneda et al., 2013), Chakravarthy and colleagues (Chakravarthy et al., 2017) observed profound loss of insulin-positive cells in pancreata from type 1 diabetes organ donors. Moreover, they also demonstrate that islets from younger type 1 diabetic individuals with shorter disease duration (4–5 years) show the presence of bi-hormonal glucagon/insulin-positive cells accompanied by loss or reduction of ARX or DNMT1, and expression of insulin, Pdx1, or Nkx6.1. Notably, islets from older type 1 diabetic subjects with longer diabetes duration demonstrated loss of both ARX and DNMT1 with co-expression of NKX6.1, but undetectable Pdx1 or presence of bi-hormonal cells (Figure 1). These results strongly suggest that ARX and DNMT1 are also required to maintain α-cell identity in humans and points to the potential molecular bases for the observed α-cell dysfunction in diabetic subjects. The prospect of identifying "drugable" targets to bypass dedifferentiation and allow direct α- to β-cell conversion by genetic reprogramming holds great appeal for future treatment for diabetes. Identification of new molecules and pathways that can be targeted for developing drugs/compounds to enhance the generation of functional β-cells is critical for transforming α-cells into β-cells, and the results obtained here highlights the importance of these studies.

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Dietary Fat Inflames CD4$^+$ T Cell Memory in Obesity

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T cells promote inflammation in obesity, but how metabolic stress associated with obesity alters T cell responses remains unclear. In this issue of *Cell Metabolism*, Mauro et al. (2017) demonstrate that saturated fatty acids directly increase effector-memory T cell formation by amplifying T cell antigen-receptor-induced PI3K/Akt signaling.

Obesity is a growing healthcare epidemic affecting over 30% of adults in the United States alone. The complex interplay of genetics and metabolic dysregulation underpins the onset and severity of obesity. Further, cellular and soluble mediators of the immune system drive chronic, low-grade inflammation in obesity. Consequently, disorders such as type 2 diabetes and cardiovascular disease can develop, while immune responses against infectious agents and cancers are diminished (Gerriets and MacIver, 2014). The front-line defenses for combating obesity are limiting dietary nutrient intake and increasing energy expenditure through exercise. How changes in energy or nutrient homeostasis contribute to the immune cell dysfunction that drives obesity-associated inflammation is unknown. In this issue of *Cell Metabolism*, Mauro and colleagues (2017) show that saturated fatty acids (SFAs) increase T cell antigen receptor (TCR) clustering and signaling through the PI3K/Akt axis and fuel fatty acid oxidation (FAO) in metabolically stressed environments. These processes drive the differentiation of CD4$^+$ effector-memory (T_{EM}) cells that traffic into non-lymphoid and inflamed tissues (Figure 1).

Among immune cells, T cells promote obesity-associated inflammation via their cytotoxic activities and by secreting cytokines (Gerriets and MacIver, 2014). T cells are activated when the TCR binds its cognate peptide-major histocompatibility complex (MHC) molecule, which is presented by dendritic cells (DCs). Co-stimulatory and cytokine receptor signals also direct T cell differentiation into effector T cell subsets and memory T (T_M) cells, which are divided into T_{EM} cells, central-memory T (T_{CM}) cells, and tissue-resident memory T (T_{RM}) cells (Mueller and Mackay, 2016). Upon migrating into adipose tissue, activated T cells cause adipocytes to release additional inflammatory mediators, further exacerbating inflammation. Activated T cells that migrate into other tissues also play deleterious roles in obesity-related diseases like