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An Evolutionary Perspective on Immunometabolism

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Abstract

Metabolism is at the core of all biological functions. Anabolic metabolism uses building blocks that are either derived from nutrients or synthesized *de novo* to produce the biological infrastructure, while catabolic metabolism generates energy to fuel all biological processes. Distinct metabolic programs are required to support different biological functions. Thus, recent studies have revealed how signals regulating cell quiescence, proliferation, and differentiation also induce the appropriate metabolic programs. In particular, a wealth of new studies in the field of immunometabolism has unveiled many examples of the connection between metabolism, cell fate decisions, and organismal physiology. Here we discuss these findings under a unifying framework derived from the evolutionary and ecological principles of life history theory.

Introduction

Metabolism is the core process underlying all biological phenomena. All biological processes require energy sources and metabolic building blocks. Metabolism generally falls into anabolic, energy-consuming, biosynthetic pathways and catabolic, energy-producing pathways. Historically, our knowledge of these core biochemical pathways was primarily gleaned from the study of post-mitotic cells. Recent studies in the immune system have demonstrated a dynamic and finely-tuned connection between metabolic programs and the specialized cellular functions they support during the course of the immune response. A number of specific regulatory pathways demonstrating the crucial role of metabolism in immunity have been elegantly characterized and have resulted in the emergence of the new field of immunometabolism. Several excellent recent reviews summarize these advances (1–6), and demonstrate that on the cellular, tissue and organismal level, there is a critical role for metabolism in controlling immunity and that inflammation, in turn, has a profound impact on metabolism. This reciprocal relationship is fundamental to the immune response, and is at the center of a myriad of modern human diseases including obesity, diabetes, sepsis, and autoimmune/autoinflammatory diseases.

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At the heart of immunometabolism is the regulated allocation of metabolic resources (energy and building blocks) required to support host defense and survival. Here we discuss a unifying framework for these complex interactions based on general concepts of life history theory that explains evolutionary patterns of resource allocation in diverse environments.

Life History Theory as an organizing principle in biology

All living creatures, from bacteria and protozoa, to plants and metazoan animals, use different strategies to optimize reproductive success in the face of constraints imposed by the environment. These strategies are specific combinations of so called 'life history traits', such as size at birth, temporal pattern of growth, age and size at reproductive maturity, fecundity and lifespan, which vary vastly among species. For example, krill grow to only a couple of centimeters and lay thousands of eggs per brood, while the blue whales that dine on them can grow to nearly one hundred feet and only give birth once every several years. Life history theory aims to explain this tremendous diversity life-styles through analysis and modeling of various resource distribution strategies in the context of species-specific sets of environmental challenges (7).

Since its conception in the 1950s, life history theory has clearly demonstrated that in order to maximize reproductive success, organisms must effectively optimize distribution of finite resources into growth, reproduction, and environment-specific survival strategies (maintenance) (7). Traditionally, life history theory has identified growth, reproduction, and maintenance as the three fundamental biological programs into which resources can be invested depending on the quality of the environment. Favorable environmental conditions, including abundance of nutrients, promote investment into the anabolic and energy-consuming processes of growth and reproduction, while unfavorable conditions, including nutrient scarcity, require reallocation of available resources into stress-specific catabolic and energy-saving maintenance mechanisms (7).

Two types of Maintenance Programs: Defense and Dormancy

There are two ways the environment can be unfavorable: absence of sufficient resources (typically nutrients), or presence of factors with negative impact on fitness (e.g., predators, pathogens and toxins). Accordingly, maintenance programs induced by these adverse environments are of two types: *dormancy* and *defense*, respectively (Fig. 1). Scarcity of resources induces states of dormancy, where non-essential functions, including growth and reproduction, are temporarily suppressed. The dormancy programs promote energy conservation, rely on catabolic metabolism and are generally associated with high resistance to environmental stressors. At the extremes, these programs can take the form of suspended animation, such as hibernation and dauer. Hibernating mammals, which build up tremendous stores of fat reserves prior to hibernation, decrease metabolic rate dramatically and rely on catabolic programs associated with the metabolism of fatty acids (8). Hibernating mammals have elevated resistance to multiple stressors, including oxidative damage (9), traumatic injury (10), and hypothermia (11). Dormancy programs in lower organisms, such as dauer in *Caenorhabditis Elegans* (12) and extreme abiotic states in tardigrades (13) also show pronounced resilience to environmental stressors. Concordantly, transcriptional analyses of

these organisms demonstrate a shift towards catabolic programs and fatty acid metabolism (14, 15).

Like dormancy, defense programs occur at the expense of growth and reproduction, but unlike dormancy, they are energy-consuming and rely on anabolic metabolism to fuel protective responses against pathogens and other hostile environmental factors (Fig. 1B). For example, immune response to pathogens relies on anabolic programs associated with glucose and glutamine utilization, necessary to support leukocyte proliferation and biosynthesis of proteins and other biomolecules involved in defenses (1–3). Thus, dormancy and defense, while both being part of maintenance, rely on different metabolic programs. It should also be noted that response to some adverse environments can belong to either dormancy or defense, depending on the animal group. For example, the maintenance program induced by cold temperature is dormancy in poikilothermic animals and defense in homeothermic animals.

Although life history theory was originally developed as an organizing framework for evolutionary ecology, similar principles can also be applied at the level of organisms and cells. In this context, growth, reproduction, and maintenance can be referred to as *life history programs*. This perspective can provide a unifying framework for control and coordination of cellular and organismal metabolism.

Hypothalamus as a central coordinator of organismal life history programs

On the organismal level, the growth, reproduction, and maintenance programs identified in life history theory bear distinct resemblance to the three neuro-endocrine pathways known as the hypothalamic-pituitary (HP) axes (Fig. 2). Control of somatic growth is largely governed by the growth hormone – insulin-like growth factor (GH-IGF) axis (16). Growth hormone (GH) is secreted from somatotroph cells in the anterior pituitary gland. The secretion of GH from the anterior pituitary is promoted by growth hormone-releasing hormone (GHRH) produced by neurons in the periventricular nucleus of hypothalamus. GH acts through growth hormone receptor on hepatocytes and other cell types to promote secretion of insulin-like growth factor 1 (IGF-1), which acts on multiple tissues to promote anabolic growth programs. Reproduction is regulated by the hypothalamic – pituitary – gonadal (HPG) axis (17). This system begins with hypothalamic neurons in the arcuate nucleus and preoptic area, which secrete gonadotropin-releasing hormone (GnRH). GnRH acts on gonadotrophs in the anterior pituitary gland to induce secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which promote a variety of sex-specific reproductive functions, in large part by inducing gonadal secretion of the sex hormones, testosterone and estrogen. Finally, the hypothalamic – pituitary – adrenal (HPA) axis controls glucocorticoid production, which, in addition to sympathetic tone, is a common feature of the response to a variety of environmental stressors (infection, cold, predation, etc.) (18). Neurons in the paraventricular nucleus of the hypothalamus secrete corticotropin-releasing hormone (CRH). CRH induces corticotrophs in the anterior pituitary gland to release adrenocorticotrophic hormone (ACTH) into the blood stream. ACTH then acts on the cells in the cortex of the adrenal gland to promote glucocorticoid secretion. Thus, these three hypothalamic-pituitary axes act as central coordinators of organismal life history programs.

Life history programs on an organismal level are coupled to specific metabolic programs. The GH-IGF axis ultimately results in secretion of IGF-1, which has been shown to promote anabolic metabolism, growth and storage of excess energy (19). Similarly, sex hormones have well known anabolic effects, which can facilitate energy storage in various ways, such as increased muscle and adipose mass (20). In contrast, the effect of glucocorticoids on tissues is primarily catabolic (21, 22). Thus, the physiological effects of the three hypothalamic-pituitary axes correspond to the three life history programs (growth, reproduction and maintenance), with growth and reproduction being anabolic and maintenance being catabolic programs.

As all three of these axes are initiated at the level of the hypothalamus, the hypothalamus can be thought of as the sensor of environmental quality that then directs engagement of appropriate organismal life history programs. Evidence for hypothalamic sensing of environmental quality is abundant. The medial basolateral hypothalamus is particularly well-positioned for direct sensory function because it is not protected by the blood brain barrier, allowing it to access and evaluate the contents of the blood (23). Neurons in this anatomic area, including neuropeptide Y/agouti-related protein (NPY/AgRP) and pro-opiomelanocortin (POMC) neurons, can sense nutritional status, either directly (24, 25), or through the effects of insulin and leptin (26). The hypothalamus has also been shown to sense other environmental conditions, including hot (27) and cold (28) temperature, thirst (29, 30), and infection (31, 32). Importantly, there is strong evidence that hypothalamic sensing of a hostile environment can lead to direct suppression of the GH-IGF and HPG axes at the hypothalamic level. Following the example of NPY/AgRP and POMC neurons above, alpha-melanocyte stimulating hormone secreted by POMC neurons (in response to nutrient abundance) has been shown to activate a large fraction of GnRH neurons, while NPY, which can be secreted by NPY/AgRP neurons (in response to nutrient scarcity), has been shown to suppress GnRH neurons (33). NPY/AgRP neurons have also been shown to inhibit Kiss1-expressing neurons (34), which are critical drivers of reproductive maturation and function. AgRP neuron activation may also lead to suppression of the GH-IGF-1 axis (35). Finally, CRH can directly suppress GnRH secretion as well as GHRH-induced GH secretion (36). Taken together, these examples illustrate how the hypothalamus controls the choice of life history programs as a function of the quality of the environment and orchestrates the suppression of growth and reproductive functions, while engaging maintenance programs in unfavorable environments.

Cellular Life History Programs

At the cellular level, life history programs of cell growth, reproduction (proliferation), and maintenance are reflected in the organization of cell signaling pathways. Engagement of the cellular equivalents of life history programs is dictated by sensing of local cellular environment (nutrient and oxygen availability and various stress factors) and global organismal state (which, in turn, reflects organismal environment).

Cells receive information about the organismal environment via various endocrine signals, including signals for growth (GH, IGF-1 and other growth factors), reproduction (estrogen and androgen) and maintenance (glucocorticoids), as well as endocrine hormones which

communicate systemic status, such as those permissive for growth and reproduction (i.e. insulin and leptin) or maintenance (i.e. glucagon, ghrelin, fibroblast growth factor (FGF) 21 and inflammatory cytokines). Interestingly, GH has a dual role in controlling organismal life history programs: in addition to being involved in the GH-IGF-1 axis that controls growth and anabolic metabolism, GH is induced by ghrelin during fasting and promotes lipolysis and gluconeogenesis to enable adaptation to starvation (37, 38). Which of the two opposing pathways is induced by GH is likely dictated by the metabolic status of the organism, such that GH promotes IGF-1-mediated anabolic growth programs in fed states, while in fasted states, GH promotes catabolic maintenance programs. The details of how these effects of GH are regulated remain to be established.

Local cellular environment is sensed by various nutrient sensors, including AMPK (ATP), ChREBP (glucose), GCN2 and mTOR (amino acids), SREBP-2 (sterols), PPAR α and PPAR γ (fatty acids) (39, 40), while oxygen level is sensed by HIF-1/2 – PHD sensors (41). In addition to nutrient and oxygen availability, cells sense the local presence of various negative micro-environmental factors, including pathogens (Toll-like receptors, RIG-I, MDA-5), oxidative stress (NRF-2), DNA damage (p53), deviations in pH (GPR132, GPR4, GPR68 and GPR65), heavy metals (MTF-1) and protein damage (XBP-1 and HSF-1) (42). Activation of these pathways is generally known as the cellular stress response, which is a form of cellular defense against negative micro-environmental factors.

Cells engage in their own version of life history programs based on the local environmental and organismal state: when the environment is sensed as favorable, cells grow and proliferate and engage specific signaling pathways and transcriptional programs that execute these cellular functions. When the environment is sensed as unfavorable, cells engage defense or dormancy programs orchestrated by the corresponding signaling and transcriptional programs (Table 1). The functions of p53 provide a particularly well-studied example illustrating the regulation of cellular life history programs: in response to sensing adverse cellular state (DNA damage and other stressors), p53 suppresses growth factor signaling and anabolic metabolism required to support cell proliferation, while promoting catabolic metabolism, autophagy and dormancy (43).

Cellular detection of nutrient scarcity leads to activation of catabolic processes characterized by engagement of AMPK, FOXO1/FOXO3a, fatty acid oxidation and autophagy pathways (44). Additionally, these programs repress the anabolic processes of cellular growth and proliferation programs through suppression of PI3/AKT and mTOR pathways (45–47). A fundamental aspect of a cell's life history program choice is between quiescence (and self-renewal in stem/progenitor cells) and proliferation and differentiation. Stem/progenitor cell quiescence and self-renewal is promoted by resource scarcity and is controlled by the same pathways that control dormancy - AMPK, FoxO, STAT3 and SMADs - while proliferation and differentiation is promoted by PI3K-AKT, mTOR and other regulators of anabolic metabolism (4). Interestingly, asymmetric cell division of stem cells results in unequal partitioning of these signaling components between self-renewing and differentiating daughter cells (48–51), reflecting the fundamental role these pathways play in cell fate decisions along life history programs. Quiescence/dormancy and self-renewal rely on catabolic metabolism, including OXPHOS, while cell activation, proliferation and

differentiation require glucose and glutamine, aerobic glycolysis and anabolic metabolism. This is clearly seen in the well-studied examples of T cell metabolism, where naïve and memory T cells (self-renewing/quiescent states) rely on OXPHOS, while activated/effector T cells rely on aerobic glycolysis and require activation of PI3K-AKT and mTOR pathways (1).

Thus, when viewing metabolic reprogramming from a cellular life history perspective, it is clear that the same signaling pathways and transcriptional programs that enable specific cellular functions such as proliferation, also engage specific metabolic programs to support these functions. Growth and proliferation and other resource-utilizing processes are supported by anabolic metabolism, while maintenance relies on either catabolic (dormancy) or anabolic (defense) metabolic programs, as we discuss next (Fig. 3A).

Dealing with Infection: Immune Resistance (Defense) and Tolerance (Dormancy)

Survival of infections requires reducing microbial burden (through immune resistance mechanisms) and tolerating the damage of infection (through various tissue protective and survival mechanisms unrelated to pathogen control) (52, 53). Immune resistance requires the proliferation of immune cells and generation of lipid and protein mediators that direct the immune response. These rely on the same energy-consuming anabolic pathways as growth and proliferation induced by growth factors. Thus, the immune response corresponds to the defense component of maintenance programs (Fig. 3B). On the other hand, at least some tolerance mechanisms, which confer stress resistance and tissue protection from inflammatory and pathogen-induced damage, may largely rely on catabolic metabolism and correspond to the dormancy component of maintenance programs. Indeed, as noted earlier, dormancy programs rely on catabolic metabolism and confer stress-resistance. We further propose that these dormancy programs are likely induced by specialized signals (including adenosine, ketone bodies, FGF21 and glucocorticoids) that coordinate organ-specific switches to tissue protective, dormant metabolic states.

Immune Resistance (Defense)

It is now well established that for immune cells to execute their specialized functions during an infection, they must engage anabolic metabolism. Under homeostatic conditions (in the absence of infection) macrophages maintain homeostatic proliferation in the presence of mitogens (growth and proliferation) in a c-Myc-dependent fashion, but upon activation with LPS actively suppress c-Myc expression and switch to a mTOR-HIF1 α – dependent metabolic program (54). This example illustrates that while both growth/proliferation and defense rely on anabolic programs, they have distinct features and are controlled by different signaling and transcriptional programs (in this example, c-Myc *versus* HIF1 α). In addition to activating anabolic metabolism, TLR signals induced by LPS in macrophages actively suppresses catabolic programs. LPS stimulation leads to inhibition of AMPK (a key activator of catabolic metabolism) (55) and up-regulation of iNOS and NO production, which nitrosylates proteins in the mitochondrial electron transport chain, leading to suppression of oxidative phosphorylation (OXPHOS) (56, 57). In contrast, the inflammatory

functions of macrophages are dependent on aerobic glycolysis and anabolic programs. Indeed, upon stimulation by LPS, macrophages activate mTOR (58) while increasing μ -PFK2 and thus enhancing aerobic glycolysis (59). In a coordinated fashion, LPS activates mTOR-HIF1 α pathways leading to increased transcription of GLUT1 (60) to fuel aerobic glycolysis. The production of IL1 β also requires the activation of mTOR-HIF1 α (61, 62) as well as fatty acid synthase (63) and the suppression of AMPK and autophagy (64, 65). AMPK suppression in macrophages has also been shown to be critical for maximal induction of TNF, IL6 and eicosanoids (66). In all cases, limiting glucose or interfering with the subsequent anabolic pathways ablates macrophage inflammatory responses (59–62).

Upon activation, dendritic cells (DCs) also switch to aerobic glycolysis and actively suppress OXPHOS through the actions of NO and mTOR-HIF1 α (67). mTOR-HIF1 α has been shown to be required for upregulation of the co-stimulatory molecules CD80 and CD86 (68) as well as the production of cytokines (69). Thus, dendritic cell functions are also coupled with supportive anabolic metabolic programs.

Aerobic glycolysis in activated T cells generates the supply of substrates used for growth and proliferation and regulates the efficient production of effector cytokines critical for the immune response (3, 70). Unlike macrophages and DCs, T cell activation initiated by TCR/CD28 also augments OXPHOS to support rapid increase in energy demand (71, 72). It was recently shown that subsequent to TCR engagement, the mitochondrial proteome is remodeled to promote one-carbon metabolism (73). Ablation of SHMT2, the first enzyme in this pathway, impairs CD4 T cell survival and proliferation (74). Consistent with this is the observation that unequal elimination of mitochondria in daughter cells subsequent to TCR activation leads to different functional outcomes (48, 75). Maintaining mitochondria was linked to anabolic metabolism and enhanced glycolysis via PI3K and mTOR pathways and suppression of AMPK and autophagy, while mitochondrial clearance was linked to catabolic program activated by FOXO1 (75). This process was shown to be critical for control of differentiation (defense, PI3K, mTOR) versus self-renewal (dormancy, FOXO1) (75). Consistent with these findings, one general feature of long-lived memory T-cells is their dependence on OXPHOS metabolism and fatty acid utilization and active suppression of glycolysis and glucose utilization (70, 76).

Given that immune cell activation requires anabolic metabolism, one way anti-inflammatory signals can operate is by suppressing nutrient acquisition and anabolic programs in immune cells. Indeed, IL10 negatively regulates macrophage inflammatory response by suppressing GLUT1 cell surface expression, glycolytic flux and mTOR activity, while simultaneously promoting OXPHOS and mitophagy, which negatively regulate macrophage activation (64). TGF β was also recently shown to negatively regulate macrophages by interfering with mitochondrial dynamics (77). In T cells, engagement of the inhibitory receptor PD1 leads to inhibition of glycolysis and promotion of fatty acid oxidation (78, 79). Taken together, these examples suggest that one major mode of action of anti-inflammatory and immune-suppressive signals might be through the suppression of anabolic metabolic programs required for activation of immune and inflammatory responses (Fig. 3B).

Disease Tolerance (Dormancy)

Surviving an infection requires both pathogen clearance (resistance to infection) and tissue protection from pathogens and inflammatory damage (tolerance to infection). While immune resistance relies on anabolic metabolism, we propose that some (but not all) aspects of tolerance may primarily be based on catabolic dormancy programs. Indeed, the inflammatory response activates many components of dormancy programs typically induced by nutrient scarcity (Fig. 4A).

A prominent component of acute inflammation illustrating this point is sickness behaviors, which include anorexia, loss of libido, social withdrawal, fatigue and somnolence (80). Sickness behaviors are thought to have a protective role during an infection, although there is limited understanding of the mechanistic basis for this notion. However, sickness behaviors can be seen from the perspective of life history programs as organismal states associated with dormancy and organ protection. All sickness behaviors appear to be induced through the effects of inflammatory mediators, especially prostaglandins, on the corresponding areas of hypothalamus (81, 82). Thus, sickness behaviors can be thought of as behavioral manifestations of divestment in growth and reproduction (anorexia and loss of libido) and entry into dormancy (hypersomnia, fatigue, malaise, social withdrawal). Consistent with this, under inflammatory challenges, the HPA axis (for maintenance/catabolic programs) is engaged while the HPG and IGF-1 pathways (growth and reproduction/anabolic programs) are suppressed (83, 84). Inflammatory mediators such as TNF, IL6, IL1 β , Type I IFN, and prostaglandins have all independently been shown to directly induce anorexia (82, 85, 86). In addition to the catabolic state induced by activation of the HPA axis, TNF directly liberates free fatty acids through lipolysis (87) while simultaneously reducing glucose utilization in skeletal muscle and adipose tissue by both decreasing insulin secretion by pancreatic beta cells and by inducing insulin resistance in these organs (88, 89). Leptin resistance has also been demonstrated in a variety of inflammatory contexts (90). Furthermore, inflammation and inflammation-induced anorexia induce a modified version of a fasted metabolic state, which is characterized by lipolysis and the liberation of free fatty acids from adipose tissue as well as PPAR α -regulated synthesis and secretion of ketone bodies and FGF21 by the liver (91). Moreover, both fasting and infection-induced IL6 induce hepatic triglyceride secretion (92). Plasma Angptl4 levels also rise during inflammation, which inhibits lipoprotein lipase activity in adipose tissue, such that the increased triglycerides in circulation are readily available for utilization rather than taken up for storage (93). The ability to produce glucocorticoids, liberate alternative fuels through lipolysis, triglyceride secretion, perform ketogenesis, and induce FGF21 have all been shown to be necessary for surviving inflammatory conditions (91, 94, 95). Conversely, agonism of PPAR α and FGF21 pathways has been shown to improve survival (96, 97).

It is becoming increasingly clear that a shift to dormancy-associated metabolic programs in vital organs during an immune response confers tissue protection. For example, alternative fuels such as ketone bodies have been shown to have direct cytoprotective effects, primarily by reducing oxidative damage (98, 99), but also by directly signaling to negatively regulate inflammation, as in the cases of the beta-hydroxybutyrate receptor Gpr109a (100, 101) and the effect of ketone bodies on the NLRP3 inflammasome (102). On the cellular level, upon

oxidative stress, hematopoietic stem cells shift metabolic programs to OXPHOS and fatty acid metabolism in a cytochrome c oxidase 2-dependent fashion, which improves their survival (103). Indeed, engagement of catabolic/maintenance programs have been observed to confer stress resistance in a variety of settings such as in the beneficial tissue-protective effects seen in calorie restriction (104), ischemic preconditioning (105) and therapeutic hypothermia (106).

In summary, the inflammatory response to infection (a maintenance program) suppresses growth and reproduction and is a composite of resistance (defense component of maintenance) that relies on anabolic programs and promotes pathogen clearance and tolerance (dormancy component of maintenance) that relies on catabolic programs and promotes tissue protection (Fig. 4B). Finally, it should be noted that while dormancy is perhaps the most universal mechanism of tolerance, there are many other processes that can promote survival, depending on what is the limiting factor in a given context. For example, tissue repair is an anabolic process (and thus fits better with the definition of defense), but it can clearly contribute to tolerance. Dormancy, on the other hand, can make tissues less susceptible to damage in the first place.

Summary and Perspectives

The evolutionary perspective described above provides a new framework for the conceptualization and study of how metabolic programs support organismal, tissue, and cellular processes in changing, and not always welcoming, environments. The application of life history theory is particularly informative because it describes the logic of how resources are allocated between growth, reproduction, and maintenance programs as a function of environmental quality. We suggest here that maintenance can be divided into two metabolically distinct programs: the energy-preserving, catabolic dormancy programs and the energy-consuming anabolic defense programs. Importantly, this life history theory perspective can effectively be applied within the lifespan of an individual organism and an individual cell to examine how each entity adapts to its ever-changing environment.

When this framework is applied in the context of the immune response, it becomes clear why metabolic reprogramming on both the cellular and organismal level are critical aspects of the host response to infection. On the cellular level, activated immune cells largely require glucose to mount a robust response. This is consistent with the anabolic processes that immune cell activation entails, including rapid proliferation and synthesis of biomolecules, including cytokines, antimicrobial proteins and lipid mediators. Simultaneously, tissues not directly involved in the immune response engage catabolic metabolism and switch fuel usage from glucose to fatty acids and ketones which support tissue protective pathways, since dormancy programs are generally highly resistant to stress.

Life history programs encapsulate the fundamental processes of life. Species, organisms, and cells must all grow and reproduce/proliferate or survive dynamic environments with a limited pool of resources. Proper allocation of these resources (metabolic programming) is necessary to achieve these basic processes of life. Metabolic and inflammatory disorders, such as diabetes, obesity, sepsis and autoimmune and autoinflammatory diseases, are

increasing at alarming rates with little progress made to mitigate mortality and morbidity despite significant technological advancements. The evolutionary perspective on immunity and metabolism may provide a useful framework with which to understand the biology underlying these diseases.

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Figure 1. Dormancy and defense are distinct programs of maintenance.

Favorable environments promote investment into growth and reproduction. Unfavorable environments are of two types – resource scarcity and presence of insult (pathogen, toxin, etc.) – and both lead to divestment in growth and reproduction.

A. Resource scarcity induces dormancy states, which are characterized by divestment in non-essential functions, energy conservation, and reliance on catabolic metabolism. These programs are generally tissue- and cyto-protective.

B. Presence of insults induces defense states, which are characterized by energy consumption and anabolic metabolism. Components of the system that are not required for defense engage dormancy both for protection and to divert resources to the high energy consuming defense arm.

Figure 2. Hypothalamus as a central coordinator of organismal life history programs.

The growth, reproduction, and maintenance arms of life history theory correspond on the organismal level to the growth hormone - insulin-like growth factor (GH-IGF), hypothalamic - pituitary - gonadal (HPG), and hypothalamic - pituitary - adrenal (HPA) axes, respectively. These axes all initiate at the level of the hypothalamus, and can be engaged or disengaged depending on inputs reporting on the quality of the environment. The GH-IGF axis regulates hepatic secretion of IGF-1, which is known to be essential to growth. The HPG axis controls the gonadal secretion of sex hormones, which are necessary for reproductive maturation and function. The HPA axis governs adrenal secretion of glucocorticoids, which are a common component of responses to environmental stress.

Figure 3. Cellular life history programs and their corresponding metabolic programs.

A. Cells generally utilize aerobic glycolysis and anabolic pathways after receiving growth and differentiation signals in order to grow and proliferate and actively suppress catabolic pathways. Signals that inhibit differentiation and proliferation and promote quiescence generally suppress anabolic pathways and utilize catabolic pathways associated with fatty acid oxidation (FAO) and oxidative phosphorylation (OxPhos).

B. Inflammatory and immunostimulatory signals (e.g. TCR, CD28, toll-like receptors) are mitogenic signals for immune cells and utilize the same pathways as growth and differentiation factors. These signals direct activation of macrophages, dendritic cells and T cells. Anti-inflammatory signals, such as IL10, TGF β (macrophages) and PD1 (T-cells), inhibit metabolic pathways associated with activation and drive catabolic pathways and FAO. Similarly, signals such as IL4 (macrophages)(107) and IL7 (T-cells) promote corresponding quiescent cellular states (alternatively-activated macrophages and memory T cells, respectively) which also utilize FAO and catabolic pathways.

Figure 4. Inflammation Engages Both Defense and Dormancy Programs. Dormancy programs are induced by resource scarcity. Resource scarcity is sensed by the hypothalamus and endocrine organs which then send signals that activate catabolic cellular and organismal programs associated with quiescence and stress-resistance. Defense programs are induced by environmental insults such as infectious agents. These are sensed by the immune system which then use inflammatory mediators to activate anabolic cellular and organismal programs associated with proliferation and biogenesis.

A. During the inflammatory response to infection, inflammatory mediators engage dormancy-associated programs. While the immune system is engaged in defense programs, other parts of the organism are engaged in dormancy programs, which confers stress resilience and tissue protection.

B. The host response to infection is divided into immune resistance and immune tolerance. Immune resistance is a defense life history program utilized by the immune system and utilizes corresponding anabolic metabolic programs. Immune tolerance is a dormancy life history program activated by the immune system and utilizes corresponding catabolic metabolic programs.

Table 1.

Cellular life history programs and their associated signaling and transcriptional programs. ER, estrogen receptor; AR, androgen receptor; RIP140, receptor interacting protein 140; Gai and Gas, Gs and Gi a subunits; ATF4, activating transcription factor 4; GSK3b, glycogen synthase kinase 3b; GR, glucocorticoid receptor; PGC-1a, peroxisome proliferator-activated receptor g coactivator 1-a; ERRa, estrogen-related receptor a; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein.

	Growth/Proliferation	Maintenance/Dormancy
Cellular Level Signaling	PI3K - AKT	AMPK
	mTOR	GCN2 - ATF4, AMPK
	c-Myc, ChREBP	FoxO
	STAT5	STAT3, SMAD2,3
	Ras-Raf-Erk	GSK3b
	ER, AR	GR, PPARa
	RIP140	PGC-1a, ERRa
	Gai	Gas - cAMP - CREB
Organismal Level Signaling	Insulin	Glucagon
	Leptin	Ghrelin
	IGF1, Sex Hormones	Glucocorticoids
	Growth Hormone *	Growth Hormone *

* Growth Hormone is induced in both favorable and unfavorable environments. How it instructs growth as part of the GH-IGF axis, while also acting downstream of ghrelin to promote adaptation to nutrient scarcity is unknown.