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Defining the Research Landscape for Dermal Neurofibromas

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Neurofibromas are benign nerve sheath tumors composed of a heterogeneous admixture of Schwann cells, perineural cells, fibroblasts, and bone marrow-derived monocytic cells, including mast cells and macrophages. These tumors most typically arise as solitary sporadic lesions, where they can appear as localized cutaneous neurofibromas, diffuse neurofibromas, or localized intraneural neurofibromas. The cutaneous neurofibroma is the most common form in which tumors grow as soft nodular or polypoid masses, whereas the intraneural variety causes segmental fusiform nerve enlargement. Microscopically, these peripheral nerve sheath tumors are hypocellular lesions embedded within a collagenous matrix, and are typically S100 β protein-immunoreactive containing few proliferating (Ki67⁺) cells. Occasionally, other variants, such as diffuse plexiform neurofibroma, may less commonly develop in the general population.

While these peripheral nerve sheath tumors most commonly present as non-syndromal lesions in people without any known genetic condition, dermal neurofibromas (DNFs) represent one of the defining clinical features of the Neurofibromatosis type 1 (NF1) tumor pre-disposition syndrome. Affecting one in 3,000 individuals worldwide, NF1 is caused by a genetic mutation in the *NF1* gene on chromosome 17, such that all individuals with NF1 are born with one dysfunctional *NF1* allele (germline *NF1* gene mutation).

The development of neurofibromas, the most frequent tumor in NF1, and malignant peripheral nerve sheath tumors represents a serious complication of this disorder, with significant associated morbidity and mortality. As such, nearly all adults with NF1 harbor DNFs, while nearly one-third of all affected individuals manifest plexiform neurofibromas. Although they are similar at the cellular and ultrastructural level, plexiform neurofibromas are thought to be congenital, involve multiple nerve bundles and progressively enlarge throughout life. Dermal neurofibromas, on the other hand, are exclusively in the skin and occur in most individuals with NF1 (see Image). Histologically indistinguishable from their non-syndromic sporadic counterparts, NF1-associated DNFs typically arise in early adolescence, where their formation often heralds the onset of puberty, implicating a direct or indirect hormonal influence. During adolescence, pregnancy and menopause, the number

of these tumors usually increases, and some adults with NF1 will harbor hundreds, or even thousands, of these tumors, leading to severe disfigurement.

However, unlike sporadic DNFs, NF1-associated benign peripheral nerve sheath tumors arise following somatic loss of the one remaining functional copy of the *NF1* gene in Schwann precursor cells, leading to increased activation of the growth control pathways regulated by the *NF1* protein (neurofibromin). In this regard, NF1-DNF Schwann-like cells exhibit elevated RAS pathway activation. Moreover, these tumors are composed of a diverse collection of non-neoplastic cell types, including fibroblasts and mast cells, as well as a rich extracellular matrix. Each of these cellular or acellular components provides supportive cues that facilitate tumor formation and continued growth. Studying the interplay between tumor cells and their microenvironment in the context of NF1-DNFs has the potential to define how stromal cell types interact with neoplastic cells to orchestrate tumorigenesis and continued expansion.

Gene Mutations

Interestingly, a series of genetic studies have begun to reveal that not all germline *NF1* gene mutations are equivalent. In this respect, numerous families have now been identified in which individuals with specific germline *NF1* gene mutations exhibit many of the other typical clinical features of NF1, but do not develop dermal neurofibromas. Further examination of the impact of these interesting germline *NF1* gene mutations on the function of the neoplastic and non-neoplastic cells in DNFs may yield critical insights into the pathogenic mechanisms underlying tumorigenesis.

The temporally and spatially distinct clinical presentation of dermal versus plexiform neurofibromas supports the hypothesis that these neurofibromas may originate from different progenitor cells. Another indication of the dual origin of dermal and plexiform tumors is that mice that develop plexiform tumors with 100 percent frequency fail to develop dermal tumors, consistent with the idea that different cells of origin exist. The fact that in humans dermal tumors appear in adolescence, as well as the increasing appreciation for the existence of a variety of adult tissue stem cells led to the consideration that an adult progenitor cell population in the skin could be the cellular source for these tumors. In fact, one of us has shown that a population of neural crest-derived progenitor cells residing in the dermis, termed skin-derived precursors (SKPs), is the cell of origin for NF1-associated dermal neurofibromas. In addition, we generated a mouse model for this complex cutaneous tumor.

Nf1-deficient SKPs have the capacity to engender plexiform or dermal neurofibromas, a process that is contingent on their local microenvironment, and these progenitor cells exhibit the same properties as the embryonic Schwann cell progenitors that give rise to plexiform neurofibromas. These studies reveal that loss of *Nf1* gene expression in SKPs is required, but is not sufficient, for neurofibroma development, revealing critical roles for the tumor microenvironment in neurofibroma genesis. In addition, when *Nf1* gene expression is deleted only in the skin, it takes 6-7 months before dermal neurofibromas appear at the same site. This delay in tumor appearance, together with the restricted location, suggests that the dermal neurofibroma cell of origin resides in the skin, and that additional genetic

and/or microenvironmental cues are required for tumor development. Consistently, these dermal neurofibromas are always in proximity to an enlarged cutaneous nerve, and have a large number of mast cells infiltrating the tumor, which have been shown to be essential for neurofibroma development.

A further physiological similarity between the mouse model and the human condition was the influence of hormonal state. When *Nf1*-homozygous SKPs were autologously implanted, either intradermally or subcutaneously, they efficiently gave rise to dermal neurofibromas only in mice that were pregnant at the time of implantation, and not in male mice or in non-pregnant female mice. This result indicates that the hormonal milieu during pregnancy can facilitate induction of dermal neurofibroma development from *Nf1*-deficient SKPs in the skin. This finding is in agreement with the human clinical scenario, where NF1 patients typically begin to develop dermal neurofibromas around puberty, and the number and size of dermal neurofibromas increases during pregnancy in female patients.

More Research Needed

While currently understudied, DNFs represent a new area for intense scientific investigation. Using NF1 as a tractable experimental platform, future research could focus on several areas germane to benign tumor biology and eventually patient treatment.

First, defining the contribution of non-neoplastic cells, like fibroblasts and mast cells, provides unique opportunities to determine how signals from the tumor microenvironment dictate tumor formation and growth. These signals, which could be growth factors, sex hormones or cytokines, might represent alternative targets for therapeutic drug design.

Second, the rich extracellular matrix that envelops these tumors may provide instructive cues for tumor growth, as the proteins that comprise these matrices often concentrate growth factors important for tumor growth. Third, dissecting the growth control pathways in the neoplastic cells using NF1 as a genetic tool is also likely to provide key insights into the mechanisms that maintain tumor growth. In this regard, the signal transduction molecules that mediate DNF proliferation become potential targets for neoplastic cell therapies.

Lastly, the finding that individuals with specific germline *NF1* gene mutations do not develop DNFs provides an opportunity to define the conditions required for tumorigenesis in an unprecedented manner. Future laboratory investigation using novel *Nf1* genetically-engineered mouse models, NF1-patient-derived stem cells, and unique in vitro organoid platforms are likely to transform our understanding of these common tumors and enable more rapid progress toward effective therapies not only for individuals with NF1-DNFs, but also for similar tumors arising in the general population.

Biographies

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Representative DNFs from an adult with NF1.