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Antenatal Thymosin β4: a New Tool for Accelerating Fetal Development in Preterms? Thymosin Beta-4: a Breakthrough in the "Physiological" Regenerative Medicine in Preterm Newborns

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Abstract: To prevent the health risks related to prematurity, multiple drugs have been introduced in clinical practice in recent years. This paper focuses on a new "physiological" regenerative approach to be started in the perinatal period, particularly on very low birth weight preterm infants. This new preventive approach underlined the necessity to start regenerative medicine very early after birth, a period in which kidney, brain, pancreas, and lung stem cells maintain their proliferative and differentiating abilities. Among the multiple factors proposed in the literature as potential growth promoters for preterm neonates, thymosin beta-4 (Tβ4) has been indicated as one of the most important candidates for regenerative medicine.

Keywords: regenerative medicine; preterm birth; thymosin beta-4 (Tβ4).

1. Introduction

Preterm birth is a major challenge for most health care systems worldwide, with most perinatal deaths occurring in preterm infants [1]. Preterm delivery represents a risk factor not restricted to the newborn's survival, is associated with neurological impairment and disability occurring later in life [2-4]. Multiple drugs have been introduced in clinical practice in recent years to prevent the health risks related to prematurity. Among them, antenatal administration of corticosteroids to pregnant women with the preterm birth threat has been shown to accelerate lung maturation, allowing a better postnatal survival rate in preterm newborns [5, 6]. Further

studies have shown that antenatal corticosteroids represent the most important available tool to decrease the insurgence and severity of respiratory distress syndrome and mortality from premature birth [7, 8]. The limit of corticosteroid treatment is linked to their ability to accelerate lung maturation exclusively, whereas prematurity is associated with delayed development of the whole human body. Among the conditions influencing brain and kidney development in neonates, premature birth represents one of the most important factors [9-11]. Nephrogenesis halts few weeks after birth, with the disappearance of multipotent stem/progenitor cells of the metanephric mesenchyme and the process blocks mesenchymal-to-epithelial transition that originates new nephrons [12-15]. Consequently, preterm infants are characterized by a much lower nephron burden than at-term newborns [16, 17]. A low nephron number at birth may have significant consequences later in life, given that subjects with few nephrons should be considered at risk of developing kidney insufficiency in childhood and adulthood [18, 19]. Another organ particularly susceptible to the consequences of prematurity is the brain, whose development may be altered by preterm birth [20, 21].

2. Alterations in neuronal brain connectivity

Alterations in neuronal brain connectivity and low neurons number caused by preterm birth can predispose to impaired cognitive performance and severe neurological and psychiatric disorders [22-27]. Preterm-born children showed perinatal neurodevelopmental insults in neurogenesis and impairment in neuronal migrations [28] as those hypothesized in the neurodevelopmental theory of schizophrenia [29]. In fact, preterm delivery may be a co-determinant of the risk of nonaffective psychosis in adulthood [30].

Taking all these data together, an important challenge is facing gynecologists and neonatologists: how to improve organ development in preterm infants to avoid the consequences due to the scarcity of well-developed cells in the various organs?

3. New "physiological" regenerative approach

To answer this question, some years ago, a new "physiological" regenerative approach to be started in the perinatal period was hypothesized, particularly focused on very low birth weight preterm infants [31]. The relevance of this hypothesis was the original timing of the regenerative approach. Contrary to the vast majority of regenerative projects, focused on organs affected by severe pathological changes, this new preventive approach underlined the necessity to start the regenerative medicine very early after birth, a period in which kidney, brain, pancreas, and lung stem cells maintain their proliferative and differentiating abilities. The abundance of progenitor stem cells in the preterm kidney represents an optimal target for starting a regenerative medicine immediately after birth [32]. This peculiar type of regenerative medicine was defined as "physiological" since it was considered a substitutive of human organs' physiological development interrupted by preterm delivery. In the following years, the neurodegenerative approach has had a recent impetuous development [33, 34].

4. Thymosin beta-4 (Tβ4)

Among the multiple factors proposed in the literature as potential growth promoters for preterm neonates, thymosin beta-4 (Tβ4) has been indicated as one of the most important candidates for regenerative medicine [35]. Tβ4 is a member of thymosins, a small peptide family is expressed in most human cells [36]. Goldstein AL first described thymosins in 1966

as peptides purified from the calf thymus [37]. Tβ4 is detectable in all the cells, tissues, and bodily fluids of humans. The best-known function of Tβ4, a 43 amino acid peptide, is its ability to sequester actin monomers. Thanks to this ability, Tβ4 plays a major role in cell migration and in multiple biological functions, including cell survival, cell protection from peroxide damage, angiogenesis, tissue repair, hair growth, and wound healing [38]. Interestingly, Tβ4 is highly expressed in human newborns' saliva, but only scarcely in adults' saliva [39]. Immunohistochemical studies showed a high and disseminated expression of Tβ4 in the normal liver [40] and liver tumors, including hepatocellular carcinoma [41]. Tβ4 is highly expressed in the fetus, particularly in the fetal gut, pancreas, and liver, reinforcing the hypothesis of a major role for Tβ4 in developing the gastrointestinal tract [42]. Tβ4 is also involved in human nephrogenesis, mainly expressed in the stromal-interstitial cells in the cortex and the fetal kidney's renal medulla [43].

A breakthrough in the project aimed to introduce Tβ4 in clinical practice is represented by the recent publication of an experimental study demonstrating the ability of thymosin Tβ4, when administered to pregnant mice, to stimulate fetal growth and organ development [44]. Newborns from pregnant mice treated with intraperitoneal Tβ4 before preterm delivery showed the acceleration of lung, heart, and kidney development compared to control animals. Given that Tβ4 is a natural compound and not a drug, these preliminary experimental data represent a new base to start the proper trials for introducing the use of Tβ4 in clinical practice.

5. Conclusions

Unlike the "physiological" regenerative hypothesis, which indicated the postnatal period as the time for starting the regenerative approach, according to the recent experimental data, the trials could focus on the last weeks of pregnancy, with the administration of Tβ4 in women with a programmed preterm delivery. This original regenerative approach aims to transform a newborn susceptible to developing chronic kidney or brain disease later in life, into a resistant subject, with positive consequences on the health system.

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Conflicts of Interest

The authors declare no conflict of interest.

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