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The perinatal period as a delicate time of transition. The possible implications of maternal stress in relation to cancer onset in intrauterine life

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ABSTRACT. – The perinatal period represents not only a transitional phase but a set of processes with respect to which both mother and child, whom she carries in her womb, are exposed to a series of factors capable of bringing about significant morphological and epigenetic changes. While these are, on the one hand, promoters of neurobiological and psychic changes, on the other, they confirm the presence of a real intrauterine exchange which, depending on the mother's background, is capable of translating into neurochemical baggage ready to be transmitted to the fetus. In fact, while the latter, from a genetic point of view inherits a parental heritage, *vice versa* from an epigenetic point of view it will acquire a morphological and behavioral framework correlated with a future adaptive and/or dysfunctional mode of expression. Maternal health therefore reflects a psychic and biological condition which, during pregnancy, can bring about considerable changes in the fetus as a reflection of its own way of being in the world. Therefore, the presence of a dysfunctional emotional self-regulation mode in pregnancy, if cumulative, can lead in the long term to the onset of a chronic and/or repetitive stress condition, which risks affecting at a biological level an internal portion of chromatin and more specifically the length of telomeres. These consequently affect the possible increase in DNA methylation related to the possible onset of carcinogenesis.

Key words: carcinogenesis; experiential background; pregnancy; stress; emotional self-regulation; DNA methylation.

The perinatal period in relation to maternal background

Pregnancy represents a time of great changes, both intrapsychic and biological, which on a morphological/cerebral level are inscribed in the mother figure. Whilst the mother is the bearer of her own neurophysiological and experiential background, she is also the main channel of communication

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and/or connection between her own psychosomatic set-up and the fetal one she is carrying in her womb. Intrauterine life thus proves to be fully sensitive and vulnerable to the structural and morphological maternal changes respectively (D'Amore, 2019), and, from an epigenetic point of view, is able to transmit its neurobiological patterns via the placenta, which can be translated into a true epigenetic imprinting. Specifically, in fact, the figure is able to transfer its own psychobiological scaffolding ready to be converted in the fetus in the form of both an initial chromosomal architecture and an initial mode of expression. It is thanks to this vision that fetal life is fully affected by maternal life and, even more so, by its way of expressing emotions and self-regulating them. Above all, its biological substrate, which can be expressed in a secretion of neurotransmitters ready to delineate a new texture within the fetus. What is interesting is precisely the relationship between the maternal experience and the prenatal (gravid) dimension, with respect to which the fetus fully absorbs a new (maternal) language and a new way of being in the world (Crews *et al.*, 2014). However, the question arises as to whether one's psychobiological background being transmitted via the fetus may have a dysfunctional impact on the future offspring, thus leading to maladaptive imprinting. On the basis of the above, one's past can not only be biologically passed on via the placental route, but in a transgenerational perspective (Barker, 1995) it can affect the future neurotransmitter set-up of the fetus and future gene expression patterns, leading to the biochemical process termed methylation. The latter in fact not only describes a true mode of gene expression, but at the same time allows us to understand how vulnerable chromatin and its internal structure may be depending on what has been passed on from the mother (Champagne & Curley, 2009). As the final portions of chromatin, telomeres may or may not functionally confirm the stability of the gene material, but from a structural point of view they describe how chronic and cumulative stress over time can lead to the onset of carcinogenesis, the onset of which could be traced back to the perinatal period. Wanting to examine this close relationship in more detail in conjunction with the perinatal period, it has been documented how a persistent condition of stress during this period can have direct effects on the telomeres of the future child (Epel & Blackburn, 2004). In fact, by adhering to the concept proposed by Barker, concerning the transgenerational transmission of one's own experience, several authors have confirmed that maternal telomeres are statistically the same both in infants and in adulthood. This makes it plausible to conceive of possible cancer onset as a process influenced not only by maternal experience but also by what will be transmitted via the placenta to the fetus (Kelly-Irving & Lepage, 2013). The latter may thus inherit a genetic architecture which on a structural and functional level would increase the risk of developing cancer.

What we wish to propose is therefore the vision of pregnancy not only as a moment of multifactorial metamorphosis but as a moment of strong vulner-

ability in which both chronic stress and one's own physiological and experiential background may reflect the prelude to probable carcinogenesis (Dujits & Zeegers, 2003).

In support of what has just been described and with a view to highlighting the close relationship between the possible onset of cancer in adulthood starting right from pregnancy, several studies have confirmed how maternal stress is capable of morphologically influencing the brain of the fetus (Thaker & Han, 2006). Specifically, a study examining young people aged between 13 and 15 who had been exposed to maladaptive maternal behavior (drug use and/or smoking) during the prenatal period confirmed that what had been transmitted through the fetus had spilled over into various brain districts, causing a reduction in the dorso-lateral prefrontal cortex, the orbito-frontal cortex and certain structures of the basal ganglia. Moreover, to confirm the extent to which the maternal brain (Kolb & Gibb, 2011) is capable of leaving imprinting in the fetal brain, another study conducted in 2004 (Liu & Lester, 2013) made it possible to highlight the extent to which, through the concept of epigenetics, a behaviour is capable of leaving its lasting imprint on the brain's biology, thus designating the presence of what is called an epigenetic marker.

The role of stress in the possible onset of carcinogenesis

On the basis of what has been proposed so far, if carcinogenesis, thanks to the epigenetic vision, reflects a set of several factors in synergy with each other and capable of affecting the individual's physical and cognitive health, on the other hand, the respective individual experiences (Parkin *et al.*, 2011) would seem to confirm how the self-regulation methods adopted in the past are more likely to have repercussions in the here and now. Thus, determining the repetition of a script already experienced and translating into a recruitment of those (cerebral) districts which, in the maladaptive manner occurring in the past, risk affecting subjective integrity in the present. Bringing about a real modification that can be followed by the onset of a state of mind which risks altering both the neurobiological circuits and one's own homeostasis respectively (Siegel, 2017). The dimension of the past therefore calls into question the range of experiences which, if not integrated, symbolised and transformed into a valid additional tool for one's own development, can have negative repercussions at both the psychic and biological levels. Making one's own experience a focal point around which one's own adaptive capacities risk coming to a halt or even undergoing a veritable crystallisation. The ways in which we come into (or have come into) contact with surrounding stimuli are then instantly converted into biochemical factors, which, depending on their respective coping and/or resilience styles, can trigger a progression or, on the

contrary, a blockage of change. In the case of carcinogenesis, as pointed out by Renan (1993), it is, therefore, possible to witness a real halt to normal neurochemical activity, which, instead of reflecting a fluid, adaptive and linear process, triggers a repetitive automatism, which risks affecting not only the expressiveness of the genes themselves, but also the activity of the various brain circuits wired and/or involved in maintaining the homeostasis of the entire organism (Eng & Kokolous, 2014). In this regard, a study conducted by Eng and Kokolus (2014) showed how dysfunctional and constant neurochemical activity over time is capable of destabilising the body's homeostatic and psychosomatic balance, thus leading to an increase in cell proliferation (Kroenke *et al.*, 2011). Specifically, the authors pointed out that an increase in stress hormone neurotransmitters (and the respective elevated cortisol levels) corresponds to an increase in cell proliferation. It was also made possible to highlight how, at an immunological level, the proliferative effect, induced by cortisol, stimulates both the production of insulin and its metabolites, concomitantly inhibiting (in relation to the above) the expression of certain genes (p53 and BRCA-1) directly involved in regulating cell apoptosis (Qin *et al.*, 2015). In fact, the latter not only proves to be a great resource against uncontrolled cell proliferation but is directly proportional to the expressiveness of the genes, which, from an epigenetic point of view, can be affected by the changes taking place and thus trigger different and sometimes dysfunctional activity. Further data in the literature (Ridout *et al.*, 2015), have in fact highlighted to what extent the stress hormone can have a considerable and negative influence on the onset of the pathology described here. The increase in cortisol has in fact proved capable of provoking a real imbalance in the immune response (Eng *et al.*, 2014), with respect to which an increase in Th2 and Th17 activity has been recorded and evidenced, which as a whole have proved to be inadequate in destroying malignant cells (Bottaccioli, 2020). What has emerged so far is therefore a description of a homeostatic balance which, from an epigenetic point of view, may affect not only the psychosomatic unity of the individual, but also his or her organic functions, which in the long run may also, and above all, affect the immune system. In fact, precisely on the basis of the immune imbalance and its type of response to Th2-Th17 cells, the inflammation that emerges is likely to correlate with the development of metastases, which are the main cause of death.

The structure of chromatin and the possible repercussions of its structural change

Wanting to examine in greater detail the relationship between stress, the epigenetic dimension and possible carcinogenic onset, a further process that has been investigated concerns the reduction in length of telomeres, *i.e.*, the

end portions of the compact heterochromatin (Entringer & Epel, 2011). Structurally and functionally, they not only provide stability to chromosomes, but at the same time, as true portions of the latter (*i.e.*, chromosomes), any shortening can affect both the stability of the genome and its mode of gene expression (Epel & Blackburn, 2004). Thereby endangering its mode of expression with consequent carcinogenic alterations. This process, related to epigenetics, allows us to understand how cancer is a multifactorial pathology and at the same time the reflection of an attitude of the organism, which is not always predictable, precisely because it is in contact and in constant interaction with various aspects; first and foremost its own experience (Lillberg & Verkasalo, 2003). Time, therefore, reflects an evolutionary window through which it becomes possible to understand to what extent one's own self-regulation modalities, experienced and acquired during childhood, can be translated into an emotional, genetic and yet not always necessarily linear language. Epigenetics therefore provides a key that makes it possible to abolish those cause-and-effect links that for centuries have been dominant both in the scientific panorama and in the way of interpreting the relationship between the individual and his or her illness. If, therefore, from a psychoanalytic point of view, the past and even more so childhood reflect two very important phases, from a neurobiological point of view it is fascinating to understand how what is inscribed in our genome in the form of lived experiences can, on the one hand, reconfirm an ancestral and recurring mode of self-regulation and, on the other, be transmitted intrauterinally. Indeed, based on various studies, it has been possible to document how chronic stress can cause telomere shortening early in life (Blaze *et al.*, 2015).

A broader view of a process sensitive to the slightest changes

Cancer is thus not only a pathological condition characterized by the uncontrolled proliferation of cells with the capacity to infiltrate the body's normal organs and tissues, altering their structure and respective functioning, but a multifactorial disease. In fact, this characteristic highlights the strong relationship between two interdependent keys: the genetic and the epigenetic. While for years the former offered a valid view limited to genomic alterations and chromosomal abnormalities, epigenetics now offers an additional lens through which to view carcinogenesis as the reflection of several alterations. Thus, offering a more holistic representation of the carcinogenic process taking place within the body. However, on a more microscopic level, several studies have confirmed that epigenetic alterations play a fundamental role relating to the modulation and expression of genes involved in the cancer process (Shen & Laird, 2013); with respect to which some authors have confirmed that not a true modification of the DNA structure occurs, but rather a

set of functional modifications which, when constant and repetitive, could result in a dysfunctional and cumulative instability, which may lead to the instability of the genome itself (Doll & Peto, 1981). In our presentation of this overview, we wish to propose the concept of a pathology related not only to several factors but also characterized by a genesis that is not necessarily confined to the classical laws of cause and effect. Thereby pointing out that the possible onset is related to our environment, to the lifestyle one chooses to acquire, but above all, and even more so, to the life events that can translate into both a psychic and somatic trace; with respect to which one's coping and self-regulation mechanisms will resort to a network of adaptive and/or dysfunctional tools by means of which one can orient oneself in everyday life. What is most important is precisely how the combination of several factors, in synergy with one's own experiential background, can have an impact on both an intrapsychic and psychobiological level, giving rise to what Siegel (2017) defines as the state of mind, and which Militello (2022) describes as epigenetic attitude.

The role of methylation in carcinogenesis in the mother-embryo dialogue

From a biochemical perspective, DNA methylation represents the best-known set of epigenetic modifications (Marafante, 2012). Specifically, while from a structural point of view, this process presents an accentuation or decrease (which can be subdivided into hyper- and hypo-methylation), from a functional point of view it fully reflects the close relationship between the microstructure of chromatin and the external world; in the case of pregnancy, the maternal world. Enhancing both the degree of suppression and the degree of expression of the gene itself. In relation to carcinogenesis, the possible presence of abnormalities in DNA methylation may lead to changes in the spatial organization and remodeling of chromatin, which in turn assumes a conformation that may make it more open (where the gene becomes active), or in the case of de-methylation more compact, closed and therefore inactive. Determining which genes will be active and which will not (Biava, 2001). Indeed, in the case of hypermethylation, those genes that act as tumor suppressors, called oncosuppressors, are inhibited. The change in chromatin architecture has been described as corresponding in a directly proportional manner to a different mode of gene expression; as described above a true expression or silencing (Olumi *et al.*, 1999). According to Jean Pierre Issa's (1997) view and in agreement with the data in the literature, the origin of cancer is related to the change in epigenetic patterns involved in aberrant DNA methylation, described as the biochemical modification of a gene through the addition of a molecule called methyl, which silences its

activity. The set of biochemical processes present in pregnancy thus not only fully reflect the experiential past of the individual, in this case, the mother, but also the set of psychic and neurobiological factors that may be transmitted to the offspring via the fetus and which may lay the foundations for a mode of epigenetic expression which may or may not promote both the fetal health and that of the future child.

The molecular mechanism, that is evident within the dialogue between mother and child, is that of the regulation of certain key genes and proteins (Militello, 2022) that characterize the cell cycle. Specifically, in fact, this regulation is directly involved in the cellular blockage of possible tumor cells. Through this process, it is also possible to see how certain onco-repressor genes are activated, which have the task of correcting any genetic damage present in the cell by repairing the mutations present in the organism.

However, as the number of mutations increases both in number and in complexity, it becomes more difficult for the onco-repressor genes themselves to activate the mechanisms of programmed cell death called apoptosis in order to safeguard cell equilibrium. By placing this process in embryonic regulation, it becomes clear that it is possible to program (thanks to onco-repressor genes) the fate of the cell, thereby preventing multiplication in an undifferentiated manner and consequently allowing programmed death. However, what is interesting to note is precisely the manner in which substances that inhibit possible tumor growth are only present at specific moments in embryonic differentiation. Thus, thanks to this view, the hypothesis that the cell differentiation stages of the embryo contain regulatory networks (and/or links) capable of leading tumor cells towards re-differentiation, either adaptive or on the contrary dysfunctional (Skobe & Fusening, 1998), is increasingly strengthened. Going into greater detail, these regulatory networks appear at certain stages of cell differentiation including gastrulation. Therefore, in relation to the respective maternal background, it is possible to speculate that it may negatively interfere with cell life by promoting apoptosis or new cell differentiation. At the basis of this embryonic process, differentiation is accompanied by factors that, if recruited, can cooperate in unison by controlling and monitoring the differentiation of each cell. Increasingly enhancing a vision that takes into account a microscopic process in constant interaction with maternal biological patterns, transgenerational epigenetics (Barker, 1995) makes it possible to highlight the set of processes that can influence two very important levels: the one inherent to differential gene transcription, and the one relating to nuclear RNA selection. Both processes, on the basis of what we wish to propose, are of fundamental importance precisely because they monitor and control gene expression, which as Militello (2022) and Bottaccioli (2020) point out, is directly involved in the possible onset of carcinogenesis. Thus, confirming how methylation from the perinatal period onwards reflects a

selection of those genes whose mode of expression will influence possible onset. Taken together, these processes of a selective nature fully describe the existence and dynamism of a complex system with respect to which a variation in cell differentiation and its internal architecture corresponds to a different mode of expression, which may be adaptive or dysfunctional.

The epigenetic dimension as a new key to interpretation

On the basis of what has been outlined in this article, Jean Pierre Isa (Militello, 2022, p. 89, orig. ed.), an oncologist and scholar of the epigenetic origin of tumors, argues that the origin of the cancer process is predominantly confined to changing epigenetic patterns and aberrant DNA methylation processes. These have been shown to leave an epigenetic mark transgenerationally. Therefore, embryonic cell differentiation may also be affected by altered DNA methylation in spermatozoa, which, as Militello (2022) points out, may be carriers of a dysfunction capable of impairing future cell division and/or differentiation from the prenatal period onwards by means of what Carmen D'Amore calls epigenetic memory.

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