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REVIEW

New Frontiers: Umbilical Cord Mesenchymal Stem Cells Uncover Developmental Roots and Biological Underpinnings of Obesity Susceptibility

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Abstract

Purpose of Review To review evidence supporting human umbilical cord mesenchymal stem cells (UC-MSC) as an innovative model system advancing obesity precision medicine.

Recent Findings Obesity prevalence is increasing rapidly and exposures during fetal development can impact individual susceptibility to obesity. UC-MSCs exhibit heterogeneous phenotypes associated with maternal exposures and predictive of child cardiometabolic outcomes. This recent evidence supports UC-MSCs as a precision model serving three purposes: (1) as a mechanistic tool to interrogate biological underpinnings of obesity in human studies, (2) as a sensitive index of early life causes and determinants of obesity, and (3) as a marker and transducer of susceptibility, highlighting populations most at risk for future obesity.

Summary Data from UC-MSCs emphasize nutrient sensing and lipid partitioning as phenotypes most relevant to neonatal and early childhood adiposity and implicate a role for these cell-autonomous features of mesodermal tissues in the biological underpinnings of obesity.

Keywords Mesenchymal stem cells · Childhood obesity · Pregnancy · Adipose · Skeletal muscle

Introduction

This review is grounded in the developmental origins of disease hypothesis (DoHAD) which posits that exposures during sensitive periods of early-life development alter the structure and function of cells, tissues, and organs–with important implications for offspring health and disease. Adverse exposures during organogenesis can lead to permanent structural changes in organs or tissues contributing to changes in tissue function, or may also alter cell-autonomous pathways contributing to disease risk throughout life. Human umbilical cord mesenchymal stem cells (UC-MSC) can elucidate the *latter* pathway as a representative cell population integral to the development of offspring mesodermal tissues, importantly skeletal muscle and adipose. Work from our group and others demonstrates UC-MSCs exhibit heterogeneous phenotypes associated with maternal exposures and predictive of child adiposity and cardiometabolic outcomes.

Here, we present evidence supporting UC-MSC as an innovative model advancing obesity precision medicine. Our conceptual model, depicted in Fig. 1, conveys the utility of UC-MSC serving three purposes: (1) a mechanistic tool to interrogate biological underpinnings of obesity in human studies, (2) a sensitive index of early life causes and determinants of obesity, and (3) a marker of susceptibility via cell-intrinsic changes to mesodermal tissues, highlighting populations most at risk for obesity. We begin with a brief overview of the fetal origins of obesity, then describe the origin of UC-MSCs and their practical and theoretical applications in human obesity research. We will describe the convergence of the UC-MSC model with pre-clinical and adult human obesity data to clarify how UC-MSCs inform

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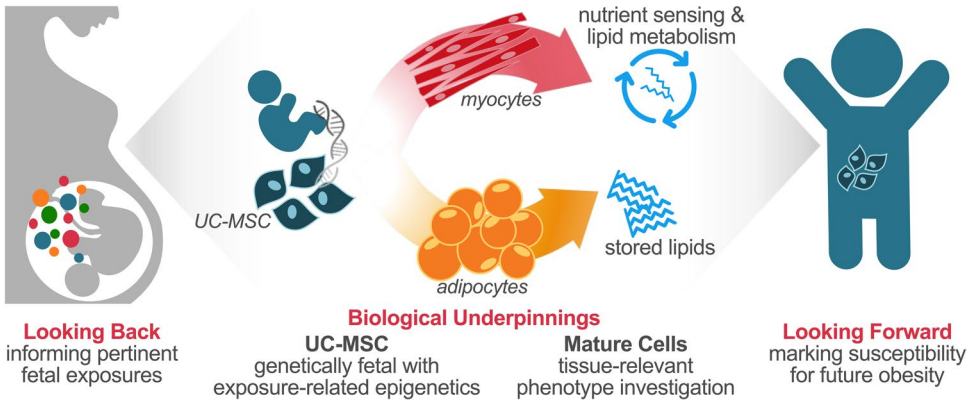

Fig. 1 Schematic depicting the utility of the UC-MSC model for interrogating the biological underpinings of obesity, as a sensitive index looking back to fetal exposures most pertinent and looking forward to identify those most susceptible to obesity

pathways and etiology of obesity. Finally, we conclude by reviewing the body of human UC-MSC literature in the context of later life obesity risk and impactful randomized clinical trials.

Developmental Roots of Obesity

Obesity Prevalence and the Developmental Origins of Disease

Obesity prevalence has substantially increased over the last 60 years, with obesity rates tripling (13% to 43%) and Class III obesity increasing tenfold (1% to 10%); leading to the classification of nearly 70% of all adults as overweight or obese [1]. Likewise, childhood obesity has nearly doubled in the U.S. in the last 20 years [2] and children with obesity are at greater risk for maintaining obesity into adulthood [3, 4], contributing to insulin resistance, chronic low-grade inflammation, and metabolic dysfunction over the lifecourse [5–7]. Over the last 60 years, the United States and other industrialized countries have experienced pervasive shifts towards what is known as an "obesogenic" environment, but the impact of adverse environments are not equal across the lifespan. In one of the earliest reports of the early life influences on chronic adult disease nearly 40 years ago, David Barker and Clive Osmond noted that infant mortality rates and birth weights were associated with deaths from ischemic heart disease decades later [8]. Since then, epidemiological and animal evidence supports that adverse exposures during pregnancy provide important and independent contributions to risk for many common, complex diseases across the lifespan, including obesity.

Developmental Exposures that Predispose Toward Obesity

Box 1. Terminology for the Impact of Early Life Exposures

The term 'developmental programming' is commonly used as a catchall phrase to describe adaptations to environmental cues during fetal or early life development.

However, the term 'programming' implies determinism that is not always borne out. Terms like "susceptibility" or "predisposition" more accurately reflect the large degree of heterogeneity in offspring outcomes following fetal exposures. In this review, we will use the term 'developmental susceptibility'

Exposures during early life, particularly during the critical window of fetal development, have a significant impact upon one's individual *susceptibility* to the adverse effects of our pervasive obesogenic environment across the lifespan (reviewed here [9]). The vast majority of human research has focused on weight-based assessments of maternal adiposity (e.g., pre-pregnancy BMI/obesity status or gestational weight gain) or clinical diagnoses (e.g., gestational diabetes mellitus [GDM]) [10, 11] and these factors will, therefore, serve as the foundation for this review. A recent meta-analysis synthesizing data from nearly 90,000 children reported exposure to obesity in utero increased odds of obesity 264% through age 14 [10]. Most striking, an individual participant data meta-analysis of over 160,000 children shows that over half of those exposed to obesity in utero (53%) developed overweight or obesity by 18 years (BMI > 85th percentile) [11]. While this cycle of obesity undoubtedly includes the influence of shared genetic and post-natal environment [12], evidence for the independent impact of prenatal environment comes from animal models [13], epidemiology [14], and human studies among sibling pairs born before and after a significant change in the intrauterine environment [15, 16].

Specific, pertinent exposures implicated in the developmental susceptibility for obesity can be quite varied, and changes to maternal nutritional or physical activity status, chemical exposures in the form of pollutants, drugs or alcohol, or alterations in circulating hormone levels (linked to nutritional status or psychological or biological stress) are also implicated [17]. In animals and humans,

many obesity-associated traits in maternal circulation are promotive of offspring adiposity and obesity, including elevated maternal insulin, oxidative stress, inflammation, or lipid availability (free fatty acids [FFA], triglycerides) [18–23]. Furthermore, there's evidence that these factors associate with offspring metabolic health independent of maternal obesity status [13, 23]. Yet, only factors that cross or are metabolized through the placenta, or that otherwise impact placental health or function, can biologically impact the fetus. Notably, maternal body-size or weight itself cannot affect the fetus. Considering the substantial heterogeneity of the circulating maternal milieu in the context of obesity, deeper understanding of the biological underpinnings of developmental susceptibility for obesity will require moving beyond weight-based measures of exposure, rather quantifying those that translate to biological exposures in the fetal compartment. This work demonstrates the independent impact of fetal exposures on offspring obesity risk, yet we do not understand how this process occurs in humans or what even the *most pertinent* exposures are, which will be critical information for developing optimal interventions that target specific driving exposures in children who are at greatest risk for obesity.

Advantages and Limitations of UC-MSCs

Biological Relevance of Mesenchymal Stem Cells

Box 2. Advantages & Limitations of UC-MSCs

Translational Impact
- UC-MSCs exhibit heterogeneous phenotypes associated with maternal exposures & predictive of child cardiometabolic outcomes

Non-Invasive
- UC-MSCs enable us to define *human* mesodermal tissue phenotypes, without invasive sample collection

Cell-Autonomous Investigation
- Obesity-exposed UC-MSCs phenocopy maternal obesity & established obesity adipocyte and myocyte phenotypes but are not confounded by systemic or niche-specific factors

Limitations
- UC-MSC naïveté to tissue environments limits some translatability to human, *in vivo* tissue development
- We do not know whether exposure-related UC-MSC phenotypes match developed mesodermal tissues
- Timing & mechanisms for exposure-induced impacts on UC-MSC phenotypes are unclear

Alterations in metabolic pathways relevant to obesity risk have been observed as early as blastocyst implantation [24]. Morover, consistent changes have been observed across fetal tissues, including umbilical cord, liver, and cardiac muscle, suggesting that exposures during the periconceptional window can lead to early stem cell lineage adaptations or concurrent adaptations in multiple tissues [25–27]. In the embryo, gastrulation forms three germ layers of progenitor cells that will further develop into all fetal tissues: endoderm, ectoderm, and mesoderm. It is the mesoderm and the mesenchymal progenitors (i.e., MSCs) that develop the mesodermal tissues during organogenesis–adipose, bone, cartilage, skeletal muscle, Thus, MSC niche of the developing embryo will eventually give rise to all muscle subtypes: cardiac, smooth, and skeletal muscle tissues; connective tissues: chondrocytes and fibroblasts of cartilage, ligaments, and tendons; bone; and all adipose tissues: visceral and subcutaneous, including brown, beige and white.

Concurrent with fetal development, the umbilical cord is formed from the extraembryonic mesoderm within the amniotic cavity [28]. The umbilical cord originates from the embryoblast (i.e., is genetically fetal) and umbilical cord Wharton's Jelly is an incredibly rich source of fetal MSCs [29], easily accessible, noncontroversial, and can be non-invasively cultured from typically discarded umbilical cord tissue at birth. Wharton's Jelly MSCs express markers consistent with primitive, multipotent stem cells [30, 31]. MSCs are an inherently heterogeneous cell population with multiple defining markers: cluster of differentiation (CD)73, CD90, and CD105, are characteristically plastic adherent, and must demonstrate ability to differentiate to mesodermal lineages [32].

Technical Advantages of UC-MSCs

Although umbilical cord blood and cord blood cells are also readily available from discarded tissues after birth, these only available in limited quantities. UC-MSCs are highly proliferative, can be extensively expanded in culture, and can be cryopreserved for repeated use for over a decade (or more), making them a highly feasible and practical human cellular model. As progenitors for mesodermal tissues, we can test not only the initial stem cell state (e.g., proliferative capacity, lineage preference), but we can induce in vitro differentiation to tissue relevant phenotypes (e.g., adipocytes, myocytes), which may better reflect later life offspring outcomes. This also allows us to test how the initial stem cell state contributes to the development of differentiated cell phenotypes (e.g., how does the initial epigenetic signature impact the development of myocellular metabolism or the immune activating properties of adipocytes). Furthermore, as a living resource, we can mechanistically interrogate the pathways involved.

Theoretical Advantages of UC-MSCs

The susceptibility to and biological underpinnings of obesity are multifactorial, with evidence to support cell and

tissue-specific changes as well as multi-organ systemic changes. UC-MSCs have the potential to inform both empirical frameworks. First, MSCs are multipotent progenitors with the capacity to differentiate into pertinent peripheral tissues for interrogating the biological underpinnings of obesity: adipose and skeletal muscle. Second, UC-MSCs can serve as a representative stem cell population reflecting change across tissues, either due to *early* stem cell lineage events or broad gestational exposures impacting multiple systems, including umbilical cord. Moreover, interrogating cells or tissues with the capacity to perpetuate long-term obesity risk is optimal. Most research in this field uses terminally differentiated cells with finite lifespans (e.g., monocyte lifespan ~ 2–7 days [33], adipocyte lifespan ~ 10 years). For example, many interrogate the influence of fetal exposures on white umbilical cord blood cell epigenetic signatures, though easily collected and measured, have a relatively short life span and are representative of immune cell populations. We posit that investigation of stem cell populations, including UC-MSCs, allows for focused interrogation of cells pertinent to long-term obesity risk.

Importantly, fetal MSCs are not only the building blocks for the diverse mesodermal tissues during fetal organogenesis, but MSC progenitors *originating from the same fetal MSC niche* are retained in these developed tissues for postnatal growth and repair across the lifespan (e.g., adipose derived stem cells [ADSC] [34], skeletal muscle satellite cells [35], bone marrow MSC [36], and synovial MSCs [37]). Thus, phenotypic changes to the initial MSC lineage may not only alter tissue development in utero but may maintain tissue phenotype throughout life. For example, adipose-derived MSCs from adults with established obesity or type 2 diabetes exhibit perturbations to lipid accumulation and proliferation during *in vitro* adipogenesis [38, 39] which correlates with the *in* vivo metabolic phenotype of the donor [39], suggesting *capacity for adipogenesis is intrinsic to the progenitor cell*. Likewise, for muscle, ourselves and others have shown satellite cells from adults with established obesity and/or insulin resistance exhibit altered lipid metabolism when differentiated to myotubes *in vitro* [40–42]. These satellite cell metabolic outcomes often track or correlate with the *in vivo* metabolic phenotype of the donor [40, 42], suggesting that altered lipid metabolism is a cell-intrinsic feature of obesity that can be measured in cells and tissues of MSC origin.

Adult progenitor cell studies do not address whether cell-intrinsic phenotypes are present prior to the development of obesity or simply represent a 'metabolic memory' from the tissue niche. UC-MSCs were not developed in the fetus with tissue-specific factors that may impart such 'memory', as observed with visceral or subcutaneous adipose depots [43], but still exhibit heterogeneity in epigenetic and metabolic phenotypes based on pregnancy characteristics [44–73] that correlate with infant and child obesity-related outcomes [44, 53, 54, 56–60, 62–64, 66, 67, 74]. Emerging research harnesses this heterogeneity as a precision index of offspring obesity risk. But knowledge gaps remain. For example, we don't yet understand how or when UC-MSCs develop these metabolic phenotypes. Related, we don't know whether UC-MSC features directly mirror molecular phenotypes of developed fetal or infant tissues. Addressing these questions will be important to the field. Nevertheless, UC-MSCs *do* retain clinically relevant phenotypic heterogeneity, representing an important advance in obesity medicine.

Looking Under the Hood: UC-MSCs as Tool to Interrogate Biological Pathways Implicated in Obesity

Early Work Implicating the MSC Niche in Obesity-Linked Pathways

A foundational aspect of our early using work using human infant UC-MSCs was to verify that observations from animal models of maternal obesity, primarily offspring mesodermal phenotypes, were similarly evident in human UC-MSCs differentiated to these cell types (e.g., myocytes, adipocytes). Importantly, we also evaluated undifferentiated MSCs to capture the initial stem cell settings that inform preference (i.e., lineage specification) and capacity to differentiate to specialized adipocyte or myocyte phenotypes.

Early work from Du and colleagues specifically implicated offspring MSC lineage specification in the development of excess offspring adiposity, both in adipose tissue mass, and in ectopic lipid stores in skeletal muscle tissues [75, 76]. They hypothesized that disruption to the glycogen synthase kinase (GSK)−3β/β-catenin pathway, a primary driver of MSC myogenesis and inhibitor of adipogenesis [77, 78], results in reduced muscle fiber size and greater fat deposition in skeletal muscle from obesity-exposed fetuses [75, 76]. Our first UC-MSC report similarly showed lower inhibitory phosphorylation of GSK-3β and lower β-catenin in undifferentiated MSCs from obesity-exposed infants [44] and, as in animal tissues, differences in mesodermal phenotypes with *in vitro* differentiation. Specifically, markers of adipogenesis (e.g., lipid content, peroxisome proliferator-activated receptor [PPAR]γ protein content) were higher in UC-MSCs from infants exposed to obesity in utero [44]. Moreover, PPARγ inversely correlated with the myogenic marker myosin heavy chain [44], suggesting perturbation to the GSK-3β/β-catenin pathway contributes to altered UC-MSC specification. Together, these data suggest UC-MSC lineage specification could impact offspring body

composition, with preferential recruitment toward adipose tissue in the context of maternal obesity.

Disrupted UC-MSC Adipogenesis is Linked to Excess Adiposity

Animal models of maternal obesity demonstrate altered adipose-resident MSCs that correspond to obesity phenotypes in offspring, supporting the premise of 1) long-term impacts of obesity-induced changes to the fetal MSC niche that 2) extend to differentiated cell types (i.e., not only evident in lineage specification of stem cells). For example, in genetically identical mice, offspring of high-fat-fed dams consistently demonstrate excess adiposity [79–81], and adipose-resident MSCs (i.e., ADSCs) from these offspring demonstrate greater capacity for adipogenesis when cultured and differentiated *in vitro* [82, 83]. Importantly, this is evident in cells collected *before or after* offspring development of excess adiposity, and even when post-natal exposures are controlled by cross-fostering to lean dams during lactation [82]. To our knowledge, the only similar example in humans focuses on low birth weight as an adverse prenatal exposure. ADSCs from adults born with low birth weight demonstrate reduced adipogenesis markers and lower leptin production with *in vitro* adipogenesis, relative to normal birthweight counterparts [84]. Remarkably, this was correlated with lower circulating leptin levels *in vivo*. Together, these data suggest cell-intrinsic adipogenesis phenotypes are evident in offspring MSCs prior to the onset of overt obesity, and point to specific effects of the intrauterine environment in promoting these differences.

One adipogenesis driver implicated in maternal obesity is zinc finger protein (ZFP)423, a well-known regulator of preadipocyte specification and differentiation [85]. Greater adipose mass in offspring of obese dams is linked to elevated ZFP423 both in adipose tissue and ADSCs [82, 83]. Moreover, greater *zfp423* in obesity-exposed offspring corresponds to *fewer* numbers of ADSCs in the adult adipose depots compared with offspring of control dams [83]. When adult offspring are challenged with high fat diet, those exposed to maternal obesity exhibit reduced progenitor hyperplasia and greater adipocyte hypertrophy, accompanied by macrophage infiltration, oxidative stress, and systemic glucose intolerance [83]. We recently developed a novel model of 3-dimensional (3D) UC-MSC adipogenesis that phenocopies these animal models with adipocyte hypertrophy, reduced proliferation, and disrupted ZFP423 [53]. In 3D adipogenesis culture, UC-MSCs develop round, lipid filled cells of classic adipocyte morphology that allowed us to quantify individual cell size and number. We demonstrated human UC-MSCs exposed to maternal obesity have greater adipogenic propensity, characterized by hypertrophy and reduced proliferation. ZFP423 protein abundance was associated with transcriptomic differences in cell cycle, MSC lineage specification, and metabolism pathways, assessed prior to *in vitro* adipogenesis. Moreover, adipocyte size was inversely associated with serum adiponectin in early childhood, which could indicate long-term health consequences. These results from animals and our UC-MSCs are consistent with adipocyte hypertrophy and reduced cell number in established obesity [86, 87], and suggest disruption to MSC adipogenesis may play a role.

Disrupted Lipid Metabolism and Nutrient Sensing Pathways in UC-MSC Myogenesis

In larger mammals (e.g., sheep, primates) skeletal muscle and liver of high fat-fed dams exhibit disruption to insulin signaling, excess oxidative stress and inflammation, and deficits in oxidative metabolism and nutrient sensing pathways when compared with fetuses of control-fed dams [88–91]. Disrupted fatty acid oxidation and intramyocellular lipid accumulation are well-documented in skeletal muscle of adults with established obesity and are linked to inflammation, oxidative stress, and insulin resistance [40, 92–94]. As with ADSCs, some of these characteristics are also evident in muscle-resident progenitors from the MSC niche (i.e., satellite cells) [41, 95, 96]. Few have investigated offspring satellite cells with respect to intrauterine exposures, though McCurdy et al. [88] show deficits in oxidative metabolism in both skeletal muscle and muscle-derived satellite cells from fetuses of obese, insulin resistant primates. Disruption to energy sensing pathways, such as AMP-activated protein kinase, sirtuins, and molecular target of rapamycin, are observed in rodent and sheep offspring of obese dams [75, 89, 97–99]. We posit that disruption to nutrient sensing pathways in fetal MSC niche may play a role in altered lipid partitioning and metabolic dysfunction, impacting mesodermal tissues and tissue-resident progenitors.

We and others have observed disruption to metabolic and nutrient sensing pathways in MSCs from infants exposed to intrauterine obesity [50, 56, 60] or GDM [47, 49, 51, 73]. During myogenesis, we show this may result in excess lipid accumulation in obesity-exposed UC-MSCs [56], broadly recapitulating results from animal models of maternal obesity. We found differential DNA methylation near genes related to oxidative metabolism [56], though deeper metabolic interrogation of the UC-MSCs indicates maternal metabolic health may be more relevant than obesity per se [60, 66]. We found metabolically efficient and inefficient phenotypes within the obesity-exposed UC-MSC group when differentiated to myotubes, where inefficient UC-MSCs have lower baseline lipid oxidation and reduced response to metabolic challenge *in vitro* [60]. These differences were related

to maternal insulin, glucose, and HDL cholesterol, and to neonatal adiposity [60]. We also reported UC-MSC insulin action during myogenesis was correlated with maternal FFA and UC-MSC triglyceride deposition, but not obesity status [66]. To interrogate UC-MSC phenotypes more comprehensively, we measured lipidomics during myogenesis, performing clustering analysis of lipid species. UC-MSC clusters are largely dependent on myotube triacylglycerol stores and track with a maternal metabolic milieu composite index (i.e., triglycerides, FFA, tumor necrosis factor [TNF] α, HDL- and total- cholesterol, glucose, and insulin), independent of maternal BMI. Remarkably, cluster also tracked with child adiposity trajectory through 4–6 years of age. (*Accepted* [67]).

Together, these data support that developmental exposures can impact offspring lipid metabolism and nutrient sensing pathways in the offspring MSC niche, prior to the onset of overt obesity. This appears to manifest as adipocyte hypertrophy and altered lipid metabolism and lipid partitioning in myotubes. These UC-MSC effects are stable and cell-autonomous, such that even when cells are removed from the tissue environment and passaged *in vitro*, daughter cells retain the phenotype. These findings indicate utility of UC-MSCs for interrogation of pertinent fetal exposures contributing to heterogeneity in the susceptibility to obesity in human infants. Furthermore, they implicate characteristics intrinsic to peripheral tissues in this susceptibility that could support primary prevention efforts in a precision manner.

UC-MSCs: A Robust Tool Defining the Most Pertinent Fetal Exposures & Precision Index of Future Obesity

One of the greatest limiting factors in human cohort and interventional studies interrogating the influence of early life exposures on obesity risk is the extended length of *time for outcome measurement*. While there is evidence that prenatal exposures can influence birth weight and birth adiposity [100, 101], obesity cannot be clinically diagnosed until 2 years of age and, as previously discussed, the impact of fetal exposures on obesity risk increases as children age with the greatest effect size in children over 10 years old [11]. Thus, cohort studies with prospective exposure measurement, or randomized prenatal interventions would need to follow children over gestational development plus an additional 2 years to capture clinical obesity (or 10 + years to capture more robust effects). There is a pressing need for precision assessments *at birth* that predict propensity for obesity, informing prenatal observational and intervention efforts. We propose UC-MSCs as a promising tool to help address this critical gap.

UC-MSCs Predict Early Childhood Adiposity

There is growing evidence to support the clinical relevance of UC-MSCs, specifically that UC-MSC phenotypes prospectively associate with long-term child outcomes, including child adiposity measures. In Table 1, we describe the UC-MSC phenotypes that relate to offspring characteristics. Among 14 studies [44, 53, 54, 56–60, 62–64, 66, 67, 74], most reported UC-MSC relationships with neonatal characteristics, particularly percent fat mass (%FM) measured within the first month of life. Four studies describe relationships that extend beyond the neonatal period, reporting data up to 6 months of age and, of these, two studies from our group report relationships through early childhood (4–6 years). Although the form and phenotype of UC-MSC varies across studies, studies predominantly interrogated myocyte or adipocyte phenotypes, typically by lipid accumulation or metabolism measures. Results from these studies highlight lipid metabolism as a central pathway in the biological underpinnings of obesity. For example, UC-MSC triglyceride content during *in vitro* adipogenesis predicts *in vivo* %FM with repeated measures from birth to age 4–6 years [54]. Importantly, UC-MSC triglyceride content more robustly predicted child %FM at 4–6 years than more common neonatal predictors (i.e., birth weight, %FM at birth), and explained an additional 13% variance in child adiposity [54], indicating medium effect size. More recently, we demonstrate UC-MSC lipidomic profiles during myogenesis also predict child adiposity at 4–6 years (*Accepted* [67]). Together, these data help establish the clinical relevance of UC-MSC phenotypes, supporting their use in future studies.

UC-MSCs Exhibit Developmental Plasticity Linked to Prenatal Exposures

UC-MSC phenotypes not only predict child adiposity outcomes, but importantly, many of these features exhibit variation in response to developmental exposures. UC-MSCs can serve as sensitive markers of these exposures *at birth*, as shown in Table 2 [44–73]. Most papers demonstrating UC-MSC developmental differences are from observational mother–child cohorts, such as the Healthy Start Cohort used in our studies [44, 52–60], and include exposures measured as part of standard obstetric care, such as maternal obesity status [44–46, 50, 52, 53, 56, 57, 60, 61, 65] or GDM [47–49, 51]. Among these, intrauterine exposure to obesity is the most frequently studied. However, exciting new research from randomized clinical trials (RCT) have shown changes to UC-MSC phenotypes in response to prenatal exercise intervention [61, 63, 64].

Meta-analyses evaluating RCT pregnancy lifestyle interventions on child weight-based or anthropometric outcomes (7 studies, 2535 children) [102, 103] have concluded that

Table 1 UC-MSC phenotypes associated with child outcomes

First Author, Year	MSC Form	MSC Phenotype	Child Outcomes	Direction of association	Child Age(s)	Cohort; N
Penolazzi et al. 2009[62]	Osteocytes	**RUNX-2 and ALP activity**	Weight & gestational age at birth	+	Birth	N = 20
Boyle et al. 2016[44]	Adipocytes	**Lipid content**	%FM (PeaPod)	+	Birth	Healthy Start; N = 29
Shapiro et al. 2016[59]	Adipocytes	**PPARγ response to nicotinamide**	%FM (PeaPod)	+	Birth	Healthy Start; N = 46
Boyle et al. 2017[56]	Myocytes	**Incomplete/Complete FAO**	%FM (PeaPod)	+*	Birth	Healthy Start; N = 29
Boyle et al. 2017[56]	UC-MSC	**DNA methylation, *PRKAG2*: cg20534694**	%FM (PeaPod)	+	Birth	Healthy Start; N = 29
Boyle et al. 2017[56]	Myocytes	**Incomplete/Complete FAO**	Cord blood insulin	+*	Birth	Healthy Start; N = 29
Baker et al. 2017[57]	Myocytes	**Acylcarnitine marker of incomplete FAO**	%FM (PeaPod)	+	Birth	Healthy Start; N = 24
Baker et al. 2017[57]	Adipocytes	**Gene expression in nutrient sensing pathways**	%FM (PeaPod)	-	Birth	Healthy Start; N = 24
Baker et al. 2017[58]	Adipocytes	**Long-chain acylcarnitines**	%FM gain (PeaPod)	+	Birth, 4–6 mo	Healthy Start; N = 24
Baker et al. 2017[58]	Myocytes	**Amino acid concentrations**	%FM gain (PeaPod)	-	Birth, 4–6 mo	Healthy Start; N = 24
Erickson et al. 2021[60]	Myocytes	**Complete FAO**	%FM (PeaPod)	-	Birth	Healthy Start; N = 29
Chavez et al. 2022[66]	Myocytes	**Insulin action**	Cord blood leptin	+	Birth	Healthy Start; N = 19
Keleher et al. 2023[53]	Adipocytes	**Adipocyte size**	Peripheral blood adiponectin	-	4–6 yr	Healthy Start, N = 39
Gyllenhammer et al. 2023[54]	Adipocytes	**Triglyceride content**	%FM (PeaPod/BodPod)	+	Birth, 4–6 mo, 4–6 yr	Healthy Start; N = 124
Gyllenhammer et al. 2023[54]	Adipocytes	**Triglyceride content**	Fasting glucose	+	4–6 yr	Healthy Start; N = 124
Jevtovic et al. 2023[63]	UC-MSC	**Incomplete FAO**	%FM (skin-fold)	+	Birth	ENHANCED RCT; N = 48
Jevtovic et al. 2023[63]	UC-MSC	**Nonoxidized glycolytic metabolite**	Blood lactate	+	1 mo	ENHANCED RCT; N = 48
Jevtovic et al. 2023[64]	Myocytes	**Insulin sensitivity**	%FM (skin-fold)	-	Birth, 6 mo	ENHANCED RCT; N = 48
Jevtovic et al. 2023[74]	Myocytes	**Glucose oxidation**	Blood lactate	-	1 mo	ENHANCED RCT; N = 48
Gyllenhammer et al. 2024[67]	Myocytes	**Lipidomics, K-means cluster**	%FM (PeaPod/BodPod)	n/a**	Birth, 4–6 mo, 4–6 yr	Healthy Start; N = 31

*Identification of distinct subgroups within obesity-exposed infants resulted in three groups (normal weight- & 2 obesity-exposed, which differed by parameters listed. **Cluster analysis resulted in three groups that demonstrated differences in adiposity across repeated measures of adiposity from birth through age 4–6 years. Abbreviations: PPARγ, peroxisome proliferator-activated receptor γ; FAO, fatty acid oxidation; %FM, percent fat mass; PeaPod/BODPod, measured by air displacement plethysmography

pregnancy interventions have *small* study effects on childhood obesity and *no* effect on child anthropometrics. Louise et al. [102] conclude that pregnancy lifestyle interventions are unlikely to be successful and that pregnancy itself may be too late for interventions. Indeed, important shifts in susceptibility for obesity may occur in the periconceptional period, prior to the onset of most pregnancy interventions [104], but we would argue lack of sensitivity in offspring assessments may account for lackluster intervention outcomes. The growing emergence of UC-MSCs as a robust at-birth predictor of neonatal and early childhood adiposity may fill this gap [54]. The ENHANCED trial demonstrates

Table 2 Fetal exposures associated with differences in UC-MSC phenotypes

First Author; Year	Cohort; N	UC-MSC Form	Summary
UC-MSC Differences Based on Maternal Obesity Exposure vs. Normal Weight			
Boyle et al. 2016[44]	Healthy Start; N = 29	UC-MSC, Myocytes, Adipocytes	Obesity-exposed UC-MSCs have reduced GSK-3β/β-catenin. Adipocytes have greater PPARγ and lipid content. Lipid content correlates with neonatal adiposity
Chen et al. 2016[45]	GLOWING; N = 24	UC-MSC, Osteocytes	Obesity-exposed UC-MSCs have increased senescence markers and osteocytes have reduced osteogenesis and increased PPARγ
Boyle et al. 2017[56]	Healthy Start; N = 29	Myocytes	Obesity-exposed myocytes exhibit DNA hypermethylation of nutrient sensing/oxidative metabolism genes, metabolic sub-groups identified among obesity-exposed infants
Baker et al. 2017[57]	Healthy Start; N = 24	Myocytes, Adipocytes	Obesity-exposed adipocytes have downregulation of nutrient-sensing pathways
Badraiq et al. 2017[46]	N = 14	UC-MSC, Adipocytes, Osteocytes, Chondrocytes	Obesity-exposed UC-MSCs have lower proliferation rates and are more immunosuppressive, with hypermethylation of *PNPLA7*
Chen et al. 2018[65]	GLOWING; N = 6	UC-MSC, Osteocytes	UC-MSCs have increased senescence signaling and PPARγ
Iaffaldano et al. 2018[50]	N = 23	UC-MSC	Obesity exposed UC-MSCs have lower glycolysis and ATP-linked respiration, lower mitochondrial content
Erickson et al. 2021[60]	Healthy Start; N = 29	Myocytes	Metabolically efficient/inefficient sub-groups among obesity-exposed infants linked to mitochondrial lipid oxidation, linked to maternal glucose, insulin, HDL
Chavez et al. 2022[61]	Healthy Start; N = 19	Myocytes	Myocyte insulin action not related to maternal obesity, but correlated with maternal free fatty acids
Erickson et al. 2023[52]	Healthy Start; N = 6	UC-MSC, Myocytes, Adipocytes	UC-MSCs exhibit rhythmicity of circadian genes. Obesity-exposed UC-MSCs have greater *PER2* amplitude, related to lipid storage in adipocytes and myocytes
Keleher et al. 2023[53]	Healthy Start; N = 39	UC-MSC, Adipocytes	Obesity-exposed UC-MSCs have greater ZFP423, correlated with cell cycle, inflammation, and metabolism pathways; adipocytes are larger, but fewer
UC-MSC Differences Based on Gestational Diabetes Mellitus (GDM) Exposure vs. Non-GDM			
Pierdomenico et al. 2011[73]	N = 10	UC-MSC, Adipocytes, Osteocytes	GDM-exposed UC-MSCs exhibit normal proliferation, normal osteocytes, adipocytes have greater adipogenesis
Kim et al. 2015[47]	N = 7	UC-MSC, Adipocytes, Osteocytes	GDM-exposed UC-MSCs have lower proliferation and mitochondrial activity, greater senescence. GDM-exposed adipocytes have lower PPARγ, osteocytes lower markers
Wajid et al. 2015[48]	N = 25	UC-MSC	GDM-exposed UC-MSCs have lower proliferation, cell viability, glucose metabolism

Table 2 (continued)

First Author; Year	Cohort; N	UC-MSC Form	Summary
Amrithaj et al. 2017[51]	N = 23	UC-MSC	GDM-exposed UC-MSCs have lower insulin action, lower mitochondrial respiration, and higher ROS production
Kong et al. 2019[49]	N = 9	UC-MSC, Adipocytes, Osteocytes, Chondrocytes	GDM-exposed UC-MSCs have lower proliferation, telomerase, mitochondrial gene expression, upregulated cell cycle inhibitors; lower differentiation markers
UC-MSC Differences Based on Exercise Intervention (RCT)			
Chaves et al. 2022[61]	ENHANCED Trial; N = 20	UC-MSC, Myocytes	Exercise intervention increases UC-MSC insulin action, glucose oxidation partitioning; increases myocyte Complex I expression, but no change in lipid metabolism
Jevtovic et al. 2023[63]	ENHANCED Trial; N = 48	UC-MSC	Exercise intervention increases UC-MSC insulin action and efficiency for fatty acid oxidation
Jevtovic et al. 2023[64]	ENHANCED Trial; N = 48	Myocytes	Exercise intervention increases myocyte insulin action, which was related to increased fatty acid oxidation
UC-MSC Differences Based on Circulating Metabolic Milieu Exposure			
Gyllenhammer et al. 2024[67]	Healthy Start; N = 31	Myocytes	A composite index of maternal milieu (TG, FFA, TNFα, cholesterol, HDL-Cholesterol) corresponds to myocyte lipidomic cluster, independent of maternal BMI
UC-MSC Differences Based on Mixed Obstetric Exposures			
Penolazzi et al. 2009[62]	N = 60	UC-MSC, Osteocytes	Osteocytes from infants of younger mothers (< 32 years) have higher RUNX-2, even more with higher birthweight. No differences based on infant sex, mode delivery
Messerli et al. 2013[68]	N = 12	UC-MSC, Neural progenitor	UC-MSCs can be differentiated to neural progenitors, but no differences based on pre-term vs. full-term birth
Sukarieh et al. 2014[69]	GUSTO Cohort; N = 12	UC-MSC	SGA infants had higher UC-MSC proliferation and insulin action, lower EGR-1. EGR-1 and COX-2 overexpression increased insulin action in UC-MSCs
Joerger-Messerli et al. 2015[70]	N = 14	UC-MSC	Preeclampsia exposure increased UC-MSC neuronal and oligodendrocyte protein markers
Alrefaei et al. 2015[71]	N = 100	UC-MSC* (paraffin embedded)	Maternal age was negatively correlated with UC-MSC markers CD105 and CD29
Avercenc-Leger et al. 2017[72]	N = 50	UC-MSC, Adipocytes, Osteocytes, Chondrocytes	UC-MSC proliferation impacted by managed labor (oxytocin, amniotomy), amenorrhea weeks at birth. Chondrocyte differentiation impacted by long labor

GSK-3β, glycogen synthase kinase-3β; PPARγ, peroxisome proliferator-activated receptorγ; *PNPLA7*, tatin Like phospholipase domain containing 7; *PER2*, period 2; ZFP423, zinc finger protein 423; ROS, reactive oxygen species; TG, triglycerides; FFA, free fatty acids; TNFα, tumor necrosis factor-α; HDL, high density lipoprotein; RUNX-2, Runt-related transcription factor 2; EGR-1, early growth response protein 1; COX-2, cyclooxygenase-2; CD, cluster of differentiation

UC-MSC phenotypes are not only timely (i.e., readily available at birth without long-term follow-up), but they may also capture offspring interventional changes missed by less sensitive neonatal assessments. In this trial, exercise intervention did not change offspring birth weight, but there was evidence of decreased skin-fold measures at 1 month of age [105]. Yet, the smaller subset of UC-MSC samples (N = 41) showed that exercise increased UC-MSC fatty acid oxidation and insulin-stimulated glucose storage. These same UC-MSC phenotypes associated with lower offspring %FM at 1 month [63, 64] and 6 months [64] of age, supporting that UC-MSCs are perhaps a more sensitive index of fetal exposures linked to pregnancy intervention and child adiposity, despite smaller sample size. These studies also highlight that interventions initiated in the 2nd and 3rd trimester, as in the ENHANCED trial, may still be impactful for changing offspring obesity risk, despite missing the potentially important periconception window [61, 63, 64].

Another notable feature of the ENHANCED trial is that maternal weight-based measures were either balanced by design (matched for BMI) and/or unchanged by the intervention (gestational weight gain) [63, 105]. Despite a lack of difference in these commonly used weight-based assessments of fetal exposure, UC-MSC metabolic features were significantly changed by exercise exposure [61, 63, 64]. Though important proxies at large scale, maternal obesity and GWG are imprecise markers of metabolic health at the individual level. Presumably other metabolic features of the pregnant person (e.g., circulating metabolic milieu) were altered by exercise training, that then causally mediated UC-MSC change. Similarly, although the Healthy Start cohort originally framed UC-MSC differences based upon intrauterine obesity exposure, as detailed above, more recent reports from our group echo the concept that maternal metabolic health is likely more important in transmitting adverse MSC and later life child phenotypes than maternal weight/obesity status per se [56, 60, 66, 67]. This makes biological sense, given that only factors that cross or are metabolized through the placenta, or otherwise impact placental function, can impact the fetus. Precision obesity prevention efforts will require us to move beyond readily available clinical or weight-based exposures, and to quantify prenatal exposures/pathways that have the potential to mediate fetal physiology.

Conclusion & Future Directions

Obesity prevalence is increasing rapidly and exposures during fetal development have a significant impact on individual susceptibility to obesity across the lifespan. Yet specific, pertinent fetal exposures are largely unknown. There is a pressing need for precision obesity indicators *at birth*, informing pregnancy intervention efforts. We propose UC-MSCs as a novel tool to help address these critical gaps. UC-MSC results are quite promising for obesity medicine, both as a mechanistic tool to interrogate the biological underpinnings of obesity, and at-birth indicator of prenatal exposures and future obesity susceptibility. UC-MSC studies highlight the need to shift away from weight-based measures of fetal exposures and offspring outcomes, rather focusing on factors biologically impacting fetal physiology and precise measures of offspring metabolic health. Data from UC-MSCs emphasize nutrient sensing and lipid partitioning as phenotypes most relevant to neonatal and early childhood adiposity and implicate a role for these cell-autonomous phenotypes of mesodermal tissues in the biological underpinnings of obesity. Yet, we acknowledge the field is young, limitations remain as highlighted in **Box 2**, and much work is needed to substantiate these encouraging findings.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

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