Rejuvenating effect of pregnancy on the mother

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Aging is associated with reduced tissue regenerative capacity. In recent years, studies in mice have shown that transfusion of blood from young animals to old ones can reverse some aging effects and increase regenerative potential similar to that seen in young animals. Because pregnancy is a unique biological model of a partially shared blood system, we have speculated that pregnancy would have a rejuvenating effect on the mother. Recent studies support this idea. In this review, we will summarize the current knowledge of the rejuvenating effect of pregnancy on the mother. (Fertil Steril® 2015;103:1125–8. ©2015 by American Society for Reproductive Medicine.)

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In aging organisms, the capacity to tissues to regenerate declines and healing in response to injury is delayed (1–6). This effect, which has been observed in liver, skin, bone, the hematopoietic system, nerve, and muscle, is attributable to the altered functions of many biological processes (1, 2). These include changes in growth factors or in extracellular matrix components, accumulation of DNA damage, and decline in the responsiveness of progenitor cells (3–5). The possibility of reversing these processes is offered by heterochronic parabiosis (connecting the circulations of a young and an old mouse). In the past it was found that these procedures could restore the regenerative capacity of striated muscle in old mice and increase the basic rate of cell proliferation in aged liver hepatocytes (6, 7), an effect redemonstrated more recently. In rats, aged muscle successfully regenerates when grafted into the muscle of a young host, and young muscle displays impaired regeneration when grafted into an aged host (8, 9).

Furthermore, it has been shown that an old animal exposed to serum taken from a young animal has increased regenerative potential, similar to that of a young animal. Thus, it may be speculated that the decreased regenerative potential that occurs with aging might be a reversible process and that factors in the young animal may have a rejuvenating effect on the old.

Pregnancy can be viewed as a natural state akin to parabiosis, in which organisms partly share blood systems – in this case, an adult organism (the pregnant mother) is exposed to extremely young organisms (the fetuses). The fetus may thus have a rejuvenating effect on the mother. We recently showed that pregnancy restores the regenerative capacity of the aged liver in mice, while others have demonstrated this effect in other organs. In this review, we will summarize the current knowledge/evidence of the rejuvenating effect of pregnancy on the mother.

LIVER

The liver is an important organ within the body that has a central role in metabolic homeostasis and the production of large numbers of serum proteins. In addition, it is the main detoxifying organ of the body. The main cell type of the liver that performs most of these functions is the parenchymal cell, or hepatocyte, which makes up about 80% of hepatic cells. The other 20% comprise the nonparenchymal cells. Although adult hepatocytes are long-lived and normally do not undergo cell division, they maintain the ability to proliferate in response to toxic injury and infection (10).

Regeneration of the liver is a complex process that rapidly compensates for the acute loss of liver parenchyma that follows partial hepatectomy (surgical removal of part of the liver) (11) or as seen in patients with liver tumors or fulminant hepatitis (12). Because of

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the multilobe structure of the rodent liver, three of the liver lobes (representing two-thirds of the liver mass) can be removed by an easy surgical procedure without causing any tissue damage to the residual lobes. The latter grow in size to restore an aggregate equivalent to the mass of the original lobes. In liver regeneration there is a hyperplastic response that involves the replication of virtually all the mature functioning cells (mainly the hepatocytes) in the remnant liver, which does not require the recruitment of liver stem cells or progenitor cells.

Studies have shown that in old mice the liver regenerates significantly more slowly than in young mice (13–15), and similar observations have been made in humans (16). When young and old rats were partially hepatectomized, it was found that the rate of DNA synthesis was lower in the old group (17). Moreover, aging affects not only hepatocyte proliferation but also the liver stem cells, thereby inhibiting the regenerative capacity of aged liver (14). It is interesting that the effect of aging on liver regeneration has been suggested to be reversible. It was found that parabiosis between young and old mice increases aged hepatocyte proliferation (6).

Our group has studied the effect of pregnancy on liver regeneration (15). We used serial magnetic resonance imaging (MRI), which accurately measures liver volume. We analyzed the process of liver regeneration after a two-thirds partial hepatectomy in nonpregnant and pregnant 3-month-old (young) and 10- to 12-month-old (aged) mice. In the nonpregnant groups, the total liver volume regenerated 2 days after surgery to approximately 82% of the original size in young mice, whereas in aged mice the liver regenerated only to 46%. In contrast, liver regeneration in aged pregnant mice was dramatically more efficient, with 96% of the liver volume restored within 2 days.

Furthermore, in the aged mice, blood coagulation (indicative of the liver's synthetic capacity) was pathological in the nonpregnant group but within normal limits in the pregnant group. Posthepatectomy mortality in aged mice declined significantly, from 47% in the nonpregnant group to 9% in the pregnant group. Thus, in the aged mice the percentage of liver volume gain, liver function, and, most importantly, survival after partial hepatectomy was markedly improved by pregnancy.

We found that liver regeneration in nonpregnant mice proceeded through a hepatocyte hyperplasia mechanism in which the increase in liver volume depended mainly on cell proliferation whereas regeneration in pregnant mice was associated with an increase in the size (hypertrophy) of hepatocytes. Our results provide novel evidence that a physiologic condition (i.e., pregnancy) causes a switch from proliferation-based liver regeneration to a regeneration process mediated by cell growth.

We were able to show that the protein kinase B/mammalian target of rapamycin complex 1 (Akt/mTORC1) pathway is a key determinant of hepatocyte hypertrophy in regenerating livers of pregnant mice. Treatment with bpV(phen), an activator of the Akt/mTORC1 pathway, was found to be sufficient to activate the hypertrophy regeneration mode in nonpregnant mice. Importantly, when we subjected old female mice (18–24 months of age) to partial hepatectomy without or with bpV(phen) treatment, we found that bpV(phen) treatment resulted in a significant improvement in the survival and the recovery from partial hepatectomy compared with untreated old mice.

The bpV(phen) experiments allow us to conclusively state that the hypertrophy mode improves the regenerative capacity of old mice. Furthermore, we have shown that the survival rate of partial hepatectomy in old organisms can be improved using pharmacologic means. Our findings demonstrate that liver regeneration through proliferation, the default module in nonpregnant mice, is severely compromised by age whereas the cell growth-mediated regeneration seen in pregnant mice is relatively resistant to the detrimental effects of aging.

CENTRAL NERVOUS SYSTEM

Acute brain damage in rodents and humans during adulthood is followed by an increased proliferation of neural precursor cells, generating new neurons and neuroglia cells (such as oligodendrocytes and astrocytes). In this way, tissue integrity is restored (18–22).

One form of central nervous system (CNS) damage is caused by neuroinflammatory diseases, with multiple sclerosis (MS) accounting for a large proportion of this group. Multiple sclerosis is characterized by inflammation that targets myelin and oligodendrocytes in the CNS, causing demyelinated lesions that can lead to axonal damage and neuron loss (23). In response, new myelinating oligodendrocytes initiate the process of remyelination of these lesions, which appears to be impaired in MS patients (24).

The Pregnancy in Multiple Sclerosis (PRIMS) study (25, 26), a large prospective study, demonstrated a lower relapse rate during pregnancy, particularly in the third trimester, relative to the rate in the previous year. This was correlated with a decrease in the number and size of active white matter lesions (27). In addition, there is a decreased risk of MS in multiparous compared with nulliparous women (25, 26).

A study used a remyelinating model after acute demyelination in mice in which the detergent lysolecithin was injected directly into the spinal cord; remyelination was assessed by measurements of the lesion size. In pregnant mice (gestational day 14), the volume of the lesion was 52% smaller than that of matched virgin controls. Newly generated oligodendrocytes in the lesion site increased by 80% in pregnant mice; a significant increase in the number of remyelinated axons was also observed (28). Prolactin was thought to be the regulator of these findings because oligodendrocyte precursor cells express the prolactin receptor. In vivo experiments in which prolactin was infused into nonpregnant mice after injury showed a significant increase in the number of dividing oligodendrocyte precursor cells, resulting in generation of new oligodendrocytes compared with controls. In vitro studies in which prolactin was added to precursor cell culture medium showed that the number of oligodendrocyte neurospheres increased by 38% relative to the control.

It is interesting that studies on pregnancy-associated compounds revealed a specific factor, embryo-secreted