孕期应激对子代大鼠骨髓淋巴干细胞发育的影响

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摘要：孕期应激对子代产生的影响是多方面的，这种影响是复杂的。研究表明，出生前的应激经历可导致出生后子代长期的免疫功能改变。这些改变追其根源与骨髓淋巴干细胞的改变有关。本文综述了大鼠孕期经历应激的子代骨髓淋巴干细胞所受的影响及免疫系统的相关改变，并根据现有的研究提出假说，为进一步研究孕期应激导致子代免疫系统改变的机理研究提供新的思路。

关键词：孕期应激；骨髓淋巴干细胞；骨髓微环境

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Impacts of pregnancy stress on development of lymphoid stem cells of bone marrow in rats

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ABSTRACT: Stress during pregnancy impacts on the offspring a lot, this impact is complex. Studies have shown that prenatal stress experience can lead to long-term immune dysfunction after birth of the offspring. The root causes of these changes with recovery of bone marrow lymphoid stem cells related to the change. This paper reviews how the experience of stress during pregnancy affects the bone marrow stem cells of offspring and explains the changes in the immune system. This review based on existing researches, and proposed hypotheses for further study of the mechanism that how stress during pregnancy causes changes in the immune system of offspring.

Key words: stress during pregnancy; bone marrow lymphoid stem cells; bone marrow microenvironment

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孕期应激（prenatal stress），尤其是母亲在孕期较长时间处于慢性应激状态，会通过一系列机制对子代的生理过程产生影响，这种影响甚至可能伴随后代至成年及以后时期。众所周知，个体应激对机体免疫系统有不同程度的影响，而怀孕期间处于发育阶段的胚胎对内外环境的变化更为敏感。因而孕期应激可能对子代的生长、发育造成不可估量的影响，这种影响可能在胎儿出身后的不同发育阶段表现出来。越来越多的研究证据表明，孕期应激对子代免疫系统的改变具有深远意义[1]。

1 应激激素 GCs 对子代成熟免疫细胞的作用

对于个体，在短时间急性应激过程中，机体以蓝斑 - 交感 - 肾上腺髓质（SAM）激活为主要特征，体内儿茶酚胺类激素水平增加；但缓慢持久的应激通常导致机体下丘脑 - 垂体 - 肾上腺皮质轴（HPA axis）活化，体内糖皮质激素（GC）增加，作用于各细胞、组织以及器官，产生不同的影响。短期内 GC 的增高对机体可有多方面的代偿意义，但 GC 持续增高则会对机体产生诸多不利。GC 为脂溶性分子，易透过细胞膜进入胞体内与胞浆中广泛存在的糖皮质激素受体（glucocorticoid receptor, GR）结合[2]。令人感兴趣的是 GC 可诱导淋巴细胞凋亡。可能的机制包括通过 GR 激活 caspase 级联反应，caspase-3、caspase-8 以及 caspase-9 活化[3]。在怀孕期不同阶段、不同的动物模型，孕期应激对胎儿免疫系统所造成的影响不尽相同。研究表明，孕期应激子代终身免疫功能较正常组低，且随着子代年龄增长，差异越明显，主要表现为外周血 T,B 细胞数目减少，淋巴细胞增殖能力减弱，对抗原刺激的反应性较低。虽然 NK 细胞数量变化不大，活性却相较偏低[4,5]。

子代幼年期免疫系统的发育障碍通常不明显，但到青春期时，随着全身快速生长发育，免疫系统的发育障碍开始显现。研究表明，孕期应激的大鼠后代都表现了高度的亲炎症状态[6]。

2 应激对子代中枢免疫器官的作用

2.1 孕期应激对子代淋巴细胞产生的影响

传统研究认为应激对免疫系统的影响主要是使胸腺、脾脏、淋巴结的实质细胞发生改变，但近年来逐渐有学者通过研究证明应激也可对骨髓产生长久影响，并由此影响整个免疫系统[7]。对个体应激研究发现，应激对所有年龄的雌、雄小鼠均可致胸腺和脾脏内细胞数的显著减少以及骨髓中淋巴细胞比例下降[8]。Lourdes Dom 等通过对大鼠施加捆绑束缚应激，发现急性应激期由骨髓释放的成熟淋巴细胞增加，成熟淋巴细胞数在慢性压力期下降了，至适应期（42 日后）大大增加，最后在应激

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的恢复期后下跌[9]。

胸腺是 T 细胞发育成熟的器官，但原始 T 细胞则是由骨髓淋巴干细胞分化发育并迁移至胸腺的，其产生受骨髓造血干细胞分化及造血微环境影响[10]，而且 B 细胞和 NK 细胞后天主要也是在骨髓中产生[11]。由此分析，孕期应激可能在胚胎发育阶段对子代骨髓淋巴干细胞发育产生影响，导致出生后子代淋巴细胞数量和功能改变的可能性很大。

2.2 孕期应激影响子代淋巴细胞功能的机制

母体产生的应激激素 GCs 作用于骨髓淋巴祖细胞及骨髓微环境影响淋巴细胞发育。骨髓提供了淋巴干细胞分化为成熟淋巴细胞的微环境。Daniel A 等发现骨髓中表达 IL-7Rα 的一类干细胞具有分化为 T、B、NK 的潜能，表型为 CD34+CD45RAhiCD7+，于人类孕期 8-9 周出现[12]。IL-3 及适宜浓度的 IL-2 可调控多能干细胞的增殖，促进祖细胞生成。低浓度的 IL-2,IL-3 还可增强 NK 细胞毒性[13-14]。IL-2 对 NK 细胞的发育及成熟有着复杂的影响[15]。IL-7 通过 IL-7R 作用于 pro-B 细胞，促进 pro-B 细胞增殖分化，并能上调 CD19 和 Pax5 的表达[16]。在淋巴祖细胞中，Pax5 的表达可促使淋巴祖细胞向 pro-B 细胞分化，同时抑制淋巴祖细胞向 pro-T 细胞分化[17]。对于子代，孕期应激则可能破坏或改变骨髓微环境，导致子代骨髓造血干细胞在胚胎发育期间受到影响，进而引发出子代生后免疫系统发育的障碍。孕期应激对子代造成影响的机制包括直接影响（母体激素等物质通过胎盘直接作用于子代组织器官）及间接影响（改变胎盘功能）。通过这两条途径，孕期应激可影响子代免疫细胞功能或其他调节免疫反应的系统，如 HPA 轴[18]。Theodore A 等研究表明孕期应激最显著的特点是母体的 HPA 轴活化，母体产生大量的糖皮质激素（glucocorticoid,GC）[18]，GC 透过血胎屏障，可作用于胚胎发育期的胎儿，使胎儿 GR 数量多于正常。而通常后天接受 GC 刺激，机体可通过负反馈下调 GR 的量以达到保护目的。推测 GR 的这种负反馈调节作用是在个体后天发育中形成的。因此认为子代在胎儿期接受 GC 刺激会造成不可避免的损害[19]。研究发现孕期应激子代的胸腺，淋巴结，脾脏中有较高 GR 表达及形态学改变，且受体敏感性降低[1,20]，孕期应激子代血清中皮质醇类激素水平低于基本水平，T 细胞数量减少，且淋巴细胞增殖对丝裂原的敏感性降低[21]。

在体研究表明，应激会导致骨髓及外周血中前淋巴细胞数量减少，改变骨髓内前淋巴细胞的组成比例，并且使其对糖皮质激素的抵抗性增强[22,23]。Deborah 等利用糖皮质激素拮抗剂实验证明骨髓 B 细胞（尤其是 B 祖细胞）对糖皮质激素十分敏感，并在其作用下易发生凋亡[24]。对发育过程异常的淋巴干细胞的研究表明，由骨髓基质细胞产生的 IL-7 为 T,B,NK 细胞骨髓发育阶段所必需[10]。对于骨髓前 T 细胞，IL-3 及 IL-2 为其发育的关键生长因子[25-26]。基质细胞产生的 IL-15 也可通过一系列环节促进骨髓中 T 细胞和 NK 细胞的激活及分化，这种作用是直接而关键的，同时 IL-15R, IL- 2R 也被证明是 NK 细胞在骨髓发育中所必需[27-28]。

迄今为止，应激对免疫系统的影响多集中在研究接受应激的个体本身免疫功能的改变，但与孕期应激对子代免疫系统的发育影响的相关研究较少，其具体机制还不清楚，希望本综述能为相关研究提供新的思路。

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